Detection of Symptoms by Adolescents and Young Adults With Type 1 Diabetes During Experimental Induction of Mild Hypoglycemia

Role of hormonal and psychological variables

CHRISTOPHER M. RYAN, PHD[1]
DAISY DULAY, BS[1]
CHITTIWAT SUPRASONGSIN, MD[2]
DOROTHY J. BECKER, MBBCH[1]

OBJECTIVE — To identify hormonal, psychological, and demographic predictors of symptom detection and accuracy of blood glucose estimation during mild hypoglycemia in adolescents and young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS — During an insulin-glucose clamp study, 53 adolescents and 19 young adults estimated blood glucose levels and reported symptoms at euglycemia and after 30 min of mild hypoglycemia (3.3 mmol/l). Epinephrine and pancreatic polypeptide were measured, and both change in anxiety level during hypoglycemia and baseline level of anxiety were measured with the Spielberger Anxiety Inventory. Elevated levels of anxiety during euglycemia were used as an indicator of the psychological trait "negative affectivity." Previous studies have suggested that individuals with higher negative affectivity are more internally focused and, therefore, more likely to report somatic and visceral changes.

RESULTS — During mild hypoglycemia, 42% of the sample subjects reported an increase in autonomic symptoms; 29% reported an increase in neuroglycopenic symptoms, and 28% estimated blood glucose levels accurately (within 10% of actual). Hormonal excursions did not predict any outcome, but higher anxiety levels during the euglycemic baseline were associated with better detection of hypoglycemic symptoms and more accurate estimation of blood glucose values after controlling for change in anxiety level during hypoglycemia.

CONCLUSIONS — Psychological factors such as elevated anxiety levels ("negative affectivity") can influence blood glucose estimation and symptom detection in adolescents and young adults and may explain why some individuals are more adept than others at reducing their risk of severe hypoglycemia after participation in a formal blood glucose awareness training program.

Diabetes Care 25:852–858, 2002

Preventing the occurrence of even mild hypoglycemia is critically important for individuals with diabetes, considering the strong link between recurrent hypoglycemia and development of hypoglycemia unawareness (1). Blood glucose awareness training has been advanced as a strategy to avoid hypoglycemia by teaching individuals to use the appearance of autonomic and neuroglycopenic symptoms as indicators of decreasing blood glucose levels (2). Unfortunately, neither adults nor children are particularly adept at identifying hypoglycemia-associated symptoms or estimating blood glucose values reliably (3). One early study noted that 76% of adults with type 1 diabetes overestimated blood glucose values during experimentally induced hypoglycemia (4), and pediatric research has found that adolescents are significantly less accurate at estimating blood glucose than young adults (accuracy index 7 vs. 32%, respectively) (5). The magnitude of these errors is large: one diabetes camp–based study found low blood glucose values to be overestimated by an average of 57 mg/dl (6). Similarly inaccurate estimations have also been reported by younger children and their parents (7).

Individual differences in the ability to detect hypoglycemic symptoms have been attributed primarily to variations in the suppression of hormonal counterregulation induced by prior hypoglycemia (8), but there is increasing evidence that psychological factors may also contribute. Using structural equation modeling statistical techniques, Hepburn et al. (9) found that higher levels of neuroticism were associated with increased reporting of autonomic and neuroglycopenic symptoms in a large sample of adults with diabetes. According to personality theorists, individuals with higher levels of neuroticism are more likely to be anxious and depressed, experience feelings of guilt, have lower self esteem, be tense, shy, and moody or emotional, and seem irrational (10). One aspect of neuroticism found to be particularly relevant to health status is "negative affectivity," a psychological state that is characterized by a negative mood and elevated levels of distress, and can be measured with self-report anxiety scales (11,12). The single study to examine the relationship between this personality dimension and accurate symptom detection in children

From the [1]Departments of Psychiatry and Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and the [2]Department of Pediatrics, Ramathibodi Hospital, Bangkok, Thailand.

Address correspondence and reprint requests to Christopher M. Ryan, PhD, Western Psychiatric Institute & Clinic, 3811 O'Hara St., Pittsburgh, PA 15213. E-mail: ryancm@msx.upmc.edu.

Received for publication 25 October 2001 and accepted in revised form 8 February 2002.

