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Hormonal symptomatic and neuropsychologic responses to sugar intake in children with Attention deficit disorder

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A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Nancy Lynn Dingott

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To my parents, Marvin and Doris Dingott, with love.

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Abstract

HORMONAL, SYMPTOMATIC AND NEUROPSYCHOLOGIC RESPONSES TO SUGAR INTAKE IN CHILDREN WITH ATTENTION DEFICIT DISORDER Nancy L. Dingott, Bennett Shaywitz, Sally Shaywitz, William V. Tamborlane. Department of Pediatrics, Yale University School of Medicine, New Haven, CT.

Healthy children have more vigorous epinephrine responses to the mild reductions in plasma glucose that are seen 3 to 5 hours after oral glucose ingestion than do healthy adults. To test the hypothesis that children with Attention Deficit Disorder (ADD) might be particularly vulnerable to such glucose-stimulated epinephrine responses, 17 children with ADD (11±.6 y) characterized by standardized rating forms and 7 normal controls (9±1.0 y) were studied for 5 hours after an oral glucose load (1.75 g/kg). Plasma glucose, epinephrine, and norepinephrine profiles differed significantly between the two groups (p=.0001,.0348, .0007, respectively), with the ADD group demonstrating higher glucose and lower plasma norepinephrine and epinephrine compared to controls. Despite these metabolic differences, there were no between group differences in hypoglycemic symptoms or performance on visual search and continuous performance tests (CPT). Scores on a matching test were slightly worse (p=.0023) and matching reaction time slightly faster (p=.0039) for the ADD children both before and after glucose ingestion. Both groups had increased false positives on the CPT over time (p=.0354) and made more omissions on the CPT when epinephrine peaked (p=.0347). These changes in performance were parallel for the two groups. Thus, while children with ADD appear to have altered metabolic responses to simple sugar ingestion compared to normal children; they do not appear more vulnerable to performance decrements.

TABLE OF CONTENTS

Introduction

Background:

Blaming diet for changes in behavior in children is an attractive and popular idea. For example, in the 70's Feingold introduced a diet intended to control hyperactivity by restricting food additives and salicylates and many parents and pediatricians believed that it was effective [Harley et al., 1978]. However, a number of controlled studies indicate that an additive free diet has negligible treatment effects for hyperactivity [Kavale and Forness, 1983]. As the culpability of food additives has been undermined, attention has shifted to the possible role of sugar in exacerbating hyperactivity.

American children commonly ingest a diet high in simple sugars and parents and clinicians have long suspected that this plays a role in behavioral problems. Surveys of parents in a clinic for ADD reveal that 80% had attempted to implement a diet low in refined carbohydrates and 35% of the families felt that there was some evidence of improvement in their youngster's behavior sufficient to attempt to continue this dietary strategy [Varley,1984]. Forty-five percent of pediatricians and family practitioners surveyed periodically recommended a sugar-restricted diet for their patients [Bennett and Sherman,1983]. However, implementing such diets is very difficult; less than half of mothers who attempted to restrict their child's sugar intake were able to limit it to less than 50 grams a day [Wolraich et al.,1986]. In view of these difficulties, it is important to know whether physicians should continue to encourage parent's restrictive efforts.

Some support for the possibility that children with ADD might have altered metabolism and/or susceptibility to sugar can be extrapolated from a study of adults with hyperactivity of childhood onset who also had a hyperactive child. They were found to have global and regional reductions in cerebral glucose metabolism, particularly in areas known to be involved in the control of attention and motor activity [Zametkin et al.1990]. After eating refined carbohydrates, plasma glucose frequently falls below fasting levels and it seems logical that children with baseline deficits in attention might be more distracted by symptoms caused by the fall in glucose

A review of correlational studies suggests that high sugar consumers manifest increased rates of inappropriate behavior [Prinz et al., 1980; Wolraich et al.,1986; Kruesi et al.,1987; Kaplan et al.,1989; Prinz and Riddle,1986]. However, many dietary challenge studies have failed to demonstrate effects from sugar challenge [Gross,1984; Mahan et al.,1988; Milich and Pelham,1986; Wolraich et al.,1985; Kruesi et al.,1987; Roshon et al.,1989]. Among those that have found alterations in behavior or performance, improvements [Conners et al., 1988; Behar et al.,1984] exacerbations [Wender and Solanto,1991; Ferguson et al.,1986; Goldman et al.,1986; Rosen et al.,1988] or mixed effects [Bachorowski et al.,1990;] have been reported. One explanation for this is that the investigations vary greatly with respect to study populations, experimental design and end points evaluated.

Study Design Problems:

Interpretation of previous studies in this area has been limited because the subject populations differ widely with respect to age and

whether or not the subjects were believed to be sensitive to sugar ingestion. Hyperactive, normal, and children with a mixture of diagnoses have been studied. It is important to define the population, because children with hyperactivity might be expected to have a greater vulnerability than normal children to sugar. Alternatively, if sugar's effects are subtle, they may be more difficult to detect against the "background noise" of hyperactivity.

Establishing a homogeneous study population is difficult because it can be hard to define and diagnose children as attention disordered. Hyperactivity may well be an endpoint for many different processes [Weiss,1991]. Furthermore, attention difficulties probably occur along a spectrum [Shaywitz and Shaywitz, personal communication] making it difficult to make all or none diagnoses. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria have changed over the years and the disorder is currently classified (DSM3-R) together with conduct disorder and oppositional disorders as one of the three disruptive disorders. Many different names have been used for this syndrome of inattention, impulsivity, and hyperactivity [Shaywitz and Shaywitz,1984]. Subgroupings of children with inattention with and without hyperactivity has been attempted, but in much of the research on sugar ingestion the terms "attention deficit disorder (ADD)," "attention deficit hyperactivity disorder (ADHD)," and "hyperactive" are used rather interchangeably. The use of different criteria decreases the generalizability of results from one study to another.

Another problem in evaluating the effects of sugar ingestion concerns the selection of appropriate end points. Hyperactive children

have a variety of behavior problems and it is unknown which are most likely to be adversely affected by sugar. Most of the studies to date have measured some combination of laboratory behavior assessments, performance tasks, and/or activity measurements. Since effects are likely to be time dependent, the behavioral variable needs to be studied before and at several time points after sugar ingestion. This introduces the additional problem of practice effect.

The timing and duration of the study procedures have also varied widely between studies due in part to the lack of agreement as to when and how sugar alters behavior and learning. Most studies have directed their attention towards the early postprandial period because they postulate either an allergic (immunologically mediated) reaction [Crook,1975] or other nonimmune sensitivity such as deficiency of the enzyme sucrase. However, lack of allergic symptoms argues against IgE mediated allergy and sucrase deficiency is a rare entity with mainly gastrointestinal symptomatology, and thus probably does not account for behavioral sensitivity to sugar. Perhaps the most convincing rationale for any changes noted very shortly after sugar ingestion is that they are related to hyperglycemia. It is important to note that few studies assessed children for more than 3 hours after sugar ingestion. This is unfortunate because only longer studies can explore the provocative possibility that effects of sugar ingestion are related to the vigorous adrenergic response to a late postprandial lowering in glucose. Such a response would be expected to occur 3 to 5 hours after sugar intake.

In healthy normal subjects, as plasma glucose falls below basal levels, a series of hormonal responses act to restore normal circulating glucose concentrations [Garber et al., in Amiel et. al.,1988]. The most

important of these counterregulatory responses include a prompt suppression of insulin secretion and a brisk increase in plasma epinephrine and glucagon levels. Cortisol and growth hormone levels also acutely increase but they play a minor role in counteracting the fall in plasma glucose unless hypoglycemia is sustained. The triggering of counterregulatory hormones is believed to be responsible for the adrenergic symptoms of mild hypoglycemia such as palpitations, sweating, tremor, and anxiety. Neuroglycopenic symptoms including confusion, seizures, and coma, can also be observed with more severe hypoglycemia and they are generally attributed to cerebral glucose lack [Amiel et al.,1988].

Studies of cognitive functioning at different glucose levels, (i.e., 60,110, and 300 mg/dl), in diabetic adults found that attention and fine motor skills were slowed at low and high glucose levels [Holmes et al.,1983] but that performance was less severely impaired during hyperglycemia than hypoglycemia. The time required to solve simple addition problems was increased during hypoglycemia. Nondiabetic children would not be expected to reach blood sugars of 300 mg/dl in an oral glucose tolerance test. They would however likely dip to values near 60. Further evidence that normal children might be affected by modest excursions in glucose is offered by a study testing word recall in healthy adolescents [Lapp,1981]. Eleventh graders with glucose levels above 130 mg/dl showed significantly superior word recall compared to those with values less than 80 mg/dl.

Over the past few years, researchers at Yale and elsewhere have been evaluating factors that influence the plasma glucose thresholds that trigger release of epinephrine and the development of symptomatic and

neurophysiological changes. In healthy adult volunteers, hypoglycemic symptoms and alterations in cognitive processing of auditory stimuli at the brainstem and cortical level (as measured by brainstem and P300 potentials) were seen at glucose levels of 3.0±0.1 mM (53.6 mg/dl). The rise in counterregulatory hormones, (epinephrine and growth hormone) preceded these changes, occuring at plasma glucose levels of 3.4±0.1mM (60.9 mg/dl) [Jones et al.,1990A]. Compared to adults, children have a 10 to 15 mg/dl higher plasma glucose threshold for the release of counterregulatory hormones, development of symptoms, and impairment in cerebral auditory evoked potentials [Jones et al.,1990]. Hence, in children, rather modest reductions in glucose appear to be adequate to evoke sympathetic responses and to cause adverse cognitive effects. Most importantly, these effects are elicited by a fall in plasma glucose to levels that are commonly seen in healthy children in the late post prandial period after glucose loading [Jones et al.,1990A).

Most of the previous glucose challenge experiments have been poorly designed to detect the impact of the late fall in plasma glucose. Some experimenters gave children lunch or snacks shortly after a sugar challenge; probably preventing glucose levels from dipping even modestly below baseline. Furthermore, the effects of sugar on serotonin levels in the brain probably differ depending upon the levels of protein eaten along with the sugar [Fernstrom and Wurtman, 1971]. Sucrose increases the levels of the serotonin precursor tryptophan that crosses the blood brain barrier. Because tryptophan competes for transport with other amino acids, protein consumption may attenuate sugar's effects [Spring et al.,1987].

The importance of controlling other nutrients in the test meal is well illustrated in a study by Conners et al., [1988]. Thirty-seven psychiatric inpatients received sucrose, fructose, or aspartame following breakfast. The sucrose challenge appeared to lower minor motor activity (e.g. fidgeting) and had no effect on gross motor activity or on observer ratings of classroom behavior. Fructose seemed to significantly lower gross motor activity. However, a hierarchical regression analysis indicated that protein and carbohydrate intake at breakfast explained a greater proportion of the variance in behavior than did the challenge drinks. Moreover, when age, baseline behaviors, and breakfast foods were held constant, the sugar challenge appeared to decrease appropriate classroom behavior. This effect was statistically blocked by a breakfast meal of mixed nutrients, including protein.

In a later study, Conners et al., [1988] assigned normal and hyperactive children to three study conditions: fasting, a high carbohydrate breakfast, or a high protein breakfast, followed by sucrose or aspartame. When ingested after the carbohydrate breakfast or after fasting, the sugar challenge produced a detrimental effect on evoked potential measures of attentiveness. When ingested after the high-protein breakfast, the sugar challenge did not produce a detrimental effect. These findings point to the need to control the intake of other foods when examining the consequences of carbohydrate challenges. It is also important to note that late hypoglycemia is less likely to be observed following a high protein than a high carbohydrate meal.

Interpretation of meal challenge tests is particularly difficult in studies of diseases characterized by chronic hyper or hypoglycemia. Animal research has shown that chronic hyperglycemia decreases glucose

transport across the blood brain barrier [McCall et al.,1982 in Spring et al.,1987]. Because of this hyperglycemia induced decrease in transport, hypoglycemia can occur at normal absolute values of plasma glucose. Hence if individuals who become hyperglycemic from chronic, high intake of sugars switch to a more normal plasma glucose by fasting or other change in diet, glucose transport into the brain could be reduced with resultant symptoms of hypoglycemia [Gjedde and Crone,1981, Kanarek and Marks-Kaufman, 1979 in Spring et al.,1987]. Indeed, patients with poorly-controlled diabetes have been shown to counterregulate at higher glucose values than nondiabetic subjects [Amiel et al.,1987].

The dose and type of sugar required to cause an effect is another uncertain variable. Most frequently, the amount used in standardized glucose tolerance tests, 1.75 g/kg body weight, is given, but some researchers have tried using smaller amounts to identify the most sensitive responders or larger amounts in an effort to guarantee an effect if it exists. Since absorption rates of sucrose, fructose, and glucose vary, the time course of effects may be affected by type of sugar used.

