Relationship Between Hyperglycemia and Cognitive Function in Older NIDDM Patients

Gerald M. Reaven, MD
Larry W. Thompson, PhD
David Nahum, BS
Edmund Haskins, PhD

The nature and extent of cognitive impairment was examined in 29 healthy elderly subjects (mean age 69.8 yr) with non-insulin-dependent diabetes mellitus (NIDDM) and 30 demographically similar nondiabetic community volunteers (mean age 68 yr). Measures of verbal learning, abstract reasoning, and complex psychomotor functioning were performed more poorly by diabetic than nondiabetic subjects. Conversely, there were no between-group differences in performance on tasks involving pure motor speed and simple verbal abilities. Within the diabetic group, individuals with poorer metabolic control performed more poorly on tasks involving learning, reasoning, and complex psychomotor performance, although this relationship was not evident for simple verbal or motor tasks. These data indicate that older people with NIDDM who are functioning well and perceive themselves as in good health are likely to manifest greater deficits than healthy elderly people in processing complex verbal or nonverbal material. Possible explanatory mechanisms are discussed, and directions for future research are explored. *Diabetes Care* 13:16–21, 1990

Although the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) increases with age, neither the clinical impact of this phenomenon nor the therapeutic approach to this patient population has been well defined. There are many reasons for this state of affairs. For example, efforts to prevent development of the vascular complications associated with diabetes tend to be downplayed in older patients, presumably because the average life expectancy in this population does not justify the endeavor. This consideration, in juxtaposition with concern over the harmful impact of hypoglycemia in older individuals, leads to a treatment approach that often emphasizes doing no harm at the expense of achieving good glycemic control.

However, recognition of the dangers of hypoglycemia should not obviate consideration of the possibility that poor glycemic control may also have untoward effects in older patients with NIDDM. In particular, we were concerned with earlier studies that indicated some measurements of cognitive function were reduced in elderly patients with NIDDM compared with control subjects of similar age (1–5). On the other hand, other studies failed to detect differences in cognitive function between healthy control subjects and patients with NIDDM who were otherwise in good health (6,7). Although these conflicting results await a complete explanation, it has been suggested that factors other than diabetes may be responsible. For example, Mattlar et al. (6) raised the possibility that failure to find a difference between diabetic patients and control subjects might be because they had excluded all subjects with cardiovascular diseases (CVD).

Given this situation, it seemed reasonable to initiate this study, which had the following two goals. First, we compared multiple measures of cognitive function in a population of patients with NIDDM >60 yr of age and a group of nondiabetic subjects matched for age and other relevant variables. In particular, we used measures covering a wide range of abilities of varying levels of difficulty to determine the intertest pattern and scope of

From the Department of Medicine, Stanford University School of Medicine and Geriatric Research, Education and Clinical Center, Veterans Administration Medical Center, Palo Alto, California.

Address correspondence and reprint requests to Gerald M. Reaven, MD, GRECC (182-B), Veterans Administration Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

Received for publication 18 August 1988 and accepted in revised form 17 July 1989.

group differences. Second, we wanted to determine whether there was any correlation between the measures of cognitive function used and degree of glycemic control in diabetic patients.

RESEARCH DESIGN AND METHODS

Patients with NIDDM (n = 29) and nondiabetic subjects (n = 30) were selected from a larger group of subjects who were participating in a longitudinal study evaluating the impact of NIDDM on physical and psychological functioning in the elderly. The nondiabetic subjects were obtained from a panel of community elders who volunteered to participate in geriatric research at our facility. They were determined to be nondiabetic on the basis of history and physical examination and standard laboratory values for evaluating fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}). Patients were considered to have NIDDM if that diagnosis had been applied to them in the past and they were being treated with diet alone or diet plus sulfonylurea compounds. None of the patients gave a history of ketonuria or diabetic ketoacidosis. Urinalyses for ketones were negative when measured during the hospital stay. These characteristics make it probable that all or most of the diabetic subjects had NIDDM.