Abbreviations: CHP, Children's Hospital of Pittsburgh.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

with diabetes found that, as predicted, higher anxiety was correlated with identification of low blood glucose symptoms, as well as with beliefs and expectations about symptoms of hypoglycemia (13).

All prior pediatric studies examining symptom detection and accuracy of blood glucose estimation have used an ambulatory observational methodology in which subjects reported symptoms and estimated blood glucose levels periodically over the course of several weeks. A major problem with the use of a field study approach is the lack of experimental control. Not only do these studies rely on naturally occurring episodes of hypoglycemia, which vary in number and depth across subjects, but they require a high level of patient initiative to correctly record both symptoms and self-monitored blood glucose test results (3). Therefore, we used the insulin-glucose clamp technique (14) to determine the extent to which hormonal activation (changes in epinephrine and pancreatic polypeptide), psychological factors (hypoglycemia-associated changes in anxiety level and euglycemic baseline level of anxiety), and demographic characteristics (age and sex) affected symptom detection and blood glucose estimation during experimentally induced hypoglycemia. Drawing on the previous cross-sectional descriptive research that suggested a link between personality characteristics and symptom detection (9), and using subjects' baseline self-reported anxiety scores as an indicator of the personality trait known as negative affectivity (11), we predicted that high baseline anxiety levels would have a significant influence on symptom detection and blood glucose estimation.

RESEARCH DESIGN AND METHODS

Study subjects

A total of 53 adolescents, aged 12–18 years (mean ± SD 14.9 ± 1.9 years), and 19 adults, aged 19–30 years (24.4 ± 3.4 years) were selected from the Children's Hospital of Pittsburgh (CHP) diabetes registry to represent a wide range of glycemic control. All subjects were diagnosed before 18 years of age, had a diabetes duration of ≥2 years, and had full-scale intelligence quotients between 80 and 135. None had clinically detectable diabetes complications (e.g., retinopathy, albuminuria) or other chronic disorders (e.g., seizure disorder) and were euthyroid (some were taking L-thyroxine). As part of a larger research project on hypoglycemia-associated changes in mental efficiency, each subject participated in two clamp studies, performed in random order 2 months apart: a standard hypoglycemic clamp and either a euglycemic clamp (with or without epinephrine infusion) or another hypoglycemic clamp with α- and β-blockade. This report is restricted to symptom data from the standard hypoglycemic clamp. Subjects were told that their blood glucose level might decrease or might stay the same; they were blinded to actual blood glucose values throughout each clamp. The CHP Human Rights Committee approved this research protocol, and all subjects (and parents of minor children) gave written informed consent.

Procedures

Subjects were admitted to the General Clinical Research Center at CHP 1 or 2 days before the clamp study and completed intelligence and academic achievement tests at that time. Intermediate insulin was omitted the day before the study, and euglycemia was maintained by four injections of regular insulin before meals and an insulin infusion pump. Two intravenous catheters, one for blood sampling (dorsal hand vein) and one for glucose and insulin infusion (antecubital vein), were inserted in the nondominant arm. To achieve overnight euglycemia, a variable-rate intravenous infusion of regular pork insulin was started at 10:00 P.M. Hyperinsulinemic clamp studies were performed after a 10-h overnight fast. At 8:00 A.M., the intravenous insulin infusion rate was increased to 0.1 unit · kg^{-1} · h^{-1}, and the resulting plasma free insulin concentration was maintained at ~600 pmol/l for the entire study. Serum glucose levels were manipulated by infusing 20% dextrose at a variable rate to maintain the designated target value. Blood was obtained from a heated nondominant hand vein at 5-min intervals for determination of arterialized serum glucose concentrations. Every 15 min, blood was drawn for measurement of plasma free insulin and counterregulatory hormones.