Another problem is finding a suitable placebo. For instance, some investigators [Milich et al., 1986] have criticized the use of aspartame as a placebo, pointing out that aspartame may, itself, have adverse behavioral effects. Failure to uncover differences when aspartame is used as a placebo may be due to equally adverse effects of sugar and aspartame. One way to address this issue is to have subjects complete a trial day where no challenge drink is given [Wolraich,1985]. However, with this solution, it is impossible to maintain a double-blind. A better alternative may be to introduce an additional artificial sweetener such as saccharin or sodium cyclamate [Saravais,1990, Kruesi et al., 1987].

Correlative Studies:

Correlative studies that have examined the relationships between diet records and childhood behaviors have reported provocative findings. Prinz et al., [1980] found significant and robust correlations between reports of sugar intake and directly observed aggressive and restless behaviors in 28 hyperactive children, ages 4 to 7. In 26 normal controls, sugar intake correlated with movement but not aggression. In this study, however, sugar consumption was calculated based on the weight of the food (i.e. grams of sugar products) rather than the weight of the nutrients (i.e. grams of sucrose contained within sugar products). This methodology has been criticized due to the fact that foods have highly varied densities [Woteski et al., 1982]. However, as the authors point out, the error inherent in the method should have been randomly distributed.

Wolraich et al.,[1986] attempted to replicate the results of Prinz et al.,[1980] using the more appropriate dietary estimates based on weights of nutrients. Mothers of thirty-two hyperactive boys aged 7 to 12 years and twenty-six matched controls completed three day diet records. There were no dietary differences between groups. After controlling for age and socioeconomic status, four of 37 behavioral variables showed significant partial correlations with reported sugar intake. These were indicative of higher free-play activities, and increased off-task behavior in those children having a greater proportion of sugar in their diets. These results were corroborated by a study of seven day diet diaries of eighteen alleged sugar responders ages 2 to 6, ten of whom had psychiatric diagnoses [Kruesi et al., 1987]. This report showed a correlation between sugar consumption and duration of aggression against property. Data from

twelve normal children of similar age did not show this relationship. However, Kaplan et al., [1989], did not find such an impressive difference between normal and diagnosed groups. In their study, five out of 24 ADD and three out of 27 control preschoolers had significant correlations between daily behavior and sugar intake

In addition to exploring the relationship of sugar intake and behavior, correlative research has focused on possible interactions between sugar and attention. To evaluate the relationship of chronic sugar intake and sustained attention, diet records were collected for ninety-one five year old boys who each underwent a modified continuous performance test (CPT) [Prinz and Riddle,1986]. Twenty-three boys were high-sucrose consumers (>75th percentile), twenty-three were low consumers (below 25th percentile). Boys in the high sucrose groups had reduced attentional performance. Because the mothers of high sugar consumers were found to be less restrictive, (a potential confounder), childrearing knowledge was compared. Parental competence of the two groups appeared to be similar.

Correlational data do not indicate anything about the direction of causality. Increased adverse behaviors in children who consume more sugar does not necessarily indicate that sugar causes bad behavior. An explanation for the correlations between high sugar intake and behavioral and attentional deficits may be that impulsive, aggressive children are permitted to take more high sugar foods. Or, they may adjust their diets to compensate for energy spent in aggressive activity. The apparent lack of differences in sugar consumption between groups of normal and hyperactive children [Prinz et al.1980; Wolraich et al,1986; Kruesi et. al,1987; Kaplan et al.,1989] or of differences in overall nutrient intake

[Wolraich et al.,1986; Kaplan et al., 1989] seem to undermine these possibilities. However, one study found discrepancies in the amount of sugar intake reported by hyperactive boys and by their parents [Wolraich et al.,1986]. This discrepency suggests that correlative reports that are based on the patient's diet histories may underestimate the true amount of sugar consumed by ADD children.

Experimental Studies:

Experimental studies enable investigators to consider cause and effect and to try to quantitate the magnitude of an effect. Many challenge studies have attempted to elucidate the nature of any relationships between sugar, behavior, and performance. Methodologic and population differences are great and likely account for the variable findings, as discussed above.

Among the studies with negative results is that of Gross, [1984]. Fifty hyperactive allegedly sugar responsive boys ages 5-17 (mean age 8.6 y) were challenged with lemonade sweetened with sucrose or saccharin. There were no differences in parental ratings of the children under either condition. Similarly, Mahan et al[1988] gave an open candy bar sucrose challenge to 16 reportedly sugar responsive children. Cases demonstrating slight (nonsignificant) changes from baseline were retested using a double blind challenge. The findings showed absence of a sugar effect, even in this selected population.

Wolraich et al., [1985] studied sixteen hyperactive boys age 7 to 12 who met rigorous criteria for hyperactivity. The children received sucrose, aspartame, or no challenge 90 minutes after lunch and were studied for 3 hours. There were no significant differences on any

behavioral or cognitive data collected. To address the possibility that ingestion of food at lunch attenuated the effect of sucrose on the boys' behavior, the experiment was repeated except that the boys fasted overnight and received the challenge drink in the morning with no other food. Again there were no significant effects of sugar or aspartame.

Milich and Pelham,[1986], incorporated dietary challenges into an ongoing day treatment program for children with behavior and/or learning problems. Sixteen ADD boys fasted overnight and then randomly received sugar or aspartame on separate days. Classroom behavior, academic productivity and accuracy, noncompliance with adult requests, and peer interactions during 3.5 hours of testing were not affected by challenge substance. The authors acknowledge, however, that deleterious effects of sugar could have been masked by the behavioral intervention in effect during the study.

Behar et al., [1984] studied twenty-one reportedly sugar responsive boys ages 6.5 to 14 (mean age 10.7±1.6). Nine met criteria for ADDH, four had ambiguous diagnostic characteristics. After three days of a high carbohydrate diet and an overnight fast, subjects were challenged on three different days with glucose, sucrose, and saccharin. A significant decrease in motor activity was observed three hours after glucose and sucrose but not placebo. There were no changes on measures of behavior, attention (using a CPT), or memory.

Consistent with Behar et al.'s reported decrease in movement after sucrose is the finding of decreased frequency of minor and gross motor behavior after sucrose but not aspartame [Saravis et al.,1990]. Two hours after a standard breakfast, twenty normal 9 to 10 year old children were challenged with aspartame or sucrose and evaluated for 2 more hours.

Measures of associative learning, arithmetic calculation, activity level, and mood were unaffected by treatment. Behavior was studied during lunch 90 to 120 minutes after challenge and compared to a baseline taken 30 to 60 minutes after challenge. Minor and gross motor behaviors occurred less frequently after the consumption of sucrose than aspartame. Because there were no differences when aspartame was compared with sodium cyclamate, the authors suggest the alterations could not be attributed to aspartame. Rather, they believed that the sugar ingestion had caused a short term decrease in activity.

These results contrast to a study of thirty preschool boys, 18 of whom were alleged sugar responders, 10 with psychiatric diagnoses [Kruesi et al.1987]. The preschoolers showed less activity following ingestion of aspartame than following glucose or sucrose. Comparisons between saccharin and each sugar were not significant. Since aspartame appeared to be the disparate substance, the findings suggest that sugar did not increase activity, but rather aspartame lowered it. Such conflicting reports of aspartame's effects makes it difficult to interpret the many studies that employ this substance as the only control.

Potential confounding effects of aspartame call into question some reports of salutary effects of sugar. Thirteen children who were psychiatric inpatients ate breakfast of their own choosing followed by sucrose, fructose, or aspartame [Conners et. al., 1988]. Following sucrose compared to aspartame, children had fewer errors of omission on the CPT at 30 minutes but not 3 hours after challenge. The sucrose challenge appeared to facilitate reaction time for the earlier but not the later test. These results may indicate an early facilitating effect of small dosages of sugar on performance which would be consistent with other

studies that showed that mild hyperglycemia facilitated learning [Lapp,1981]. Alternatively, the aspartame placebo may have impaired performance. The heterogeneous nature of the sample and the fact that medication status of these children was not addressed mandates cautious interpretation.

In fact, adverse, rather than salutary effects of sugar in an ADDH population were seen in a study by Wender and Solanto [1991] comparing sugar to saccharine and aspartame [1991]. Cognitive attention and aggressive behavior were assessed in 17 children (5.5 to 7.5 y) with ADDH and in nine healthy controls. The challenges followed a controlled high carbohydrate breakfast. Children received an identical french-fry lunch 3.5 hours after challenge and then completed the final battery of testing. Aggressive behavior was not affected by either treatment. However, inattention, as measured by continuous performance test (CPT), increased from baseline compared to the 4 hour post-challenge trial only in the ADDH group following sugar but not placebo. The findings are consistent with increased vulnerability in hyperactive children. It is noteworthy that the apparent effect of sugar ingestion occured several hours after challenge. However, this is complicated by the fact that the 4 hour challenge was given after lunch.

Evidence for population variability was also demonstrated in a study of juvenile delinquents (14 to 19 y) who were assessed from 40 minutes to 3 hours after ingesting sucrose or aspartame-sweetened cereal and drinks [Bachorowski, 1990]. When the delinquents were divided based on hyperactivity ratings, the more hyperactive groups appeared to benefit from sucrose. The children who were less behaviorally disturbed tended to show slightly impaired performance after sucrose.

Confirming the importance of defining the population is a study of a heterogeneous population of 21 boys (mean age 10.7) [Rapoport,1986]. The boys underwent three 5 hour tests following glucose, sucrose, and saccharin challenges. There was no significant effect of sugar on any of the behavioral measures. However, when the group was divided into psychiatrically normal and clinically diagnosed children, each group was found to be significantly less active on sugar than on saccharin placebo. This occured at 3 hours after glucose ingestion for the diagnosed subjects and one hour after glucose ingestion for the normal subjects.

The majority of studies that report changes after sucrose remark that effects are quite subtle or are limited to occasional individual responders. Ferguson, Stoddart, Simeon,[1986] conducted two double blind challenge studies of behavioral and cognitive effects of sucrose and aspartame ingestion. In the first, eight allegedly sugar-responsive 5 to 13 year olds with a variety of psychiatric disorders were studied for 2 hours after high, moderate or low doses of sugar or aspartame. The children were not fasting. The trial showed no evidence for an effect of sucrose. In the second study, 18 nonfasting normal preschoolers were given apple juice (contains 11 g fructose) with added sugar or aspartame. The children were studied for an hour. Three of the eighteen had poorer scores on a developmental drawing test on sucrose days. Three others manifested decreased activity on the sugar days.

More striking adverse effects of sugar in normal preschoolers were reported by Goldman et al.,[1986]. Eight fasting preschool children were challenged with sucrose and aspartame and then observed for 90 minutes. Following the sucrose drink, the children showed a decrement in performance on structured tasks, including increased errors on a

continuous performance test (CPT) and more "inappropriate" behavior during free play. The differences were most pronounced approximately 45 to 60 minutes after the drinks.

In an effort to replicate and extend Goldman et al.'s work, Roshon and Hagen [1989] employed a similar design to investigate the effect of sucrose on the behavior of 12 normal preschoolers. The children were assessed for 90 minutes after ingestion. There were no significant differences between aspartame and sucrose on locomotion, task orientation, and learning.

Similarly, only minor adverse effects were noted in a double-blind within-subject challenge design of 30 preschool (mean age 5 y 4 mo) and 15 elementary school children (mean age 7y 2 mos.)[Rosen et al,1988]. Over 15 days, the children received a high carbohydrate breakfast with small amounts of protein and fat. This was followed by either 50 g of sucrose, aspartame, or a very small amount of sucrose for 5 consecutive days. Cognitive tests were given 20 to 30 minutes after breakfast. Observational measures were assessed after cognitive testing. Behavioral teaching ratings were completed prior to lunch time. The high sucrose drink caused a small increase in the children's activity level, as rated by their teachers, and a small decrement in the performance of the female subjects on a simple learning task. Observational measures and all other dependent measures failed to demonstrate any effects. It is noteworthy that while most of the measures done soon after ingestion were not affected by sugar, teacher ratings, which were conducted later in the morning showed adverse effects of sugar. This lends further support to the argument that longer lasting studies are more likely to demonstrate an effect of sugar.

Physiologic Studies:

While the design of many experimental studies probably allowed for mild hyperglycemia, most did not permit even modest declines in glucose to occur. Furthermore, few studies measured glucose, insulin, and counterregulatory hormones. Those that did measure glucose or insulin, often failed to report the actual levels [Rapoport, 1986; Behar et al.,1984.]. Despite these limitations, studies of physiologic measurements have revealed various metabolic differences in behaviorally deviant groups. Lower glucose levels, [Langseth and Dowd,1978, Gans et al,1980, Virkunen, 1982,1986, Virkunen and Huttunen, 1982] and higher early glucose values [Behar et al.,1984] following oral glucose ingestion have been reported in clinically diagnosed populations.