An attempt was made to select both diabetic and control subjects with comparable sociodemographic characteristics, who were highly functional in terms of occupational history and current daily activities, and who perceived themselves to be in reasonably good physical and mental health. Initial criteria for selection of both groups included *1)* >59 yr of age; *2)* >2 yr of high school; *3)* occupation above the level of unskilled laborer; *4)* <14 on the Beck Depression Inventory (8), suggesting minimal or no depression; *5)* no evidence of alcoholism, dementia, or cerebrovascular disease; and *6)* self-rating of health as being fair or better. Table 1 shows a comparison of diabetic and control subjects on various sociodemographic and health-related variables. Except for HbA_{1c} and FPG concentrations, there were no significant differences between the two groups. Most subjects had completed at least 1 yr of college, and all had completed high school. Most were in managerial or professional occupations, and although the initial criterion for occupation was above unskilled laborer, the final group selected were all above the level of skilled laborer. The mean health self-rating was between excellent and good for both groups. Only a few subjects rated their health as fair, and these were distributed equally across the two groups. Self-ratings of health, such as the one used here, were highly correlated with physicians' ratings of health status in elderly adults, and perceived health significantly predicted future mortality even after controlling for age, socioeconomic status, and objective physical health (9,10).

All subjects were admitted to a research ward for a 24-h stay during which the following procedures were completed: *1)* history and physical examination, *2)* electrocardiogram, *3)* urinalyses for ketones, *4)* FPG concentration, *5)* HbA_{1c} (determined on 2 occasions), and *6)* measures of cognitive and affective function. This study presents measures of cognitive function and their relationship to the level of glycemic control.

Cognitive assessment was completed in two sessions. The first was initiated ~90 min after breakfast and the second ~60 min after lunch. Tests were given in the same order for all subjects. The battery of cognitive tests used was comprised of procedures to measure diverse areas of simple and complex function. These included measures of *1)* verbal intelligence—the vocabulary and digit span subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (11); *2)* complex psychomotor skills—the block design and digit symbol subtests of the WAIS-R (11) and the trail-making (trails) tests (12); *3)* verbal learning and memory—the California Verbal Learning Test (CVLT) (13); *4)* abstract reasoning—the Wisconsin Card Sorting task (WCS) (14); and *5)* simple motor speed—the finger-tapping test (15). Whereas some tests yielded several different scores, only one was selected for each measure to reflect overall level of func-

TABLE 1
Comparison of diabetic (n = 29) and control (n = 30) subjects on sociodemographic and health-related variables

	Subjects				Frequency			
	Diabetic	Control	t	P	Diabetic	Control	χ^2	P
Age	69.8 ± 5.7	68.0 ± 5.5	1.243	0.219				
Education	14.7 ± 2.2	15.0 ± 2.8	0.481	0.632				
Occupation*	3.6 ± 1.4	3.6 ± 1.4	0.010	0.992				
Health rating†	1.8 ± 0.8	1.6 ± 0.6	1.134	0.262				
HbA_{1c} (%)	11.0 ± 2.8	5.8 ± 0.7	9.863	<0.001				
Fasting plasma glucose (mg/dl)	204.4 ± 74.7	97.5 ± 14.8	7.685	<0.001				
Sex (M/F)					19/10	16/14	0.472	0.492
Marital status (married/single)					17/12	18/12	0.000	>0.999

Values are means ± SD. HbA_{1c}, glycosylated hemoglobin.
*Scale range: from 1 (unskilled laborer) to 6 (professional/managerial).
†Health rating: 1, excellent; 2, good; 3, fair; 4, poor.

tioning for that particular measure. The above-mentioned tests are shown in Table 2.

RESULTS

Comparison of patients with NIDDM and control subjects. Table 2 shows the means and standard deviations for the nine measures of cognitive function for diabetic and control subjects. Mean scores for WAIS-R subscales indicated that subjects in both groups were in the average to above average range of intellectual functioning for their age level. Differences between the two groups were tested for the WAIS-R variable subset with multivariate analysis of variance (MANOVA; Table 3). The multivariate F for this analysis was 3.773 (df = 4,54, P = 0.009). A univariate analysis of variance was completed for each of the measures to determine which were contributing to the high level of significance. There were no significant differences between diabetic and control subjects on the vocabulary, digit span, or block design measures. However, control subjects performed significantly better than diabetic subjects on the digit symbol subtest of the WAIS-R (F = 10.916, df = 1,57, P = 0.002). A second MANOVA was completed on the remaining five neuropsychological measures of learning, abstract reasoning, and psychomotor functioning. The multivariate F was highly significant (F = 5.798, df = 5,53, $P < 0.001$). Univariate analysis of variance completed on the five variables (Table 3) revealed that control subjects performed significantly better than diabetic subjects on four of five measures; only the finger-tapping test was not significant. Thus, although there were no differences between diabetic patients and control subjects on measures of simple verbal (e.g., vocabulary and digit span) and motor functioning (finger-tapping speed), control subjects performed at significantly higher levels than diabetic patients on the more difficult measures of learning (CVLT) and reasoning (WCS) and three of the four measures of complex psychomotor abilities (digit symbol and trails forms A and B but not block design).