At the beginning of the experiment, serum glucose was clamped at 5.5–6.0 mmol/l and a stable euglycemic baseline was maintained for 60–90 min. In the last 30 min of that period, a brief battery of mental efficiency tests was administered, similar to that described elsewhere (14), and cerebral blood flow was measured (15). Just before and immediately after that assessment, subjects were asked to rate the presence and severity of a series of symptoms, to estimate their blood glucose values, and to indicate whether their blood glucose level was normal, high, or low. Hypoglycemia was induced immediately after completion of these tests by decreasing the intravenous glucose infusion over a 20- to 25-min period, until blood glucose values reached 3.3 mmol/l. The hypoglycemic nadir was maintained for 60 min. After 30 min of hypoglycemia, symptoms were ascertained and mental efficiency was assessed; immediately thereafter, symptoms were ascertained again. Euglycemia was then re-established by increasing the glucose infusion rate over a 15-min period. It was maintained for 60 min; in the last 30 min of the euglycemic period, subjects repeated the tests.

Symptom assessment

Subjects heard a list of 15 possible symptoms and rated each from 0 (absent) to 3 (severe). A relatively restricted rating scale was used because our pilot studies indicated that younger children were not able to reliably use a 5- or 7-point rating scale. Six symptoms were considered to be autonomic (sweaty, shaky, heart pounding, hungry, nervous, and stomachache); four symptoms were considered to be neuroglycopenic (blurred vision, difficulty thinking, dizzy, and sleepy); and five symptoms were considered nonspecific (headache and feeling different) or "fillers" (thirsty, ringing ears, and yellow vision) and were not analyzed further (16). If "hungry" or "sleepy" were endorsed, subjects were asked to differentiate hypoglycemic symptoms from having missed breakfast or from lying in bed. Although symptom ratings were completed periodically during the course of the study, this analysis was restricted to the symptom ratings that were made just before the mental efficiency assessment: after at least 30 min of euglycemia and after 30 min of hypoglycemia. Immediately after rating symptoms, subjects estimated their blood glucose level.

Assessment of anxiety

The Spielberger Anxiety Inventory (17) is a 20-item self-report rating scale that was administered just before the symptom

Table 1—*Characteristics of entire sample*

N	72
Age (years)	17.4 ± 4.8
Adolescents	74%
Men	49%
Duration of diabetes (years)	8.1 ± 5.5
Full-scale intelligence quotient	104.9 ± 13.1
State anxiety score at euglycemia	32.9 ± 8.1
Subjects elevated anxiety scores at euglycemia	53%
State anxiety score at hypoglycemia	35.8 ± 10.5
Blood glucose at euglycemia (mmol/l)	5.85 ± 0.5
Blood glucose at hypoglycemia (mmol/l)	3.28 ± 0.2
Subjects estimating blood glucose accurately (±10%) at euglycemia	38%
Subjects estimating blood glucose accurately (±10%) at hypoglycemia	28%
HbA_{1c} (%)	8.6 ± 1.4
Mean epinephrine increase at hypoglycemia (pmol/l)	707 ± 1,092
Subjects with clinically elevated epinephrine	34%
Mean pancreatic polypeptide increase at hypoglycemia (pmol/l)	68.5 ± 127.4
Subjects with clinically elevated pancreatic polypeptide	42%
For all subjects:	
Autonomic symptom score at euglycemia	0.8 ± 1.3
Autonomic symptom score at hypoglycemia	1.6 ± 2.2
Subjects reporting increased autonomic symptoms at hypoglycemia	42%
Neuroglycopenic symptom score at euglycemia	0.4 ± 0.8
Neuroglycopenic symptom score at hypoglycemia	0.9 ± 1.6
Subjects reporting increased neuroglycopenic symptoms at hypoglycemia	29%
For "reliable reporters":	
Autonomic symptom score at euglycemia ($N = 62$)	0.6 ± 1.2
Autonomic symptom score at hypoglycemia	1.8 ± 2.3
Neuroglycopenic symptom score at euglycemia ($N = 66$)	0.3 ± 0.8
Neuroglycopenic symptom score at hypoglycemia	1.0 ± 1.7

Data are means ± SD unless otherwise indicated.

ratings. The difference between the euglycemic and the hypoglycemic scores provided an estimate of hypoglycemia-induced change in anxiety state. To estimate the personality trait of negative affectivity, anxiety scores obtained during the euglycemic baseline assessment were dichotomized, using a value of 31 or more as indicative of higher negative affectivity. This approach was taken because self-reported anxiety has previously been found to provide a reasonable estimate of negative affectivity (12). The average score on this measure for high school students (17), and for the subjects in this study, was 30.