To evaluate whether normal children might show more pronounced responses than adults after oral glucose feeding, 14 healthy children (11.5$\pm$.8 y) and 9 healthy adults (27.6 $\pm$1.2 y) were studied following a standardized oral glucose load (1.75 g/kg)[Jones,1990]. Baseline plasma glucose and epinephrine levels in the children (83$\pm$2 mg/dl and 51$\pm$7 pg/ml respectively) did not differ from values in adults (85$\pm$2 mg/dl and 40 $\pm$11 pg/ml). Similar glucose profiles after glucose ingestion were also observed for the two groups. In particular, the glucose nadir 3-4 hours post glucose was nearly identical in the healthy children (61$\pm$1 mg/dl) and in the healthy adults (60$\pm$2 mg/dl). This delayed glucose fall caused a rise in plasma epinephrine in both groups. However, the rise in epinephrine in children was 2-fold greater than that seen in adults (445$\pm$59 vs 204 $\pm$62 pg/ml, $p<0.05$). In keeping with the increased epinephrine responses, symptoms referable to hypoglycemia (weak,shaky)

were reported by 12 children whereas only one adult reported an increase in symptoms (chi2, $p<0.01$). Thus, exaggerated epinephrine release and adrenergic symptoms were demonstrated in children but not adults following oral glucose ingestion.[Jones et al.,1990A]

Sharp rises in epinephrine and related adrenergic symptoms might be expected to cause decrements in performance. It was hypothesized that children with baseline decrements in sustained attention might be more vulnerable to these effects. The current investigation was undertaken to compare physiologic and cognitive responses to sugar intake in normal and hyperactive children.

Materials and Methods

Subjects:

Seventeen children with evidence of Attention Deficit Disorder and seven normal children were studied. All of the children were between ages 7 and 14. Eight of the children in the ADD group had been referred to the Center for Learning and Attention for evaluation of ADD; whereas the other 9 ADD subjects were directly recruited into the study. The children were evaluated for the presence of ADD by standardized parent and teacher ratings. Children's risk status for ADD as high, moderate, or low was based on Yale Children's Inventory (YCI) [Shaywitz et al.,1986] scores. Only children with a high (n=6) and moderate (n=11) risk status were included in the ADD group. Parents of the ADD patients were instructed to refrain from giving their children medications for five days prior to being studied.

Normal controls were children of University staff or siblings of patients attending the Yale Pediatric Endocrinology Clinic. They were in good health, had no known psychosocial problems, and were taking no medications. YCI scores for six of the seven normal controls confirmed that they were not at risk for ADD. YCI scores were not available for one control, but based on parental interview, patient examination, and score of 1.0 on the Conner's Abbreviated Parent questionaires [Conners , 1970], this child was not felt to be at risk for ADD. Scores of greater than 15 on this questionnaire have been used previously as criteria for ADD [Goyette et al.,1978]. None of the controls or patients had a history of diabetes, known brain injury, seizure disorder, obesity, or IQ <70.

Procedures:

The children were kept fasted except for water after midnight. At 8 a.m. they were admitted to the Children's Clinical Research Center (CCRC) where a history, physical exam, and informed consent were obtained. An intravenous catheter was inserted in a vein of the nondominant hand or forearm for blood sampling. That hand was kept in a heated box (60-65° C) to arterialize venous samples [McGuire et al.,1976].

The subjects rested for at least twenty minutes after catheter insertion before baseline blood samples were obtained for glucose, catecholamines, insulin, growth hormone, glucagon, IGF-1, and testosterone or estrogen. Glucose was ingested in the form of Glucola® at the standard dose of 1.75 g/kg body weight. Blood samples for glucose were obtained every half-hour for the first two hours and every ten minutes thereafter. Insulin, glucagon, catecholamines, and growth hormone were measured at least every half hour. Pulse was taken each hour.

Each child rated a list of twelve symptoms before and every 60 minutes after glucose ingestion. Symptoms were rated on a scale from one (not at all) to seven (extremely). Symptoms presented included pounding heart, feeling shaky, anxious, confused, weak, sweaty, irritable, and having slowed thinking. Four filler items, earache, pain in joints, watery eyes, and ringing in ears were included to control for nonspecific effects not referable to glucose and anti-insulin hormones.

Three computer tests, (the continuous performance, visual search, and matching tests), were explained and practice and baseline sessions were completed prior to drinking Glucola®. This battery of computer attention tests was repeated at the end of each hour for the next five

hours. After the children completed the computer battery for the final time they were served lunch.

Biochemical Measurements:

Blood samples for glucose were kept in 0.5 ml fluorinated tubes. All other blood samples were kept in the appropriate preservatives on ice and centrifuged by laboratory technicians, usually within 2 hours of being drawn. Plasma glucose levels were determined on ASTRA (Beckman Instruments) as soon as each patient's study was complete. Three milliliter (ml) blood samples for testosterone and estrogen were sent to the obstetrical and gynecological research laboratory (LSOG 308) for analysis by radioimmunoassay. Extraction radioimmunoassay for IGF-1 was performed on a 5 ml sample sent to the chemistry laboratory. The General Clinical Research Center Core Laboratory determined plasma levels of catecholamines (Amersham, Arlington Heights, Il), insulin (Ventrex Labs Inc., Portland, ME), growth hormone (Sanofi Pasteur Diagnostics, Austin, TX) and glucagon (ICN Biomedicals, Carson CA) levels by radioimmunoassay.

Computer tests:

For the continuous performance test (CPT) children were asked to respond to the letter X only when preceded by the letter A. There were 30 true instances and 30 "false targets," that is X without A before it. The stimulus presentation rate was initially set at 200 msec with a 500 msec interstimulus interval. These times adapted to the subjects own error rate on a trial by trial basis. Up to three hundred letters were presented.

Studies of continuous performance tests show that children with ADD usually display poor sustained attention including fewer correct detections, a higher rate of false alarms, and often a more rapid deterioration over time when compared with matched normal controls [Cooley and Morris]. The test has been shown to be sensitive to drug effects in children [Schwab and Conners, 1986].

The visual search test measures visual scanning. The screen was filled with rows of the letter I and divided into quadrants. There was one letter B on each screen. Subjects had one second to identify the quadrant containing the letter B. Low scores should indicate inattention.

In the matching task, subjects were given pairs of stimuli and asked to make same/different judgments based on a stimulus feature, size, shape, size and color. Hyperactive children might be expected to exhibit shorter (impulsive) response times and higher error scores.

Calculations and Analysis:

Comparisons of glucose baseline, peaks and nadirs and of baseline and maximum hormone responses were made. Pulse, symptom scores and computer test performance at baseline, glucose nadir, and epinephrine maximums were also compared. When the time of the epinephrine peak did not coincide with the computer testing or symptom assessment, the battery of tests given soon after these time points were used. The testing session before or after the glucose nadir, whichever was closest, was chosen for comparisons from baseline to glucose nadir.

The matching test was assessed for number of correct responses and for the time it took for the child to hit the response key (reaction

time). The visual search was graded for the number of correct responses.

The continuous performance test was evaluated for false positives (e.g. hitting the key when there was an X but no A before it), and for omissions (missing an AX sequence). Because data for one child, an ADD girl, was an extreme outlier, the data were analyzed both without this child's scores. Because baseline data for the CPT for a boy in the high ADD groups were missing, that child was not included in paired group analyses.

The data for each computer task were analyzed for changes over time and between groups. Scores following glucose nadirs and peak epinephrine values were also compared to baseline. Computer tests of attention, parent and teacher forms, except for the Conners' Abbreviated Form, were scored by researchers in the Section of of Pediatric Neurology.

All data was entered into Clinfo for analysis and expressed as means ± standard error. Using SAS, two way analyses of variance (ANOVA) with repeated measures were performed. Symptom scores were compared using the Wilcoxon Rank Sum test for paired data and the Wilcoxon Signed Rank Test for nonpaired comparisons. P values < 0.05 were considered significant.

Results

Subjects:

Although the ADD group was slightly older and heavier than controls, the differences in mean age, weight, and amount of Glucola® ingested were not statistically significant (table 1).

Metabolic and Hormonal Responses to Oral Glucose:

Baseline and oral glucose-stimulated plasma glucose responses in children with and without ADD are shown in figure 1. Analysis of the glucose profiles over time revealed slightly but significantly higher glucose values in the ADD group (figure 1). Despite these modest differences, the maximum glucose levels achieved in children with and without ADD, and lowest plasma glucose observed were virtually identical (figure 2).

Changes in islet-hormone levels are shown in figures 3 and 4. Baseline insulin and glucagon levels were similar and there was a significant rise ($p=.0001$) in both hormones after glucose ingestion that did not differ between groups. Growth hormone, as shown in figures 8 and 9, also rose significantly over time ($p=.0001$) in both groups.

Plasma catecholamine profiles before and after oral glucose are shown in figures 5 through 7. Epinephrine levels were comparable for the two groups at baseline and a sharp rise in plasma epinephrine was seen 3.5 hours after glucose ingestion in the normal controls. While epinephrine also rose in the ADD group, overall values were significantly lower ($p=.0348$). Peak epinephrine responses tended to be lower in ADD children

than controls (figure 6), but this difference did not achieve statistical significance. Plasma norepinephrine was also decreased in children with ADD compared to controls, p=.0007 (figure 7). This difference was most pronounced 3 to 5 hours after glucose ingestion. Despite changes in catecholamine levels, pulse did not change significantly in either group over time (data not shown). Mean baseline and peak/nadir glucose and hormone levels in the two groups of subjects are summarized in table 2.

Symptoms:

Hypoglycemic symptom scores were low for both groups at baseline and did not significantly increase for either group over the duration of the study (figure 10); nor were significant increases associated with the surge in epinephrine (figure 11).

Tests of Attention:

Matching Scores:

Scores on the matching test were slightly but significantly lower for the ADD group at baseline and at each trial, p=.0023 (Figure 13). Performance did not change significantly in either group over time; nor were there changes associated with the glucose nadir or following the peak in epinephrine (Figure 14).

Matching Reaction Time:

Reaction time also differed significantly between groups (Figure 15) with the ADD group having a faster reaction time relative to controls (p=.0039). This did not change over time or in association with the fall in glucose or increase in epinephrine (figure 16).

Visual Search:

There were no between group differences on the visual search task at baseline, any time point, glucose nadir or following the epinephrine peak (figure 12). There were no significant changes over time.

Continuous Performance Testing: False positives

False positives tended to increase over time (p=.0354) and significant increases were observed in association with the fall in glucose (p=.0092) and with the epinephrine surge (p=.0169). However, the ADD children did not differ significantly from controls (figures 17 and 18).

Continuous Performance Testing: Omissions

There were no significant between group differences in omissions (figure 19). There were also no significant changes over time. However, omissions after the epinephrine peak were increased compared to baseline (p=.0347) (figure 20).

Group by time interaction:

Although significant effects of group and/or time were seen as described above, there was no significant group-time interaction for any analysis.

Discussion

Many parents complain that sugar intake exacerbates hyperactivity [Varley,1984, Rapp 1978] and other adverse behaviors, although both investigators and clinicians have questioned these observations [Milich et al., 1986 review]. The purpose of this study was to determine whether children with baseline attentional deficits have a greater sensitivity to sugar as manifested by a greater epinephrine rise, more prominent adrenergic symptoms, and/or altered performance on tests of attention.

The advantages of this study include the narrow age range of the subjects, that ADD was diagnosed using the YCI, a state of the art assessment measure, and that children received no confounding meals or snacks. The long duration of the study and the measurement of plasma rather than urine catecholamines are further strengths. Weaknesses include the small sample size, particularly the limited number of normal healthy controls. Given the small numbers, the chance of type II errors is increased. Therefore, it is important to be cautious, especially in interpreting findings of no differences between groups.

Glucose:

Children with ADD group were found to have slightly but significantly higher glucose levels compared to healthy normal controls, particularly during the second and third hours of the study. Nevertheless, baseline, peak, and nadir glucose values were comparable. Moreover, the differences in glucose were small and of uncertain clinical

importance. "Abnormally high" glucose levels 30 minutes but no other time point after glucose ingestion in 4 of 21 boys of mixed diagnostic characteristics has been reported previously [Behar et al., 1984]. On the other hand, Langseth and Dowd reported that 75% of 265 hyperactive children had abnormal glucose curves, compared to normative samples, mainly characterized as "low" and "flat.". Their use of normative samples, however, undermines the results because glucose levels vary greatly depending upon whether plasma or whole blood is used, and whether arterial or venous samples are taken [Amiel,1988].

The finding of higher glucose levels is also at odds with studies of behaviorally deviant adults demonstrating lower glucose levels during an oral glucose test [Virkkunen and Huttunen,1982]. Moreover, it has been reported that juvenile delinquents have significantly lower serum glucose values than nondelinquents at fasting, 60,120, and 180 minutes after a glucose challenge [Gans et al.,1990].