TABLE 2
Measures of cognitive function in diabetic and control subjects

Cognitive measures	Subjects	
	Diabetic (n = 29)	Control (n = 30)
WAIS-R Vocabulary*	13.07 ± 2.49	12.67 ± 2.55
WAIS-R Digit Span*	11.10 ± 2.82	10.33 ± 2.26
WAIS-R Block Design*	12.17 ± 3.02	12.93 ± 2.72
WAIS-R Digit Symbol*	10.83 ± 2.35	12.77 ± 2.16
Trails test		
Form A†	42.03 ± 10.31	35.50 ± 9.03
Form B†	108.59 ± 31.60	86.97 ± 31.10
WCS‡	3.34 ± 1.99	4.97 ± 1.40
CVLT§	48.24 ± 9.62	58.87 ± 10.15
Finger-tapping speed‖	91.71 ± 11.25	88.19 ± 17.08

Values are means ± SD. WAIS-R, Wechsler Adult Intelligence Scale–Revised; WCS, Wisconsin Card Sorting; CVLT, California Verbal Learning Test.
*Age-adjusted scale scores.
†Time to completion in seconds.
‡Number of category shifts completed.
§Total correct over 5 trials.
‖Mean taps/10-s interval; combined left and right hand.

TABLE 3
Effect of diabetes on measures of cognitive function by multivariate analysis of variance

Variable subset	Multivariate F*	Univariate F	df	P
WAIS-R	3.773		4,54	0.009
Vocabulary		0.375	1,57	0.543
Digit span		1.342	1,57	0.251
Block design		1.035	1,57	0.313
Digit symbol		10.916	1,57	0.002
Learning, reasoning and psychomotor tests	5.798		5,53	<0.001
Trails test				
Form A		6.720	1,57	0.012
Form B		7.014	1,57	0.010
WCS (number of categories)		13.198	1,57	0.001
CVLT (total correct)		17.028	1,57	<0.001
Finger tapping		0.868	1,57	0.355

WAIS-R, Wechsler Adult Intelligence Scale–Revised; WCS, Wisconsin Card Sorting; CVLT, California Verbal Learning Test.
*Wilks' λ-estimate.

Relationship between glycemic control and cognitive function. Figure 1 shows the relationship of HbA_{1c} to the total number of correct responses on the CVLT

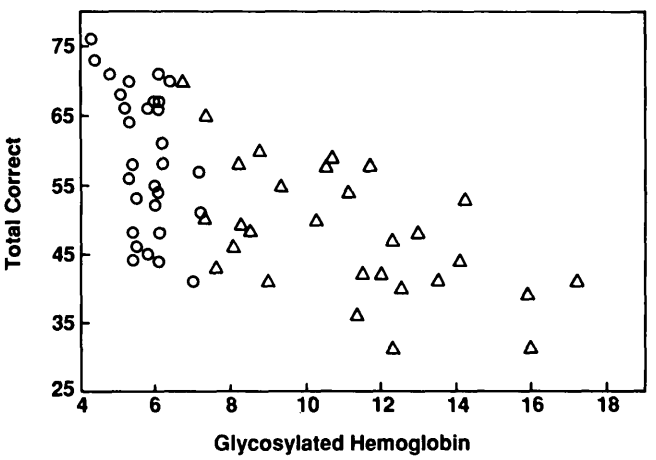

FIG. 1. Relationship between glycosylated hemoglobin concentration and number of correct responses on California Verbal Learning Test. △, Diabetic (n = 29); ○, control (n = 30).