Laboratory methods

Serum glucose was measured by the glucose oxidase method with a YSI glucose analyzer (YSI, Yellow Springs, OH). Plasma levels of epinephrine were determined in blood collected in glutathione-containing tubes and measured by a high-pressure liquid chromatographic method (LCEC capsule N-46; Bioanalytical Systems, Lafayette, IN) in the first 4 years of the study; thereafter, the ESA system (ESA, Chelmsford, MA) was used. Baseline levels of epinephrine tended to be lower with the new instrument, but incremental changes were not different. Pancreatic polypeptide was measured with a charcoal radioimmunoassay modified from that of Chance et al. (18). HbA_{1c} values were also measured by high-performance liquid chromatography (Bio-Rad, Richmond, CA). The upper limit of normal values for our laboratory is 6.1%, and the mean value for our adolescent pediatric type 1 diabetes population is 8.3%.

Statistical analyses

For both the autonomic and neuroglycopenic symptom clusters, ratings for each of the six autonomic and four neuroglycopenic symptoms were summed, and difference scores (hypoglycemia-euglycemia) were also calculated for each cluster. Analyses used summary scores, rather than individual symptom scores, because the overall pattern of symptom reporting is highly idiosyncratic across individuals (6,19). Multivariate associations were examined using hierarchical linear regression modeling for continuous outcome variables (changes in symptoms) and logistic regression techniques for dichotomous variables (blood glucose accuracy). All analyses were conducted using SPSS statistical software for Windows (version 10.1; SPSS, Chicago, IL).

RESULTS

— Characteristics of the sample are summarized in Table 1.

Autonomic symptom detection

Hierarchical linear regression techniques were used to identify multivariate predictors of symptom change from euglycemia to hypoglycemia. Hypoglycemia-associated increases in pancreatic polypeptide and epinephrine (dichotomized as values that are elevated 2 SD above the euglycemic mean) were entered on Block 1, change in anxiety score from euglycemia to hypoglycemia was entered on Block 2, anxiety level during euglycemia (dichotomized at the median) was entered on Block 3, and age and/or sex were entered on Block 4. This approach allows us to examine, in a systematic fashion, the independent contribution of changes in hormone level, changes in anxiety induced by hypoglycemia, general preexisting levels of anxiety, and other demographic variables as predictors of autonomic symptom detection during hypoglycemia. Because preliminary analyses found no relationship between symptom change and HbA_{1c}, metabolic control was not included in the multivariate modeling.

Results for all subjects are summarized in the upper left panel of Table 2. Model IV includes all four blocks of variables. It is clear that hormone changes are not significantly associated with changes in autonomic symptom reporting (Model I). On the other hand, change in anxiety score (Model II) and anxiety at euglycemia (Model III) each independently contribute significantly. Age is a marginally significant predictor (Model IV); younger subjects tended to report more autonomic symptoms. Sex was not significant and was deleted. The final model accounts for a modest 23.5% of the total variance, using the entire sample.

Table 2—*Hierarchical regression models for autonomic and neuroglycopenic symptom change from euglycemia to hypoglycemia for all subjects and for "reliable reporters"*

		All subjects (N = 70)		"Reliable reporters" (N = 62)	
Model	Change in autonomic symptoms	β	P	β	P
I	Pancreatic polypeptide	0.135	>0.20	0.303	0.03*
	Epinephrine	0.191	0.16	0.172	>0.20
	Total R^2	0.080		0.174	
II	Pancreatic polypeptide	0.137	>0.20	0.304	0.03*
	Epinephrine	0.205	0.12	0.178	0.19
	Change in anxiety score	0.247	0.03*	0.187	0.12
	Total R^2	0.141		0.209	
III	Pancreatic polypeptide	0.068	>0.20	0.226	0.09
	Epinephrine	0.225	0.08	0.188	0.15
	Change in anxiety score	0.264	0.02*	0.195	0.08
	Anxiety at euglycemia	0.238	0.04*	0.326	0.006†
	Total R^2	0.194		0.310	
IV	Pancreatic polypeptide	−0.004	>0.20	0.149	>0.20
	Epinephrine	0.233	0.07	0.189	0.14
	Change in anxiety score	0.301	0.009†	0.242	0.03*
	Anxiety at euglycemia	0.236	0.04*	0.317	0.006†
	Age (years)	−0.217	0.07	−0.244	0.04*
	Total R^2	0.235		0.361	