There are a number of possible explanations for the discrepancy in results. For example, the children in our study were younger than the subjects in most of the other physiologic studies. This is significant not only because of age-related differences in metabolism, but because studies of older subjects, particularly violent offenders and juvenile delinquents, are more likely to include people with liver damage from alcohol abuse. Also it is important to note that subjects in the various studies differ diagnostically. Another potential explanation for discrepant findings is our longer duration of study and more frequent measurement of plasma glucose. Finally, our study included girls in both the ADD (n=4 out of 17) and control (n=2 of 7) groups. However, because of the similar distribution, any gender effects should have been balanced.

Catecholamines:

This paper appears to be the first report of reduced peripheral catecholamine responses in children with ADD. In view of the widespread belief that catecholamine function and its modulation are involved in the pathogenesis and treatment of ADD, these findings are of particular interest.

The catecholamine hypothesis of Attention Deficit Disorder was first stated by Kornetsky (1970) who noted that many of the useful drugs for this disorder have marked effects upon catecholamine levels in the brain. It has been hypothesized that because amphetamines are chemically similar to norepinephrine, they can substitute for it, thereby modifying a low cortical norepinephrine level with a resultant improvement in inhibition and calming effect [Zametkin and Rapoport, 1987] In keeping with this theory, some researchers propose that children with ADD are actually hypoaroused and thus unable to inhibit impulsivity [Ross and Ross, 1976]. Others postulate that altered norepinephrine metabolism or receptor affinity leads to an overly vigilant state with an inability to filter out irrelevant stimuli [Mefford and Potter, 1989]. That most of the CNS norepinephrine cell bodies are located in the locus ceruleus, an area that mediates attention, further supports hypotheses related to norepinephrine metabolism [Panksepp,1986].

A quick review of catecholamine metabolism facilitates interpretation of the literature. In brief, the amino acid tyrosine is used to synthesize dopamine which can be further converted into norepinephrine. In the adrenal medulla and limited areas of the brain, norepinephrine can be converted into epinephrine [Ganong, 1987].

Catecholamines are inactivated via reuptake into the presynaptic terminal or by metabolic degradation by monoamine oxidase (MAO) and catechol-0-methyltransferase (COMT). The main metabolic degradation product of both peripheral and central dopamine is homovanillic acid (HVA). The main metabolites of norepinephrine are 3-methoxy-4-hydroxy-phenylglycol (MHPG) and vanillylmandelic acid (VMA) [Raskin et al., 1984]. Although catecholamines do not cross the blood brain barrier, it is believed that some peripheral measures may reflect central values [Zametkin and Rapoport,1986]. For example, MHPG is the predominant product of CNS norepinephrine and VMA is the main peripheral product [Raskin et al., 1984].

Studies comparing ADD children to normal controls have had conflicting reports of baseline biochemical monoamine metabolites in urine, platelets, and CSF [Zametkin and Rapoport, 1987]. For example, one CSF study reported lower CSF levels of the dopamine metabolite homovanillic acid (HVA) in the patient group [Shaywitz et al., 1977],.while another found no significant difference [Shetty and Chase, 1976].

Several studies of urinary catecholamines have reported that ADDH children excrete less 3-methoxy-4-hydroxyphenylglycol (MHPG) compared to normal subjects [Shekim et al.,1977,1979,1983; Yu-cun and Yu-feng, 1984]. Furthermore, Shekim reported that urinary concentrations of peripheral norepinephrine metabolites, normetanephrine and metanephrine were also lower in the clinically diagnosed population. These findings are consistent with our observation of lower plasma norepinephrine values. Other researchers, however, found no differences in MHPG between ADD children and controls, [Rapoport et al., 1978; Wender et al.,1971] and one

study found increased MHPG excretion in ADDH [Khan and Dekirmenjian,1981]. This last report, however, has been criticized because control values were considerably lower than those seen in other reports [Zametkin and Rapoport,1987].

Comparisons of platelet monoamine oxidase (MAO B), an enzyme that degrades catecholamines, include a report of lower platelet MAO activity in ADD children [Shekim et al.,1982]. Another study found that the decrease in MAO activity that typically occurs between the age of 6 and 12 occured in controls but not ADD children [Brown et al., 1984]. This is a potentially interesting finding, as relative excess of MAO activity could produce a relative deficiency of monoamines [Zametkin and Rapoport, 1987]. The lowered plasma catecholamines seen in our group of ADD children is consistent with this observation.

Further support for our finding of lowered plasma epinephrine in ADD children who were not taking medication is a report that treatment of ADD with dextroamphetamine and methylphenidate, agents of proven efficacy, is associated with increases in urinary epinephrine and its metabolite metanephrine [Elia et al., 1990]. Plasma epinephrine concentration, however, was not found to be elevated with treatment whereas urine concentration was. Because renal clearance of epinephrine was much higher for both drug conditions compared to placebo or baseline periods, clearance of a higher amount of plasma during drug therapy may explain this finding.

A number of studies have attempted to relate the pathophysiology of ADD to the pharmacology of stimulants. Dextroamphetamine and methylphenidate are the best studied and most used therapeutic agents. The main mechanism of action of dextroamphetamine is to block reuptake and

increase presynaptic release of neurotransmitters [Raskin et al., 1984]. MAO, the enzyme that degrades norepinephrine, dopamine, and serotonin is also inhibited. Methylphenidate (Ritalin) has been shown to stimulate release of dopamine. Thus both stimulants function to increase the level of catecholamines available at the synapse.

The absorption phase of the stimulants is when they are maximally effective [Shaywitz et al.,1982] This phase parallels the acute release of neurotransmitters into synaptic clefts and therefore provides additional support for deficiencies in monoamine transmission. Furthermore, animal studies show that norepinephrine depletion provides an animal model of attentional deficits [Zametkin and Rapoport,1987].

Despite this evidence, whether there is a relative excess or lack of catecholamines remains an area of debate [Zametkin and Rapoport, 1987]. Reports that dextroamphetamine decrease MHPG excretion, and the correlation of this decrease with clinical improvement argue for a pathological hyperfunctioning of the noradrenergic system in ADD. On the other hand, medications that are equally efficacious have been shown to have different metabolic sequelae. For example, Elia et al. [1990] report an increase in plasma norepinephrine when children took methylphenidate but not dextroamphetamine. The fact that norepinephrine changed in one but not another equally efficacious treatment condition cautions against deducing the pathophysiology of ADD from biochemical changes seen during therapy.

There is only one report in the literature comparing plasma catecholamines in children with ADD to normal controls [Ionescu et al.,1990]. Higher epinephrine values were reported in the patients (122±89) compared to the controls (43±22, $p<.01$). Norepinephrine did not

differ significantly between groups. However, only one blood sample was taken and dietary variables were not considered. It is worth noting that in our study, baseline catecholamines for the two groups appear comparable.

In summary, our finding of lower values of plasma catecholamines in ADD but not normal healthy children is intriguing, particularly in view of the large number of reports suggesting that altered catecholamines may account for the imbalance between inhibition and excitation seen in ADD. While the norepinephrine hypothesis has traditionally focused on central deficits, this report suggests that children with ADD may have a systemic catecholamine deficiency. Moreover, since peripheral norepinephrine is converted to epinephrine solely in the adrenal medulla [Ganong, 1987] the observation of lower levels of epinephrine in children with ADD suggest either a defect at the level of this organ or overactive epinephrine catabolism.

Symptoms:

Despite sharp rises in epinephrine, neither group reported a significant increase in total or adrenergic symptoms. Other work has reported increased symptoms in association with the vigorous epinephrine surge [Jones et al.,1990A]. Possible explanations include the fact that Jones et al. assessed symptoms each half hour and used a laptop computer while in this studies symptoms were rated hourly by oral questionnaire. Less vigorous epinephrine responses in the ADD group may partly account for fewer reported symptoms in these children.

Attention Tasks:

Given the changes in glucose, insulin, and and anti-insulin hormones over time and the group differences in glucose and catecholamine profiles, the groups might have been expected to differ with respect to performance on attention tasks. However, the lack of a significant group by time interaction on any measure, indicates that the groups responded to the experimental conditions in parallel fashion.

Visual search and matching scores were fairly constant over the course of the study. These scores did not change at the glucose nadir or when epinephrine peaked, suggesting that the oral glucose load had no effect on these measures of performance. The lack of change over time is somewhat surprising since practice effects and/or boredom, independent of metabolic effects, might have been expected to cause changes over time.

Significantly more false positives errors on the CPT occured over time in both groups, including worsening at the times of the glucose nadir and epinephrine peak. Omissions on the CPT were not significantly different from baseline for either group over time. Nevertheless, the number of omissions occuring after each child's epinephrine peak was significantly increased compared to baseline, suggesting that the adrenergic surge may have played a role in the deterioration of this measure. However, the single challenge design of the study does not allow us to conclusively attribute changes over time to glucose ingestion.

Although changes over time were parallel, the groups differed slightly but significantly with respect to matching score and reaction time. These differences were in the expected directions; that is, ADD children made more mistakes on matching and had a more rapid, impulsive

response time. Because of the stability over time, the differences can not be attributed to oral glucose ingestion.

Thus, while there were differences in hormonal responses to an oral glucose load between ADD and normal children, the impact of glucose intake on performance was equivalent. However, it remains possible that altered vulnerability to metabolic changes after sugar occurs on measurements other than the ones tested. In addition, the one-on-one laboratory setting may have served to diminish differences between normal and ADD children that would have occured in a classroom situation. Furthermore, the study was not blind, nor was there a placebo. However the observation of only minimal deteriorations when larger differences were expected argues against a placebo affect.

Conclusion

Previous studies have shown that normal healthy children have sharp adrenergic responses to an oral glucose load compared to adults [Jones et al.,1990] It was hypothesized that children with ADD might be more susceptible to symptomatic and functional impairment following oral glucose ingestion. Instead, performance decrements were parallel for both groups over time. However, compared to normal controls, ADD children displayed blunted norepinephrine and epinephrine responses to oral glucose ingestion. These findings suggest that children with ADD may have a more generalized impairment of sympathetic activation than previously suspected, involving adrenomedullary as well as central catecholamine regulation.

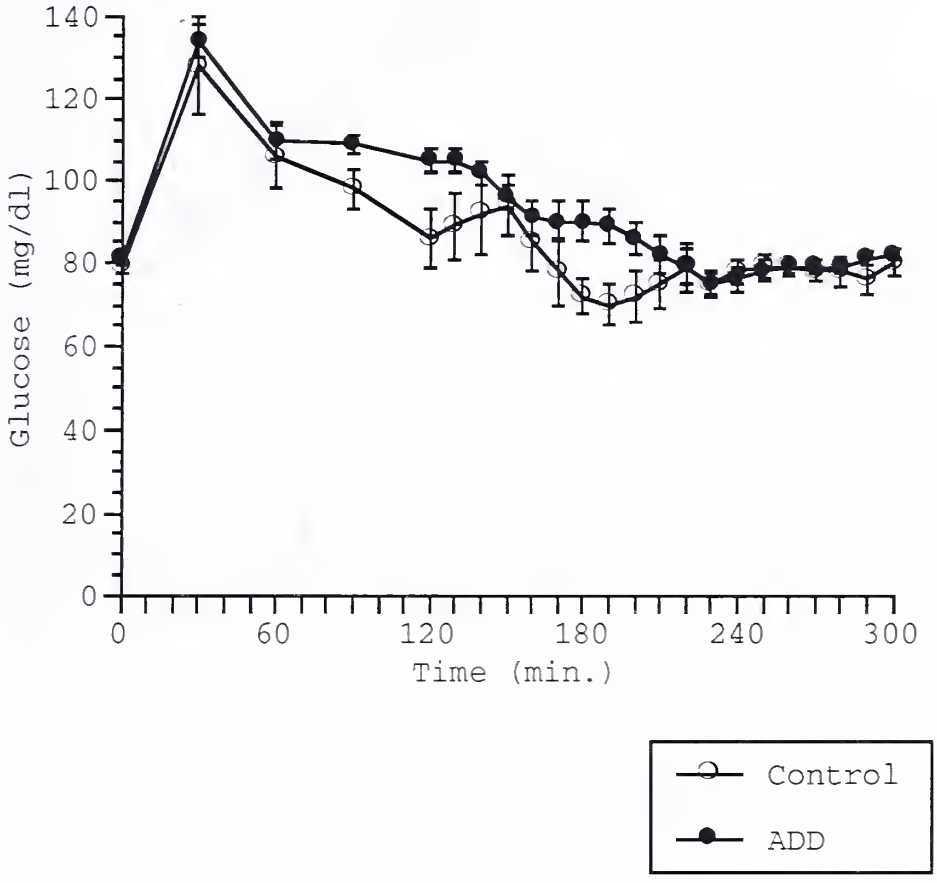
Table 1: Study Population

Subjects:	Age (years)	Weight(kg)	Glucola®(g)
ADD (n=17)	11.3±0.6	44.0±3.0	77.0±4.9
Controls (n=7)	9.4±1.0	34.4±3.6	60.4±6.2

Table 2: Baseline and Peak Values of Plasma Glucose and Conterregulatory Hormones

