Letters and Comments

Does Moderate Hyperglycemia Adversely Affect Mentation?

One of the complaints often made to physicians by undercontrolled diabetic patients is that of altered mentation, such as a decrease in memory or ability to concentrate. Such subtle complaints are difficult to evaluate. In cases where glucose concentrations or serum osmolalities are abnormal in the extreme, gross changes such as stupor or coma are common. However, little research has been reported on the effects of chronic moderate elevations of blood glucose on finer measures of cognitive functioning, in the absence of chronic severe illness, or brain dysfunction due to previous episodes of hypoglycemia.

We studied this question by administering a cognitive skills test to ambulatory undercontrolled diabetic outpatients who took the test twice at times when their blood glucose levels were markedly different. Each subject served as his own control. To minimize any effects of the subjects' knowledge of their blood glucose levels on their test efforts and to assess their ability to discriminate their glucose concentrations, subjects were not advised of their glucose levels and were asked to state their own estimate of their glucose concentrations. To eliminate the possibility of changing blood glucose concentrations affecting data interpretation, testing was brief (20 min) and was begun immediately after blood sampling. To avoid the additional variable of a second and different test, the same one was used on both occasions but after an interval of 3 mo, although subjects were not advised of this beforehand. The test was retyped in boldface 0.5-cm letters.

The subjects studied comprised 30 undercontrolled diabetic men who had previously shown large swings in glucose concentration but without hypoglycemia. All were type II (non-insulin-dependent) diabetic patients treated with insulin. The subjects, whose average age was 57.6 yr, consented to testing at 0730 with the Shipley-Hartford test, a multiple-choice measurement of vocabulary and abstract logic, which has been previously standardized (1).

Results of the subjects' ability to estimate their own serum glucose concentrations indicated a low correlation coefficient of +0.12 with the laboratory value, with most subjects erring on the side of underestimation. Shipley-Hartford test results were calculated for the first and second testing sessions to screen for learning effects and none were found. The subjects' mean low glucose concentration and serum osmolality were 188 ± 12.3 mg/dl and 288 ± 1.4 mosmol/kg, respectively, whereas the corresponding high values were 272 ± 13.5 mg/dl and 295 ± 1.6 mosmol/kg, respectively. The differences were significant ($P < .01$). The ranges for glucose and osmolality were 91–364 mg/dl and 284–311 mosmol/kg, respectively. However, when each subject's score at his higher glucose and osmolality value was compared with the score at the lower value by paired *t* test, there was no significant difference.

In contrast to this study, significantly greater accuracy in self-estimation of blood glucose has been reported, even when subjects had no previous training in home glucose monitoring (2). It is not clear whether these subjects based their estimates on discrimination of symptoms or on knowledge of their previous blood glucose trends.

Cognitive testing of type I (insulin-dependent) diabetic subjects has been reported to show mild deficits in memory, attention span, abstract reasoning, and motor coordination, but these studies are different from this one because glucose measurement at the time of testing

was not conducted, and subjects were brittle type I diabetic subjects with possible cerebral dysfunction due to hypoglycemic episodes (3–5). In type II diabetic subjects, a defect in memory retrieval has been shown (6), although the study design was different from this investigation, in that it was cross-sectional and testing was conducted at one time point. It is not clear if the defect reported is related to glucose concentrations, a feature of diabetes other than hyperglycemia, or the effect of chronic illness.

In this study, no changes in vocabulary recall or abstract logic were demonstrated as a function of spontaneous variations of serum glucose and osmolalities encountered. It is possible that other types of psychological testing or wider ranges of glucose concentration and osmolality might be necessary to demonstrate any effects of moderate hyperglycemia. However, if higher glucose concentrations are studied, they would have to be examined in healthy subjects to avoid the complicating effects of stress and chronic illness. Therefore, it appears possible that symptoms of dysmentation reported by diabetic subjects with moderate hyperglycemia may be referable to elevated glucose concentrations, osmolalities, or other associated metabolic derangement, but the degree of abnormality necessary to cause cognitive dysfunction is probably greater than that reported in this study.