		All subjects (N = 70)		"Reliable reporters" (N = 66)	
Model	Change in neuroglycopenic symptoms	β	P	β	P
I	Pancreatic polypeptide	−0.058	>0.20	−0.077	>0.20
	Epinephrine	0.121	>0.20	0.094	>0.20
	Total R^2	0.011		0.008	
II	Pancreatic polypeptide	−0.054	>0.20	−0.082	>0.20
	Epinephrine	0.147	>0.20	0.130	>0.20
	Change in anxiety score	0.496	0.0001*	0.501	0.0001†
	Total R^2	0.256		0.257	
III	Pancreatic polypeptide	−0.111	>0.20	−0.136	>0.20
	Epinephrine	0.164	0.187	0.151	>0.20
	Change in anxiety score	0.510	0.0001†	0.517	0.0001†
	Anxiety at euglycemia	0.196	0.075	0.214	0.060
	Total R^2	0.292		0.301	
IV	Pancreatic polypeptide	−0.088	>0.20	−0.122	>0.20
	Epinephrine	0.168	0.157	0.158	>0.20
	Change in anxiety score	0.506	0.0001†	0.518	0.0001†
	Anxiety at euglycemia	0.248	0.026*	0.247	0.035*
	Sex	−0.233	0.040*	0.138	>0.20
	Total R^2	0.338		0.318	

*$P < 0.05$; †$P < 0.01$.

An examination of the autonomic symptom change data indicated that 14% of the entire sample had negative scores—that is, they reported more symptoms at euglycemia (1.9 ± 0.9) than at hypoglycemia (0.4 ± 0.7). To determine whether our overall pattern of results would be altered if these "unreliable reporters" were omitted from the analyses, we repeated the hierarchical linear regression analysis. As noted in the upper right panel of Table 2, the results are essentially the same, although a greater proportion of the variance is now explained by the final model (36 vs. 23.5%), and anxiety level at euglycemia is more influential than the change in anxiety score from euglycemia to hypoglycemia.

Neuroglycopenic symptom detection

The same statistical approach was used to predict change in neuroglycopenic symptom reports for all subjects. As presented in the lower left panel of Table 2, change in anxiety score was a significant predictor for all subjects (Model II), as was sex (Model IV); level of anxiety was marginally significant (Model III). The final model (Model IV) indicates that although hormone excursions during hypoglycemia are not associated with changes in neuroglycopenic symptom reporting, change in anxiety score, anxiety at euglycemia, and sex are each significant predictors. Together, these variables explain ~34% of the total variance. Age was not associated with symptom change and was deleted. When the analyses were repeated using only reliable reporters (Table 2, lower right panel), a similar pattern of results was obtained.

Accuracy of blood glucose estimates

The subjects estimated their blood glucose levels immediately after completion of the symptom questionnaire, and difference scores (estimated – actual value) were calculated. Subjects with blood glucose estimates within 10% of actual values were considered to be accurate estimators, and 28% met that criterion. The average blood glucose error was 0.03 ± 0.2 mmol/l for accurate estimators and 1.7 ± 1.6 mmol/l for inaccurate estimators.

Hierarchical logistic regression techniques, with predictor variables entered in blocks, were used to predict accuracy of glucose estimation. In addition to the predictors described above, change in autonomic (Block 5) and neuroglycopenic symptoms (Block 6) were also included. For all subjects, neither epinephrine nor pancreatic polypeptide (Block 1) predicted glucose estimation accuracy ($P >$ 0.20), nor did the change in anxiety score from euglycemia to hypoglycemia (Block 2; $P > 0.20$). Higher anxiety at euglycemia contributed significantly to the prediction model (Block 3: $\chi^2 = 6.2$; $P =$ 0.013) as did older age (Block 4: $\chi^2 = 6.4$; $P = 0.011$) and increase in autonomic symptoms (Block 5: $\chi^2 = 5.4$; $P = 0.02$). Odds ratios (CIs) for all significant pre-