	ADD (n=17)	Controls (n=7)
Glucose (mg/dl)		
baseline	80±1.5	79±1.7
peak	137±3	131±10
nadir	63±2.6	60±4.8
Epinephrine (pg/ml)		
baseline	42±4.8	36±4.8
peak	222±37.0	308±91
Glucagon (pg/ml)		
baseline	113±10.6	131±12.3
peak	217±27	225±31.0
Growth hormone (ng/ml)		
baseline	4.8±1.9	4.2±2.2
peak	19.2±1.9	16.7±1.9
Norepinephrine (pg/ml)		
baseline	264±24.7	300±36.4
peak	326±22.2	426±55.7

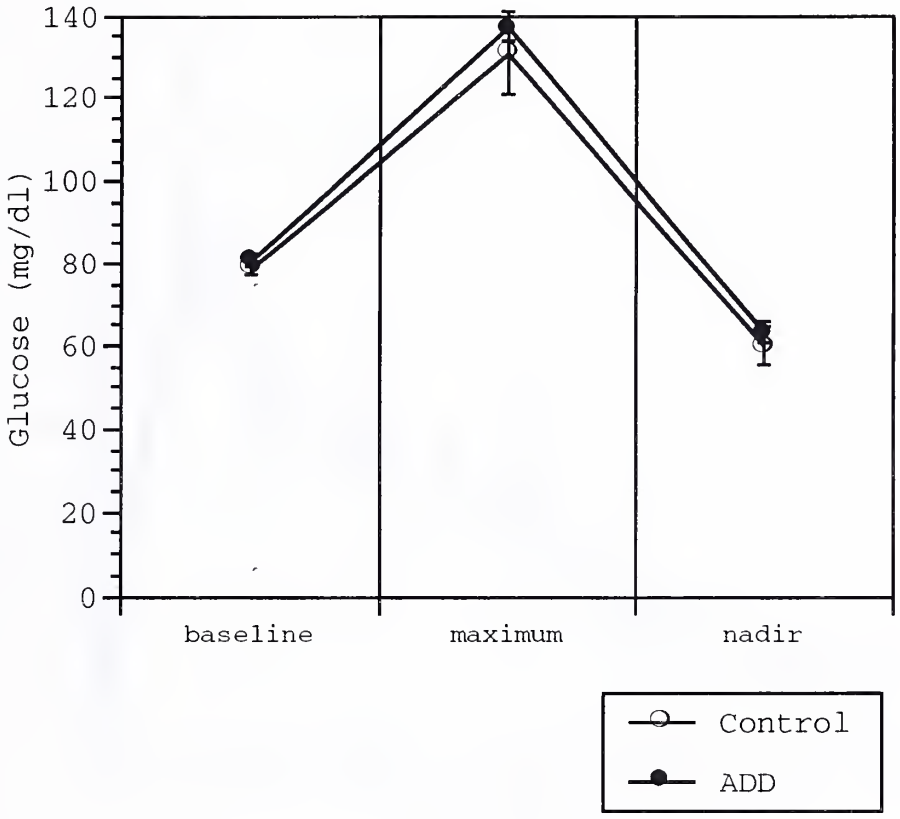
Figure 1: Plasma Glucose Following Oral Glucose Ingestion



Analysis of Variance for Glucose

	D.F.	F	P
Group	1	22.05	.0001
Time	22	17.74	<.0001
Group*Time	22	1.14	NS

Figure 2: Glucose at Baseline, Maximum and Nadir



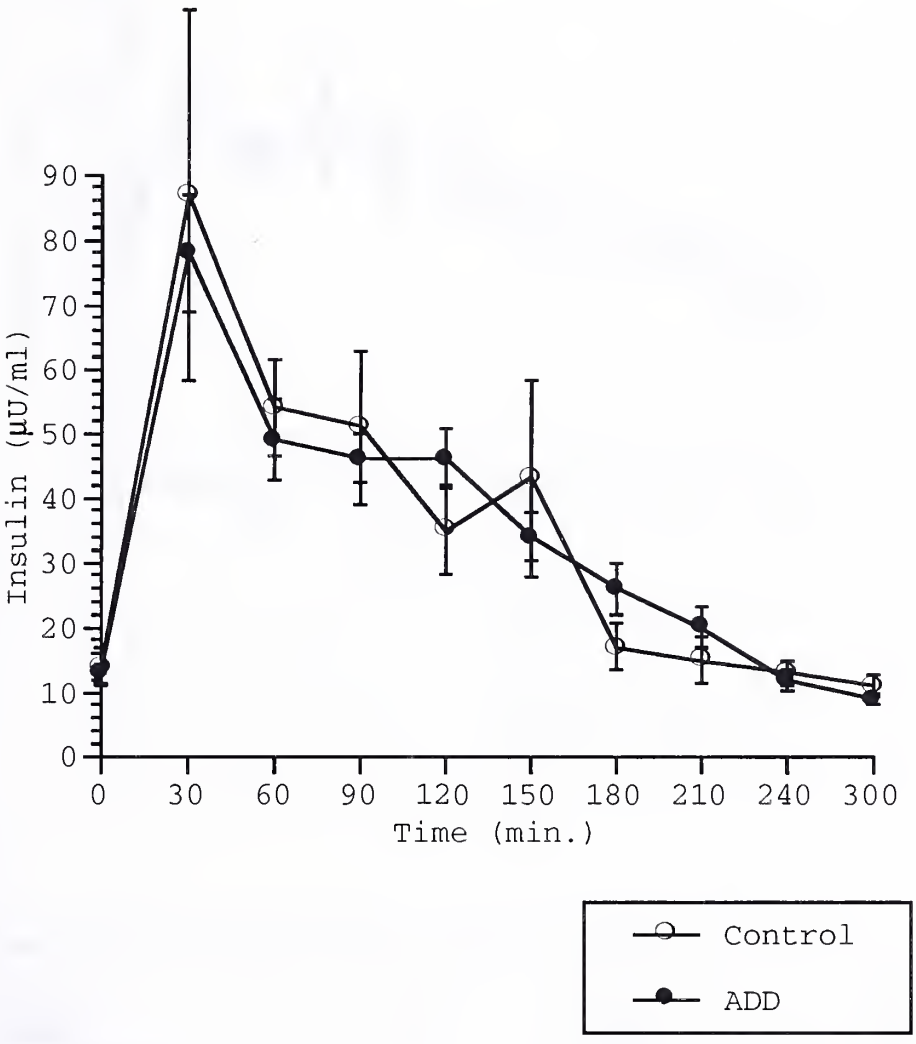
Analysis of Variance for Glucose at baseline vs maximum

	D.F.	F	P
Group	1	0.77	NS
Time	1	170.81	.0001
Group*Time	1	0.34	NS

Analysis of Variance for Glucose at baseline vs nadir

	D.F.	F	P
Group	1	0.44	NS
Time	1	39.82	.0001
Group*Time	1	0.05	NS

Figure 3: Insulin Response Following Oral Glucose Ingestion



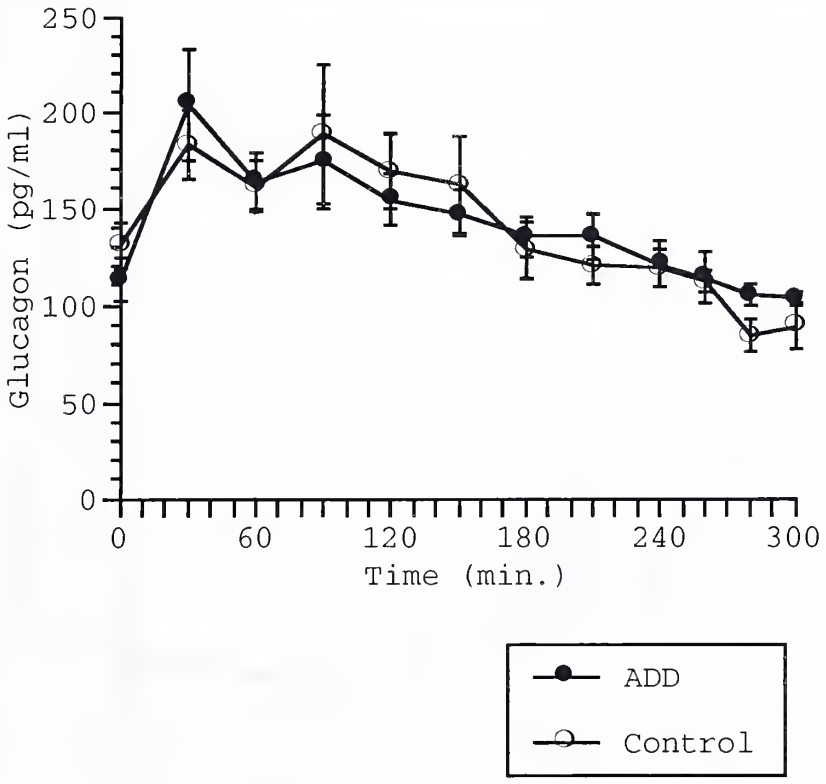
Analysis of Variance for Insulin vs Time

	D.F.	F	P
Group	1	0.05	NS
Time	11	23.93	.0001
Group*Time	11	0.47	NS

Analysis of Variance for Insulin at baseline vs Maximum

	D.F.	F	P
Group	1	0.16	NS
Time	1	44.29	.0001
Group*TIme	1	0.09	NS

Figure 4: Glucagon Response Following Oral Glucose



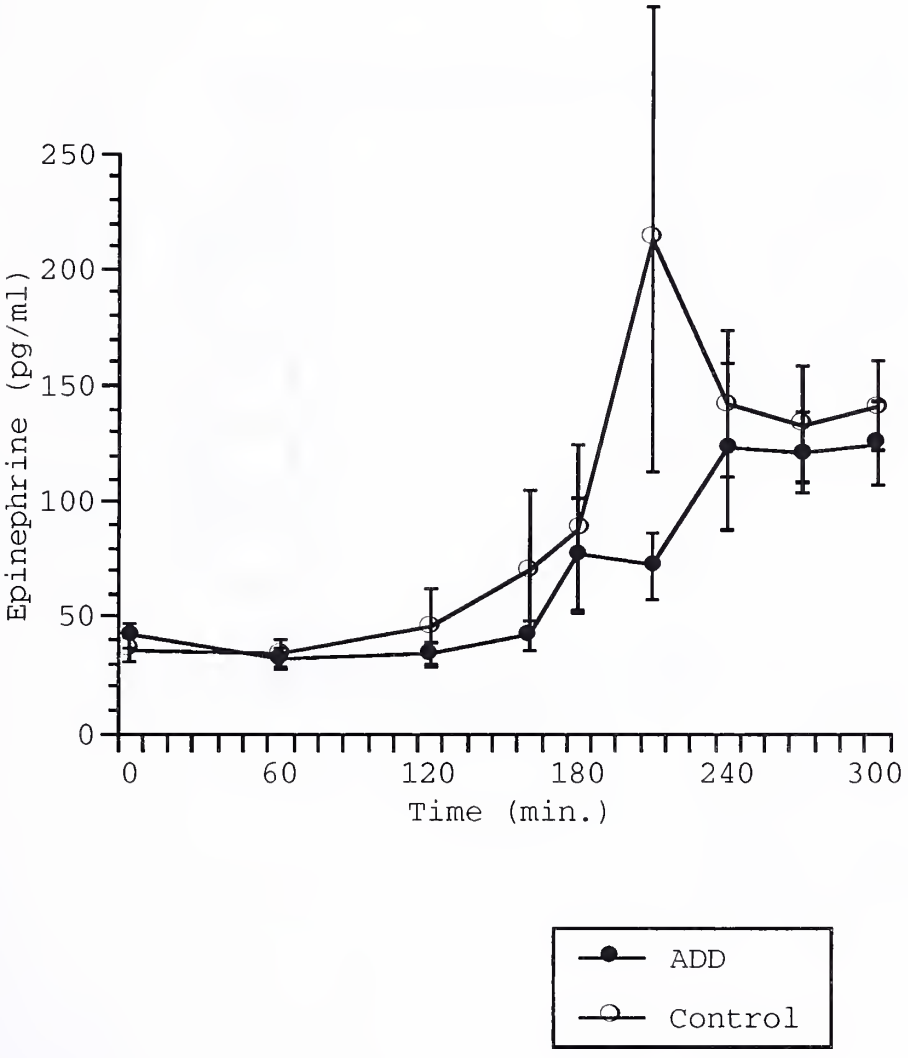
Analysis of Variance for Glucagon vs Time