TABLE 4
Relationship of glycosylated hemoglobin and fasting plasma glucose concentration to cognitive function measures for diabetic and control subjects

	Diabetic (n = 29)		Control (n = 30)	
Measures	HbA_{1c}	Glucose	HbA_{1c}	Glucose
WAIS-R Vocabulary	−0.168	−0.161	−0.075	−0.019
WAIS-R Digit Span	−0.032	−0.055	−0.147	−0.209
WAIS-R Block Design	−0.175	−0.167	−0.174	0.035
WAIS-R Digit Symbol	−0.369*	−0.299	−0.118	−0.138
Trails test				
Form A	0.411*	0.234	0.211	0.124
Form B	0.223	0.155	−0.074	−0.108
WCS (number of categories)	−0.436*	−0.500†	−0.147	−0.142
CVLT (total correct)	−0.568†	−0.469†	−0.428*	−0.286
Finger tapping	−0.208	−0.133	−0.277	−0.123

HbA_{1c}, glycosylated hemoglobin; WAIS, Wechsler Adult Intelligence Scale–Revised; WCS, Wisconsin Card Sorting; CVLT, California Verbal Learning Test.
*$P < 0.05$; †$P \leq 0.01$.

for both diabetic and control subjects. Visual inspection of this figure suggested that the greater the level of HbA_{1c}, the poorer the performance on this measure of learning. This trend was observed on four of the nine measures included. Table 4 shows the correlations between measures of glycemic control and cognitive function. The two measures of glycemic control (HbA_{1c} and FPG) were highly correlated in the diabetic group (r = 0.788, df = 27, $P < 0.01$) but not in the healthy control group (r = 0.188, df = 28, $P > 0.05$). In the diabetic group, the digit symbol subtest, trails form A, WCS, and CVLT all were significantly related to HbA_{1c}. WCS and CVLT were also related to FPG. However, in the control group, only CVLT was significantly related to HbA_{1c}, and none of the cognitive measures was related to FPG.

Effect of demographic and health-related factors. Although both groups were comparable with respect to sociodemographic factors, we decided to complete a multivariate analysis of covariance with age, education, and self-health ratings entered as predictor variables, because these measures were frequently found to correlate with measures of cognitive function. When these environmental variables were taken into account, the multivariate F for the test of the WAIS-R measures was still highly significant (F = 3.853, df = 4,51, P = 0.008). This was also true for the remaining neuropsychological measures (F = 4.782, df = 5,50, P = 0.001). Univariate analysis of covariance yielded a pattern of group differences identical to that reported in the analysis of variance above. These results suggested that the differences in cognitive function between the two groups were not due to age, education, or self-perceptions of health.

However, the question remains whether the group differences might be associated with more objective measures of health status. Although self-ratings of health are highly correlated with objective ratings, the two may not relate to cognitive function in a similar fashion (9). Recent studies reporting no relationship between diabetes and cognitive function in subjects who were healthy otherwise (6,7) have led to the argument that any cognitive decline in diabetic patients might be the result of an accompanying disease rather than diabetes. In particular, the above-mentioned studies focused on CVD as a likely candidate. In an attempt to address this issue, we grouped our diabetic and control subjects according to their level of CVD. Subjects with a normal electrocardiogram, no history of hypertension, and blood pressure <150/90 mmHg were considered to have minimal evidence of CVD. Subjects with any of these signs present were considered to have some evidence of CVD.

With the use of these criteria for classification, there were 10 subjects in the diabetic group with minimal evidence of CVD and 19 with some signs present. In the control group, there were 17 with minimal evidence of CVD and 13 with clinical signs present. Sociodemographic characteristics across the four groups showed no significant difference for age (F = 0.865, df = 3,55, P = 0.465) or educational level (F = 0.846, df = 3,55, P = 0.675). The ratio of males to females was not related to CVD in either group (χ^2 = 0.608 and 0.175 for diabetic and control groups, respectively). As expected, self-perception of health was significantly related to CVD overall (χ^2 = 16.193, df = 2, $P < 0.001$), but the relationship was not significantly different between diabetic and control groups.

Although the number of subjects per group was small when subjects were classified in this manner, the argument implicating CVD as an explanatory mechanism for the poor performance in diabetic patients was sufficiently compelling to justify further exploratory analyses, particularly because the four groups were comparable with regard to sociodemographic characteristics. Accordingly, two (diabetic vs. control subjects) by two (cardiovascular status) MANOVAs were completed on the two dependent variable subsets described above. For the WAIS-R set, the multivariate F for the effect of diabetes was 4.239, which was highly significant (df = 4,52, P = 0.005). However, neither the effect for CVD status nor the interaction of diabetes by CVD was significant (multivariate F = 0.911 and 0.767 and P = 0.465 and 0.551, respectively, df = 4,52 for both). The MANOVA for the neuropsychological variables yielded an F of 5.260 (df = 5,51, P = 0.001) for the effect of diabetes. The effect of cardiovascular status and interaction of CVD by diabetes were both nonsignificant (multivariate F = 0.908 and 0.705 and P = 0.483 and 0.622, respectively, df = 5,51 for both). Post hoc comparisons of diabetic and healthy subjects, regarding those with minimal evidence of CVD, revealed that the healthy subjects were significantly better than diabetic subjects on the trails test forms A and B, WCS, and CVLT ($P <$ 0.05 for all). There was no difference on the finger-tapping test or any of the WAIS-R subtests.