dictors are as follows: anxiety at euglycemia 3.84 (0.96, 15.41), $P = 0.057$; age 1.23 (1.06, 1.41), $P = 0.005$; change in autonomic symptoms 1.52 (1.03, 2.24), $P = 0.03$. This model correctly classified 73% of the entire sample ($\chi^2 = 19.3$; $P = 0.004$) and accounted for ~34% of the variance (Nagelkerke $R^2 = 0.341$). The addition of neuroglycopenic symptoms did not contribute to the accuracy of the model (Block 6 $\chi^2 = 0.912$; $P > 0.20$). A similar pattern of results was obtained when the analyses were restricted to the 61 reliable autonomic symptom reporters (data not shown).

CONCLUSIONS — Using an insulin-glucose clamp technique to induce controlled mild hypoglycemia, we examined the ability of adolescents and young adults with diabetes to detect autonomic and neuroglycopenic symptoms and to accurately estimate blood glucose levels. In general, our subjects were not very good at any of these tasks, despite full knowledge of the protocol as explained to them and as described in the consent form. When serum glucose values decreased from 5.5 to 3.3 mmol/l, only a minority of the entire sample (42%) reported an increase in autonomic symptoms. Furthermore, the magnitude of reported symptom change was quite small. Although autonomic symptom scores could range from 0 to 18, the highest rating in this sample was 9, and the mean increment from euglycemia to hypoglycemia for all reliable reporters was 1.2, a value that corresponds to the appearance of one symptom rated as "mild." Neuroglycopenic symptom identification was even less common: only 29% of the entire sample detected any increase, and the mean increment was only 0.7 symptom. These latter results were not surprising, however, given data indicating that the glycemic threshold for the detection of neuroglycopenic symptoms is lower than the threshold for autonomic symptoms in adults (2.8 vs. 3.6 mmol/l, respectively) (20) and children with diabetes (3.1 vs. 3.6 mmol, respectively) (21).

Our subjects were also inaccurate in estimating their blood glucose values. During euglycemia, only 38% of our sample subjects were able to estimate their blood glucose levels to within ±10% of its actual value; these figures were much poorer during hypoglycemia (28%). Subjects who were not accurate were quite inaccurate and, as a group, estimated their blood glucose levels to be euglycemic (5.3 mmol/l, on average) when they were actually hypoglycemic (3.3 mmol/l).

The primary goal of this study was to identify possible predictors of variability in symptom detection and blood glucose estimation during hypoglycemia. Of the three broad classes of variables that were examined (hormonal, psychological, and demographic), the most robust predictors of both autonomic and neuroglycopenic symptom detection were psychological. Contrary to expectation, hypoglycemia-associated increases in epinephrine and pancreatic polypeptide had little impact on symptom detection. In contrast, the presence of higher anxiety scores at the euglycemic baseline independently predicted hypoglycemic symptom score, even after controlling for changes in anxiety level during hypoglycemia.

Most work on the hormonal correlates of symptom detection has focused on the putative role played by epinephrine, and studies have demonstrated repeatedly that during moderately severe hypoglycemia, the resulting increments in epinephrine are associated with increases in symptoms in diabetic adults (22–24). Because the glycemic threshold for a clinically significant increase in epinephrine has been found to range from 2.6 to 3.6 mmol/l in adults (25), the absence of a relationship between epinephrine and symptom identification in our sample of adolescents and young adults may be a consequence of the very mild level of hypoglycemia induced or of specific characteristics of our sample. Two studies have demonstrated that children with diabetes experienced a vigorous increase in epinephrine when blood glucose values decreased more, to 3.1 (26) or to 2.8 mmol/l (27), but both studies also included subjects who were younger (27) and in poorer metabolic control (26) than our subjects. When adolescents in average metabolic control were evaluated by Bjørgaas et al. (21), only a small, nonsignificant increase in epinephrine occurred during moderate hypoglycemia (2.6 mmol/l).

We found that hypoglycemia-associated increases in self-reported levels of anxiety predicted change in autonomic and neuroglycopenic symptoms, but this was not unexpected because increased anxiety is often considered to be an autonomic symptom (28). More importantly, after statistically controlling for those changes in anxiety during hypoglycemia, we found that individuals who had higher anxiety scores during the euglycemic baseline still reported more autonomic and neuroglycopenic symptoms and estimated their blood glucose values more accurately, as compared with subjects with lower baseline anxiety scores. Depending on the analysis, a higher baseline anxiety level accounted for between 5 and 10% of the variance in symptom detection.