	D.F.	F	P
Group	1	0.11	NS
Time	11	5.88	.0001
Group*Time	11	0.14	NS

Analysis of Variance Glucagon at Baseline vs Maximum

	D.F.	F	P
Group	1	0.25	NS
Time	1	15.34	.0003
Group*Time	1	0.04	NS

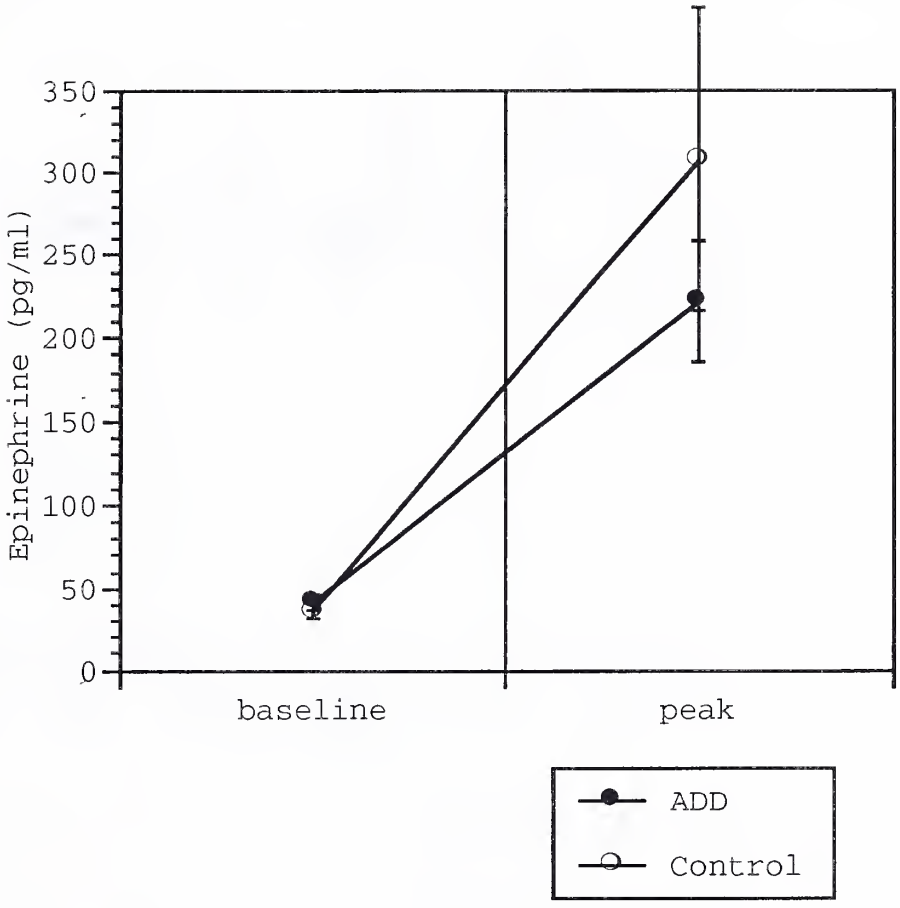
Figure 5: Plasma Epinephrine Response Following Oral Glucose



Analysis of Variance for Epinephrine vs Time

	D.F.	F	P
Group	1	4.52	.0348
Time	8	6.38	.0001
Group*Time	8	1.46	NS

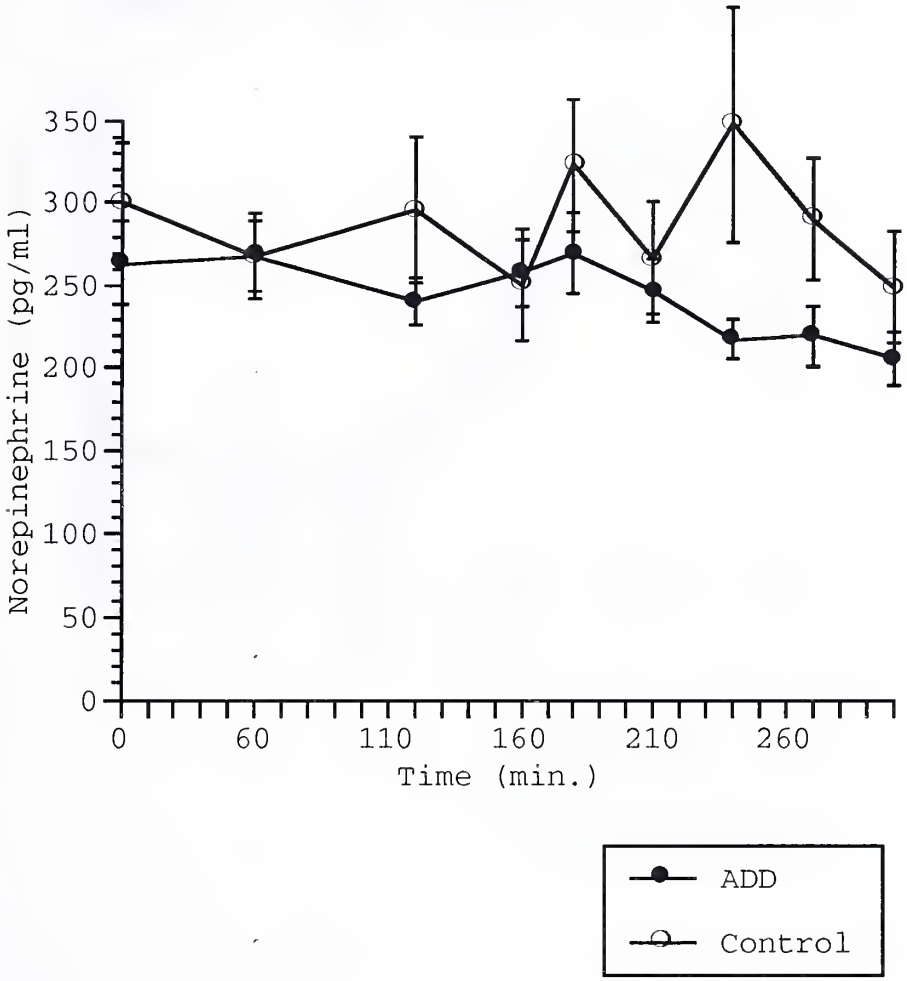
Figure 6: Baseline and Peak Epinephrine



Analysis of Variance for Epinephrine at baseline vs maximum

	D.F.	F	P
Group	1	0.81	NS
Time	1	30.04	.0001
Group*Time	1	1.21	NS

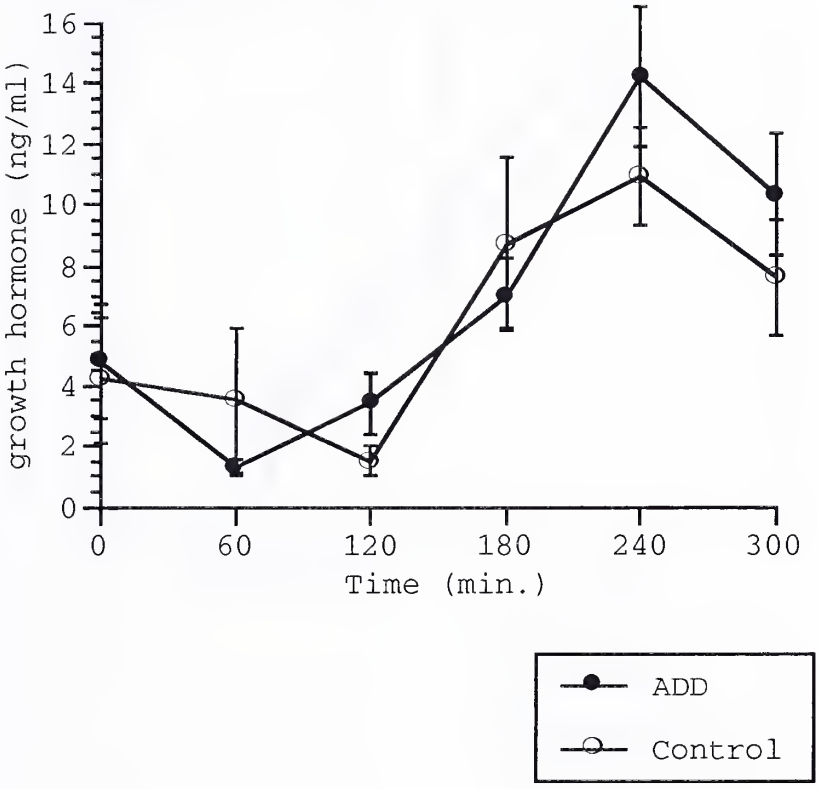
Figure 7: Plasma Norepinephrine Following Oral Glucose



Analysis of Variance for Norepinephrine vs Time

	D.F.	F	P
Group	1	11.89	.0007
Time	8	1.02	NS
Group*Time	8	0.6	NS

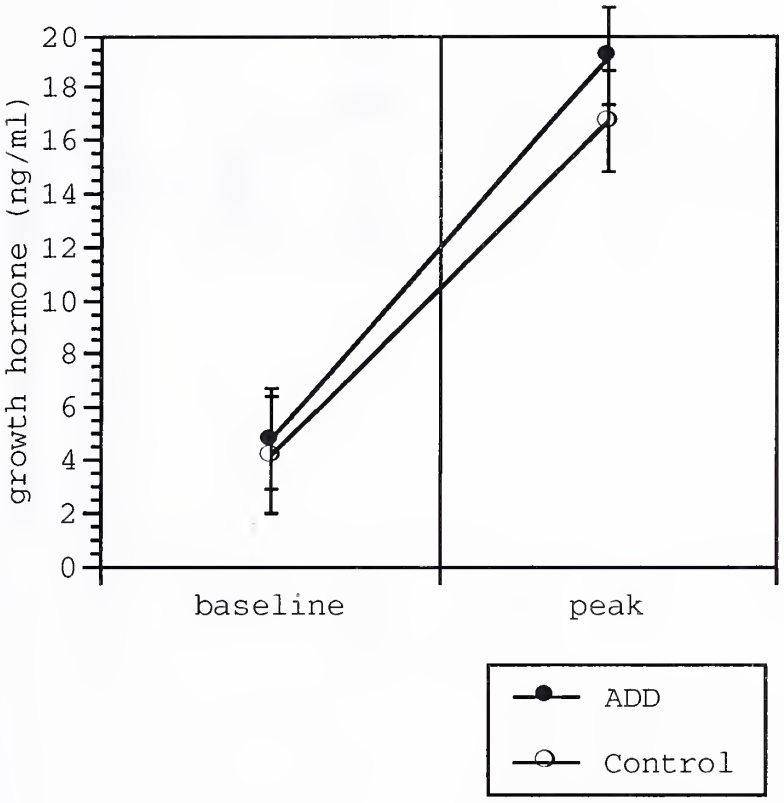
Figure 8: Plasma Growth Hormone Following Oral Glucose



Analysis of Variance for Growth Hormone vs Time

	D.F.	F	P
Group	1	0.31	NS
Time	11	6.29	.0001
Group*Time	11	0.71	NS

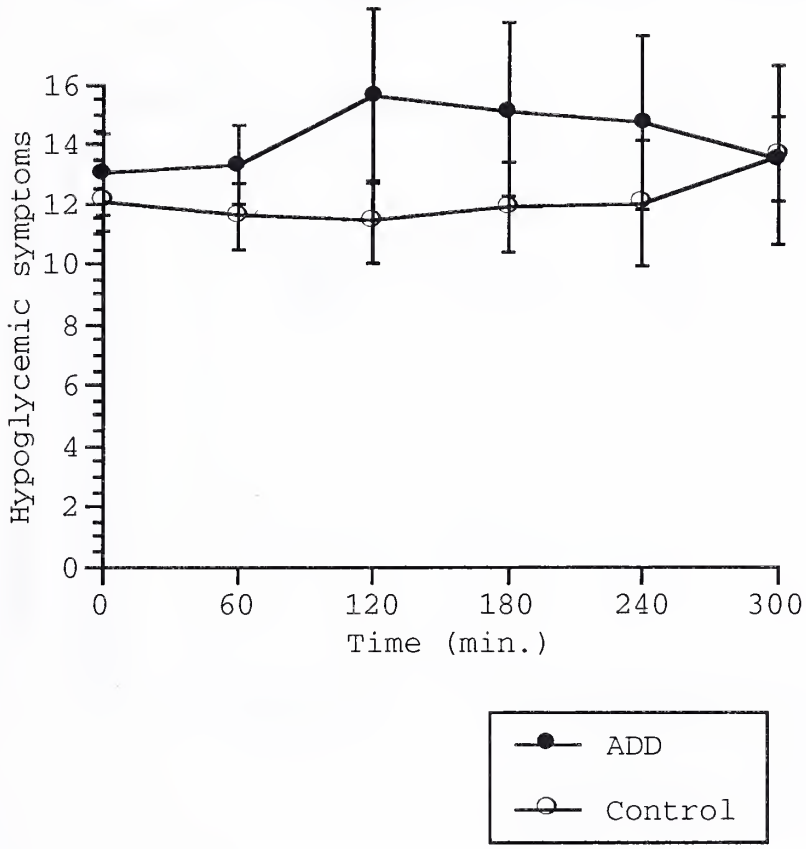
Figure 9: Plasma Growth Hormone at Baseline and Peak