DISCUSSION

Results of this study revealed that NIDDM patients performed more poorly than control subjects on cognitive measures of learning, abstract reasoning, and complex psychomotor functioning. However, performance on simple verbal and motor tasks was similar for both groups. Correlations between measures of glycemic control and cognitive function indicated that in the diabetic group, subjects with poorer control tended to perform the learning, reasoning, and complex psychomotor tasks more poorly, but no such relationship was evident for the simple verbal and motor tasks. The control group did not show a similar pattern of correlations.

These data confirm and extend results of earlier studies reporting that elderly NIDDM patients with hyperglycemia performed more poorly than nondiabetic outpatients (1,3–5) and community volunteers (2) on select measures of learning, memory, and reaction time. Similar results have also been reported in young adult insulin-dependent diabetic subjects with poor long-term glycemic control as evidenced by abnormally high levels of HbA_{1c} (16,17). Furthermore, a decline in cognitive function was seen in young adults with insulin-dependent diabetes mellitus when their plasma glucose concentrations were acutely increased (18,19).

It is difficult to reconcile the differences between our results and the studies completed by Robertson-Tchabo et al. (7) and Mattlar et al. (6). Regarding the former study, it might be that our measures assessed more complex psychological processes. With regard to the latter study, the fact that their subjects were younger than ours (mean differences were ~10 yr) may have been an important factor. A question that could be asked is whether diabetes may interact with age in its impact on cognitive processes to the extent that such problems with glycemic control may have an increasingly detrimental effect on cognitive function in the elderly that is not apparent in middle-aged subjects.

Our data indicate that the differences seen in cognitive function between patients with NIDDM and comparable nondiabetic subjects can be extended into a more elderly group. Moreover, our subjects (both diabetic and control subjects) were chosen to represent the highly functional end of the spectrum for people averaging 69 yr of age. For example, the mean level of education was higher than that of subjects included in either the Meuter et al. (1) or Perlmuter et al. (2) studies. In addition, they had held professional or managerial jobs for the most part, reported their overall physical health to be good, and were not suffering from depression. Because all of these variables may adversely affect cognitive function, they were controlled for in either the subject selection process or in the multivariate analysis of covariance analyses. Furthermore, we completed secondary analyses in which health status was more carefully controlled by use of objective ratings. Despite this, the performance of patients with NIDDM was reduced compared with the control group.

These considerations emphasize the importance of NIDDM in the genesis of the decline in learning, abstract reasoning, and complex psychomotor functioning. This study also clarifies that the differences between diabetic and healthy subjects are not likely to be seen for types of motor function that do not involve complex decisions before responding. Meuter et al. (1) do not make a distinction between simple and complex motor function in their reaction time factor. Our results also emphasize that these differences are not likely to extend to highly overlearned verbal processes implicated in simple routine day-to-day tasks. Thus, although elderly individuals with NIDDM who are not in good glycemic control are likely to have significant information processing difficulties, they may not be aware of this when conducting routine daily activities.

Finally, this study demonstrates that significant correlations were found between certain aspects of cognitive performance and degree of hyperglycemia. Of interest was the observation that impairment of learning and abstract reasoning correlated significantly with indices of both long- and short-term glycemic control. In contrast, Perlmuter et al. (2) found a correlation only with HbA_{1c} and not with FPG, whereas other researchers have not focused on within-group correlations between cognitive function and indices of glycemic control. Thus, the observation that neuropsychological defects were highly correlated with level of glycemic control was consistent with the view that hyperglycemia can adversely affect cognitive performance. Alternatively, it could be that patients with diabetes, as a group, simply have more CVD than matched nondiabetic control subjects, and the decline in cognitive function was simply another complication of the diabetic syndrome. The only way to address this question is to conduct a prospective study, in which the effect of changes in level of glycemic control on cognitive performance can be quantified.