LAWRENCE PARKER, MD
CHANG-LIM KIM, MD
EDWARD HESS, MD
JOSE RABELO, MD, PhD
RICHARD CHARTER, PhD

From the Endocrinology Section, Medical Service, and Psychology Service, University of California at Irvine-Long Beach Medical Program, Long Beach, California.

Address correspondence and reprint requests to Lawrence Parker, MD, Endocrinology Section, Veterans Administration Medical Center, 5901 East Seventh Street, Long Beach, CA 90822.

REFERENCES

1. Shipley W: A self-administered scale for measuring intellectual impairment and deterioration. *J Psychol* 9:371–77, 1940
2. Wing RR, Epstein LH, Lamparski D, Hagg SA, Nowalk MP, Scott N: Accuracy in estimating fasting blood glucose levels by patients with diabetes. *Diabetes Care* 7:476–78, 1984
3. Franceschi M, Cecchetto R, Minicucci F, Smizne S, Baio G, Canal N: Cognitive processes in insulin-dependent diabetes. *Diabetes Care* 7:228–31, 1984
4. Skenazy J, Bigler E: Neuropsychological findings in diabetes mellitus. *J Clin Psychol* 40:246–58, 1984
5. Holmes C: Neuropsychological profiles in men with insulin-dependent diabetes. *J Consult Clin Psychol* 54:386–89, 1986
6. Perlmuter L, Hakami M, Hodgson C, Ginsberg J, Katz J, Singer D, Nathan D: Decreased cognitive function in aging noninsulin-dependent diabetic patients. *Am J Med* 77: 1043–48, 1984

Nesidioblastosis Versus Islet Cell Hyperplasia

In the February issue of *Diabetes Care,* Fong et al. (1) presented three cases of nesidioblastosis occurring in adults and added these to seven previously reported cases. They speculated, based on their own experience (30% of patients) and from other literature (2), that cases of nesidioblastosis may be underreported as a cause of hyperinsulinemic hypoglycemia.

We reported a case in 1986 that met all the criteria for nesidioblastosis in an adult but titled the paper "Islet Cell Hyperplasia" as a way of making some important points (3). Our review of the literature showed that many authors had used the term *nesidioblastosis* to describe different pathological processes. Furthermore, many reports had stressed other hyperplastic changes in hyperinsulinism in addition to the budding of endocrine cells from ducts. We proposed the less restrictive definition of islet cell hyperplasia to identify the diffuse proliferation of endocrine cells with different morphological patterns and different proportions that vary from case to case.

Clearly, by conducting a literature search for adult cases of nesidioblastosis, Fong et al. easily overlooked our report. That fact reinforces the need for more discussion of our proposal to redefine the entity of hyperinsulinemic hypoglycemia where no discrete adenoma is found. The editorial by Rahier (4) emphasized the lack of specificity of nesidioblastosis in association with hyperinsulinism. We agree but stress that by avoiding the restrictive term *nesidioblastosis* and instead including all patterns of islet cell hyperplasia together, a more consistent histological diagnosis will be used. We suspect the true incidence will be ~6–7% of all cases of hyperinsulinemic hypoglycemia found by Stefanini et al. (5) in their series of 1067 cases.

As indicated by Fong et al., the diagnostic and therapeutic problems presented by hyperinsulinemic hypoglycemia remain difficult. Their observation that proinsulin values in the normal range may help to differentiate adenomas from a diffuse process may be useful. Routine serum insulin and C-peptide determinations have largely replaced proinsulin levels in the workup of insulinomas in the last several years. Especially in patients with no definite preoperative localization by radiological and pancreatic vein sampling techniques, a proinsulin measurement should now be considered. Unfortunately, because of the rarity of the condition, it will require several years for comparison data to prove the true usefulness of this measurement as a discriminating and predictive factor. Until then, physicians and surgeons involved in the preoperative management of these patients must continue to be prepared for an intraoperative decision about the extent of surgical resection.

PAUL MARGULIES, MD
ELLEN KAHN, MD