Analysis of Variance Growth Hormone Baseline vs Maximum

	D.F.	F	P
Group	1	0.46	NS
Time	1	33.64	.0001
Group*Time	1	0.19	NS

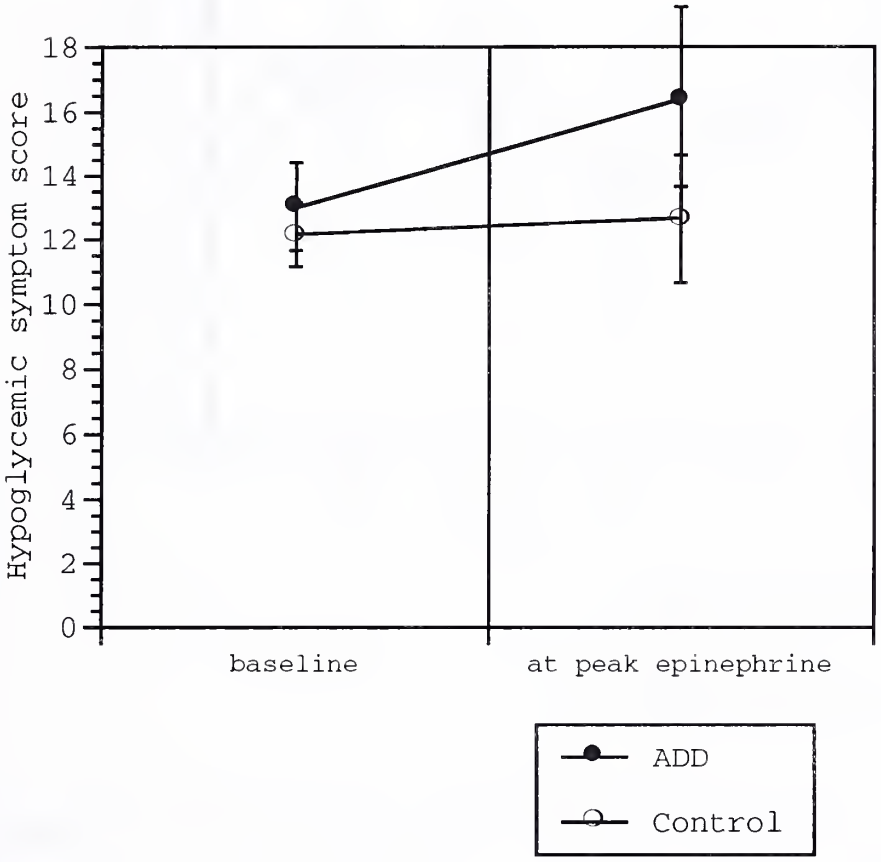
Figure 10: Hypoglycemic Symptoms Following Glucose Ingestion



Analysis of Variance for Hypoglycemic Symptoms vs Time

	D.F.	F	P
Group	1	0.53	NS
Time	5	0.40	NS
Group*Time	5	0.31	NS

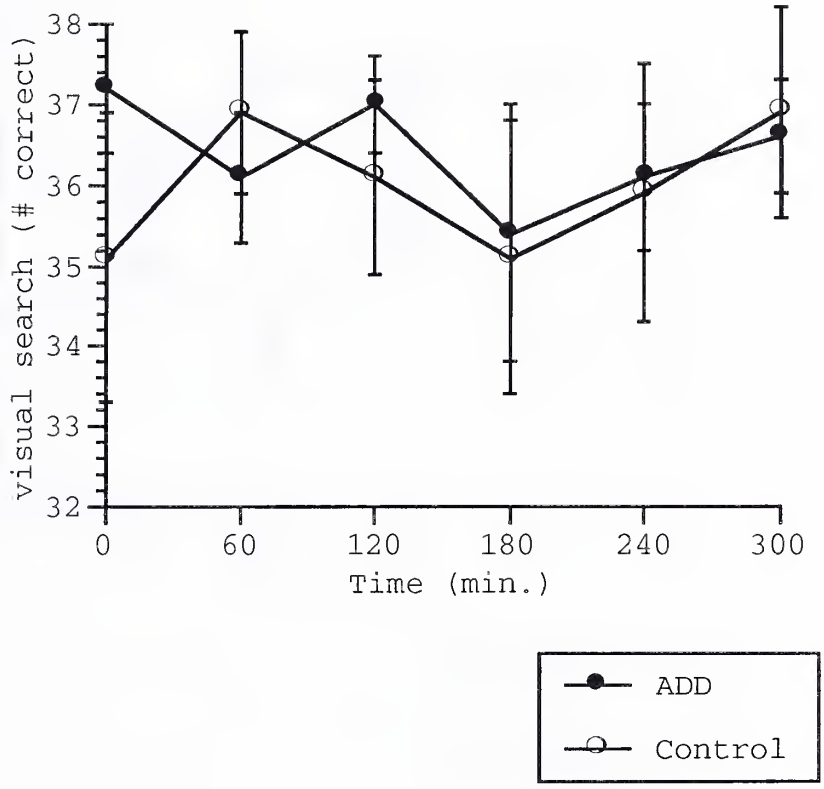
Figure 11: Hypoglycemic Symptom Scores at Baseline and Following the Peak in Epinephrine



Analysis of Variance for Hypoglycemic Symptom Scores at baseline vs peak epinephrine

	D.F.	F	P
Group	1		NS
Time	1		NS
Group*Time	1		NS

Figure 12: Number Correct on Visual Search Task vs Time



Analysis of Variance for Visual Search Score vs Time

	D.F.	F	P
Group	1	0.29	NS
Time	5	0.36	NS
Group*Time	5	0.30	NS

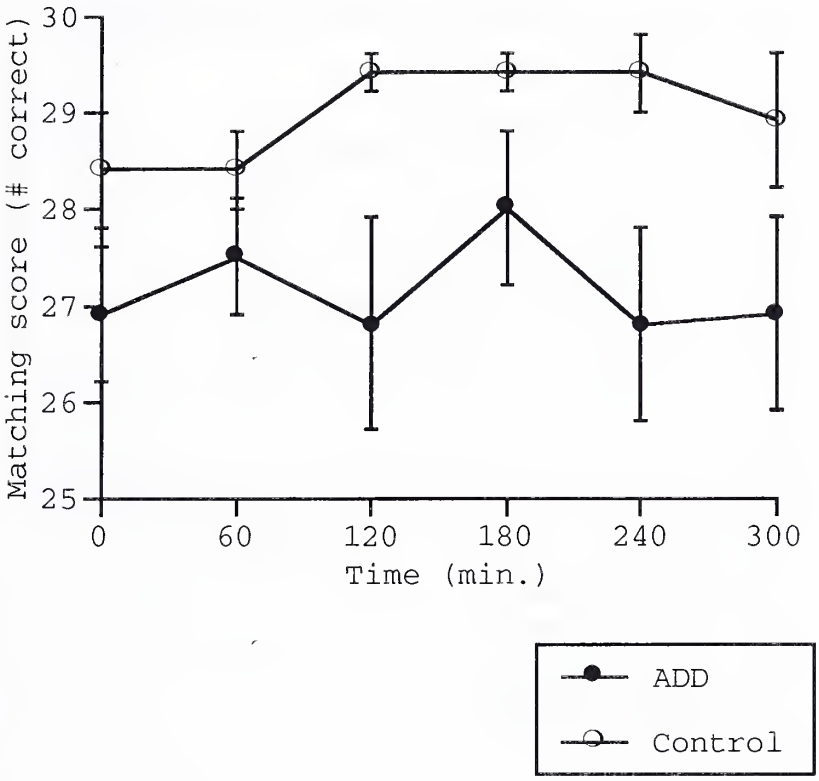
Analysis of Variance for Visual Search score at baseline vs epinephrine maximum

	D.F.	F	P
Group	1	0.32	NS
Time	1	0.05	NS
Group*Time	1	0.65	NS

Analysis of Variance for Visual Search score at baseline vs glucose nadir

	D.F.	F	P
Group	1	0.11	NS
Time	1	0.01	NS
Group*Time	1	1.02	NS

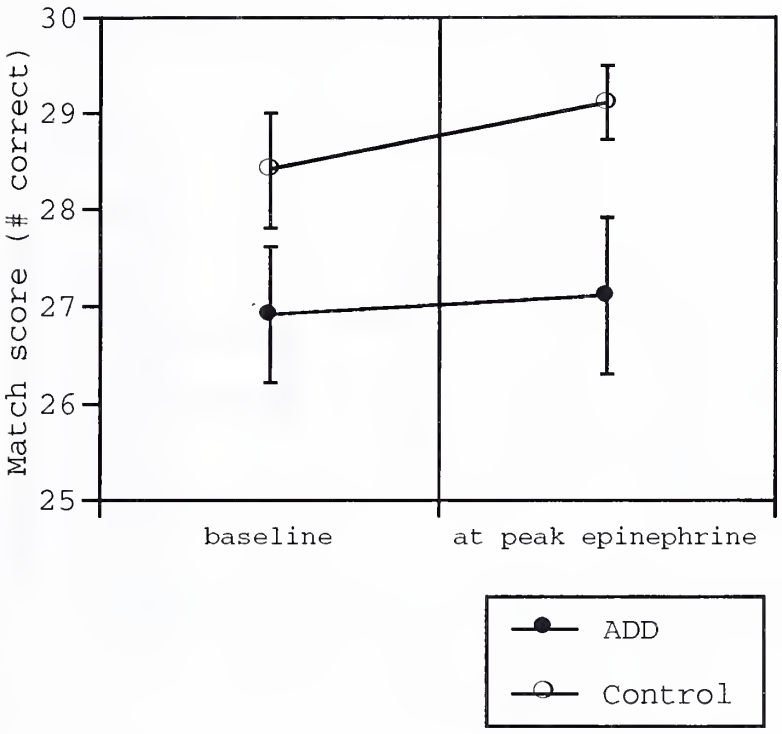
Figure 13: Number Correct on Matching Task vs Time



Analysis of Variance for Matching Score vs Time

	D.F.	F	P
Group	1	9.70	.0023
Time	5	0.23	NS
Group*Time	5	0.23	NS

Figure 14: Matching Score at Baseline and at Peak Epinephrine



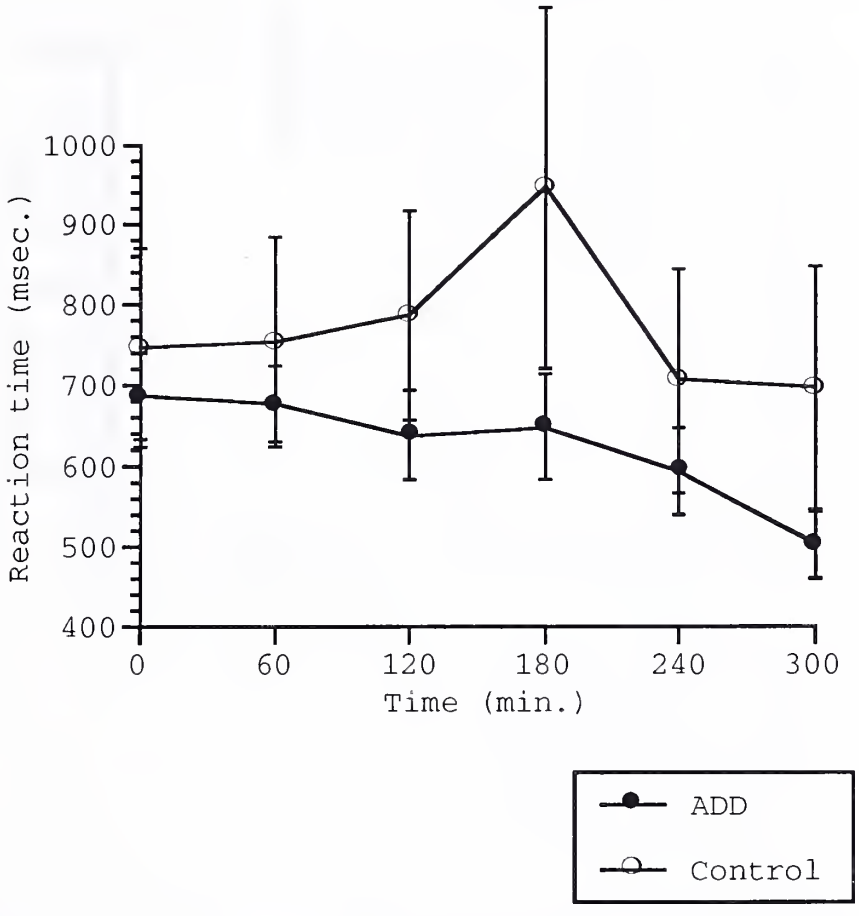
Analysis of Variance for Matching score at baseline vs epinephrine maximum