Although the possibility that improvement in glycemic control could enhance cognitive function in diabetic patients is of great interest, particularly in older individuals, it must be emphasized that the patients we studied were individuals who were in good health. Furthermore, the neuropsychological deficits we found (and those reported in the literature) appear to have minor implications for everyday functioning. Although on the one hand these observations may be comforting, longer range consequences of poor glycemic control on cognitive processes are not well established. Assuming that hyperglycemia is a causal link for observed cognitive changes, it is possible to argue that sustained poor glycemic control will lead to an accelerated decline in more complex cognitive processes that could eventually reach clinical proportions. We can only speculate at this time as to the ultimate importance of the link between poor glycemic control and cognitive performance that has been demonstrated. This is an unsatisfactory situation and one that can only be remedied by addressing these

issues experimentally. We hope that our findings will aid in stimulating efforts in this regard.

ACKNOWLEDGMENTS

This work was supported in part by National Institute of Aging Grant AG-04458 and by Roerig, a division of Pfizer Pharmaceuticals.

REFERENCES

1. Meuter F, Thomas W, Gruneklee D, Gries E, Lohmann R: Psychometric evaluation of performance in diabetes mellitus. *Horm Metab Res* 9 (Suppl.):9–17, 1980
2. Perlmuter L, Hakami M, Harrington C, Ginsberg J, Katz J, Singer D, Nathan D: Decreased cognitive function in aging non-insulin-dependent diabetic patients. *Am J Med* 77:1043–48, 1984
3. Mooradian AD, Perryman K, Fitten J, Kavonian GD, Morley JE: Cortical function in elderly non-insulin dependent diabetic patients. *Arch Intern Med* 148:2369–72, 1988
4. Perlmuter LC, Tun P, Sizer N, McGlinchey RE, Nathan DM: Age and diabetes related changes in verbal fluency. *Exp Aging Res* 13:9–14, 1987
5. Tun PA, Perlmuter LC, Russo P, Nathan DM: Memory self-assessment and performance in aged diabetics and non-diabetics. *Exp Aging Res* 13:151–57, 1987
6. Mattlar C, Falck B, Ronnemaa T, Hyyppa M: Neuropsychological cognitive performance of patients with type 2 diabetes. *Scand J Rehabil Med* 17:101–105, 1985
7. Robertson-Tchabo EA, Arenberg D, Tobin JD, Plotz JB: A longitudinal study of cognitive performance in noninsulin dependent (type II) diabetic men. *Exp Gerontol* 21:459–67, 1986
8. Beck AT, Ward C, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. *Arch Gen Psychiatry* 4:561–71, 1961
9. LaRue A, Bank L, Jarvik L, Hetland M: Health in old age: how do physicians' ratings and self-ratings compare? *J Gerontol* 34:687–91, 1979
10. Mossey JM, Shapiro E: Self-rated health: a predictor of mortality among the elderly. *Am J Public Health* 72:800–808, 1982
11. Wechsler D: *Wechsler Adult Intelligence Scale-Revised (WAIS-R)*. Cleveland, OH, Psychol., 1981
12. Reitan R: Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 8:271–76, 1958
13. Dellis DC, Kramer JH, Kaplan E, Ober BA: *California Verbal Learning Test*. Cleveland, OH, Psychol., 1986
14. Heaton R: *Wisconsin Card Sorting Test: Scoring Form and Instructions*. Odessa, FL, Psychol. Assess. Resour., 1981
15. Reitan R, Davison L: *Clinical Neuropsychology: Current Status and Applications*. New York, Wiley, 1974
16. Franceschi M, Cecchetto R, Minicucci F, Smizne S, Baio G, Canal N: Cognitive processes in insulin-dependent diabetes. *Diabetes Care* 7:228–31, 1984
17. Holmes C: Neuropsychological profiles in men with insulin-dependent diabetes. *J Consult Clin Psychol* 54:386–89, 1986
18. Holmes CS, Hayford JT, Gonzalez JL, Weydert JA: A survey of cognitive functioning at different glucose levels in diabetic persons. *Diabetes Care* 6:180–85, 1983
19. Holmes CS, Koepke KM, Thompson RG, Gyves PW, Weydert JA: Verbal fluency and naming performance in type I diabetes at different blood glucose concentrations. *Diabetes Care* 7:454–59, 1984