	D.F.	F	P
Group	1	4.27	.0447
Time	1	0.27	NS
Group*Time	1	0.10	NS

Analysis of Variance for Matching score at baseline vs glucose nadir

	D.F.	F	P
Group	1	4.27	.0448
Time	1	0.88	NS
Group*Time	1	0.14	NS

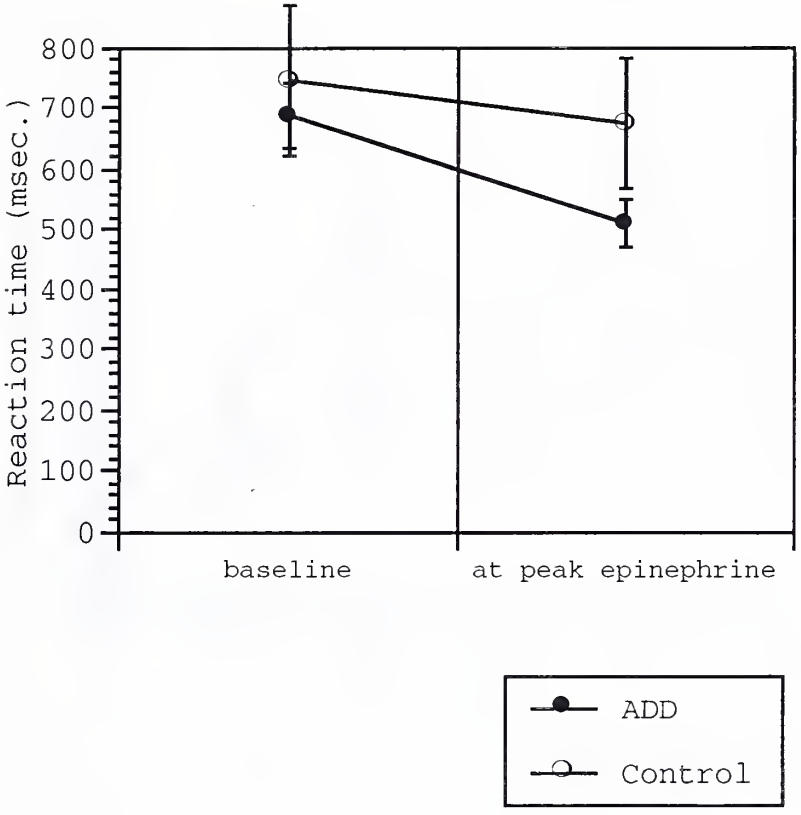
Figure 15: Reaction Time on the Matching Test vs Time



Analysis of Variance for Reaction Time on the Matching Test vs Time

	D.F.	F	P
Group	1	8.63	.0039
Time	5	1.23	NS
Group*Time	5	0.49	NS

Figure 16: Reaction time on Matching at Baseline and Peak Epinephrine



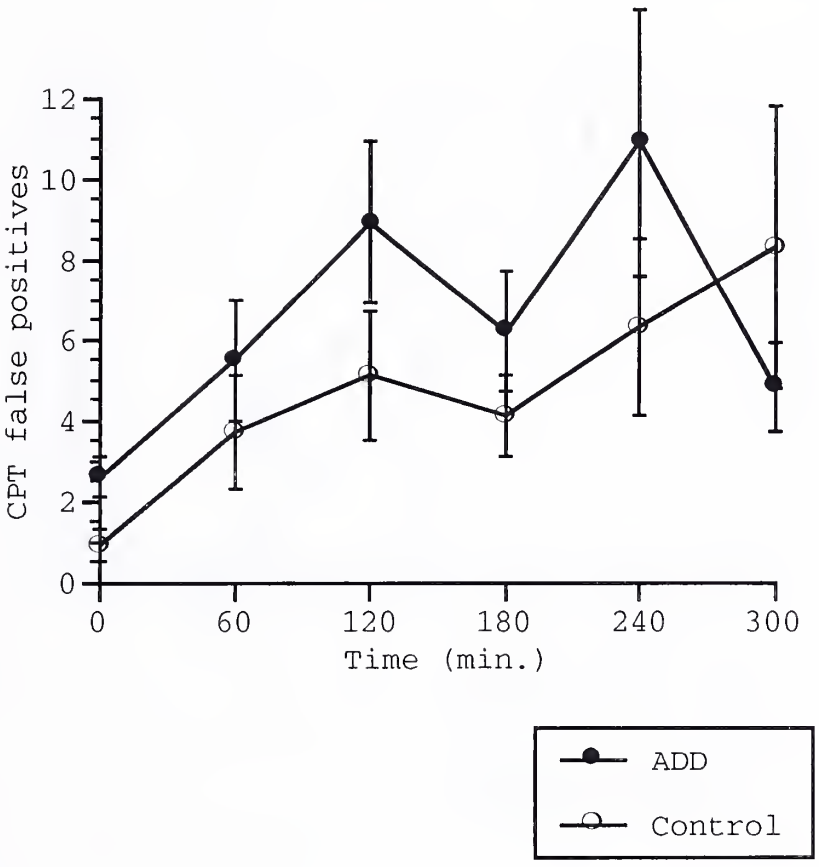
Analysis of Variance for Reaction time at baseline vs at epinephrine maximum

	D.F.	F	P
Group	1	2.36	NS
Time	1	2.88	NS
Group*Time	1	.54	NS

Analysis of Variance for Reaction time at baseline vs at glucose nadir

	D.F.	F	P
Group	1	3.65	NS
Time	1	0.06	NS
Group*Time	1	1.65	NS

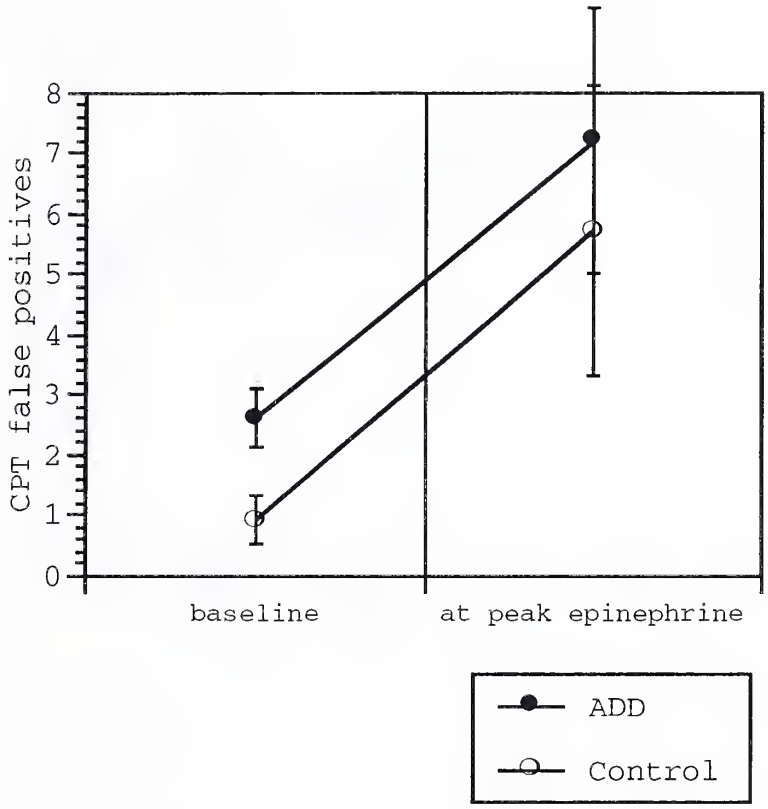
Figure 17: False Positives on a Continuous Performance Test vs Time



Analysis of Variance for CPT false positives vs Time

	D.F.	F	P
Group	1	2.32	NS
Time	5	2.48	.0354
Group*Time	5	1.01	NS

Figure 18: False Positives on a Continuous Performance Test at Baseline and Peak Epinephrine



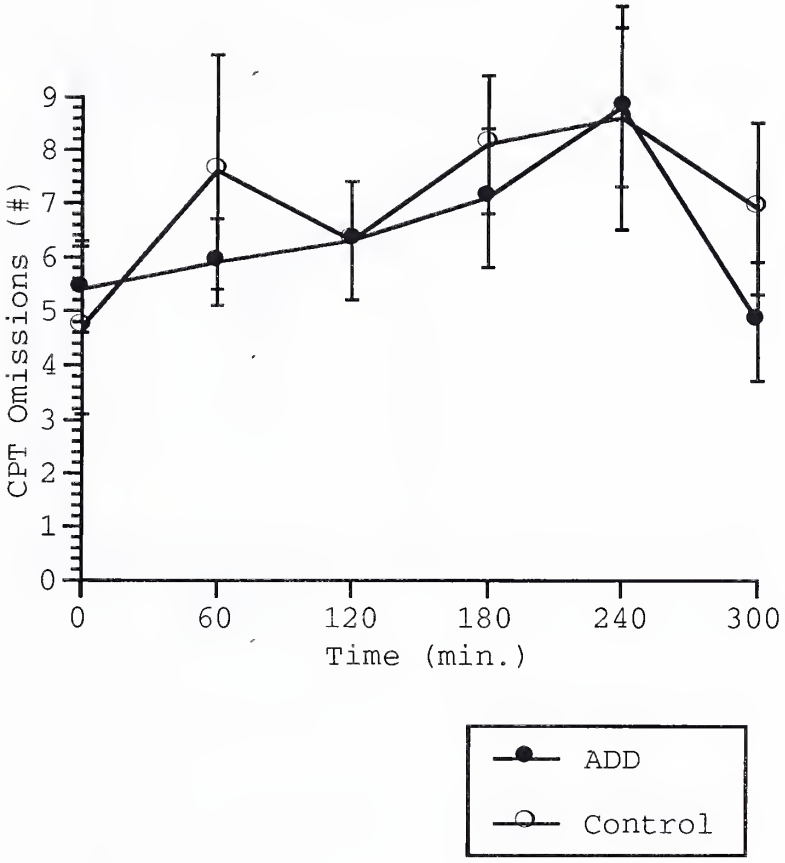
Analysis of Variance for CPT false positives at baseline vs epinephrine maximum

	D.F.	F	P
Group	1	0.78	NS
Time	1	6.23	.0169
Group*Time	1	0.00	NS

Analysis of Varíance for CPT false positives at baseline vs glucose nadir

	D.F.	F	P
Group	1	0.66	NS
Time	1	7.52	.0092
Group*Time	1	0.01	NS

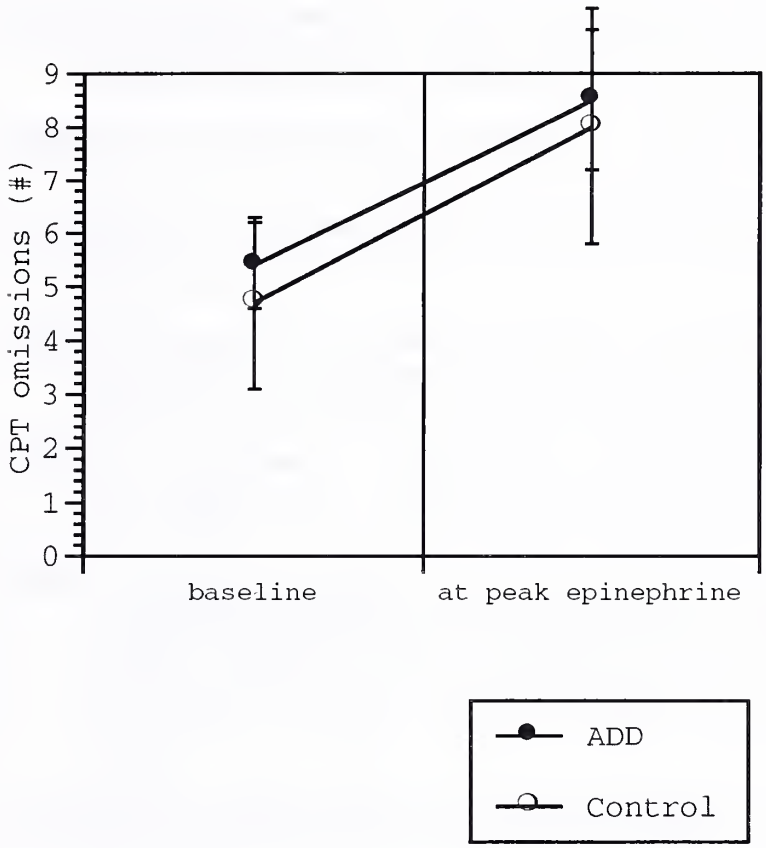
Figure 19: Omissions on the Continuous Performance Test vs Time



Analysis of Variance for CPT omissions vs Time

	D.F.	F	P
Group	1	0.27	NS
Time	5	1.53	NS
Group*Time	5	0.21	NS

Figure 20 Omissions on the Continuous Performance Test at Baseline at Peak Epinephrine



Analysis of Variance for CPT omissions at baseline vs epinephrine maximum

	D.F.	F	P
Group	1	0.18	NS
Time	1	4.79	.0347
Group*Time	1	0.00	NS

Analysis of Variance for CPT omissions at baseline vs glucose nadir

	D.F.	F	P
Group	1	0.25	NS
Time	1	3.47	NS
Group*Time	1	0.00	NS

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