Personality theorists have used high anxiety scores as an indicator of the psychological trait "negative affectivity" and have described individuals with that trait as being introspective, apprehensive, vigilant, and negativistic (11). Even when overt stressors are absent, these individuals are more likely to experience high levels of distress and dissatisfaction in many situations. Higher levels of anxiety or negative affectivity are also predictive of subjective somatic complaints (12,29). If individuals who score high on measures of negative affectivity are hypervigilant (searching constantly for signs of trouble), they may be more likely to pay attention to relatively small changes in internal somatic or visceral sensations (30). Not only should this hypervigilance lead to earlier detection of physical symptoms (e.g., autonomic symptoms during mild hypoglycemia), but it should facilitate the identification of a hypoglycemic state if those symptoms and other visceral changes are used by that person to identify symptoms or estimate blood glucose values.

Our data on both symptom detection and blood glucose estimation accuracy are consistent with that interpretation. For example, the most influential predictors of accurate estimates included higher baseline anxiety score, larger change in autonomic symptoms, and older age. Together, these variables explained ~34% of the variance in accuracy of blood glucose estimation. The better estimation skills of our older subjects might reflect their more extensive experience with hypoglycemia and/or blood glucose monitoring because, contrary to expectation (31), they did not manifest a greater frequency or severity of defective counterregulation (and concomitantly greater estimation errors because of hypoglycemia unawareness) despite their longer duration of diabetes.

Compared with previously published

results, our subjects were more accurate at estimating their blood glucose values than children who were studied in naturalistic settings (5). Variations in level of environmental stimulation may account for these between-study differences. Because attention to internal cues declines as external cues become more available and more salient (32), one would expect individuals evaluated in an ever-changing, environmentally stimulating field setting to be less accurate at identifying hypoglycemia as compared with being evaluated while lying in a hospital bed during a hypoglycemic clamp. Support for that possibility comes from a study of diabetic adults demonstrating that field study data underestimated ratings of hypoglycemia unawareness when compared with data from an experimental clamp study (33). Other psychological characteristics, such as expectations about the effects of hypoglycemia (i.e., symptom beliefs), may also influence detection of hypoglycemia (34), but those were not assessed in our study.

Detection of symptoms and accurate estimation of blood glucose values are critical for prevention of severe hypoglycemia (35). In their biopsychobehavioral model of risk of severe hypoglycemia, Gonder-Frederick et al. (36) emphasized the importance of psychological factors in accurately detecting and interpreting the physical symptoms associated with biochemical hypoglycemia and in initiating appropriate self-treatment behaviors that can reduce the risk of an episode of severe hypoglycemia. One psychological characteristic with the potential to reduce the risk of severe hypoglycemia is fear of hypoglycemia, and it has been suggested that individuals with high levels of fear may maintain somewhat higher glycemic levels, may prematurely treat decreasing (but not yet hypoglycemic) blood glucose levels, and may over-interpret somatic sensations as symptoms of hypoglycemia (36). Fear of hypoglycemia is higher in adults who have previously experienced frequent or severe hypoglycemia (37) and in those who score high on measures of anxiety and neuroticism (9), but whether it is merely a surrogate for the more enduring psychological trait of negative affectivity is an interesting issue that has not yet been addressed. What is clear, however, is that in addition to pathophysiological factors such as failure of autonomic response, personality traits such as negative affectivity can have a measurable impact on blood glucose estimation and symptom detection and may explain why some individuals are far more likely than others to benefit from participation in formal blood glucose awareness training programs (35).

Acknowledgments— This work was supported, in part, by National Institutes of Health Grants 5M01-RR-00084 and 2R01-HD-29487, the Juvenile Diabetes Foundation, the Diabetes Action Research and Education Foundation, and the Renziehausen Fund.

References

1. Ovalle F, Fanelli CG, Paramore DS, Hershey T, Craft S, Cryer PE: Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. *Diabetes* 47:1472–1479, 1998
2. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W: A multicenter evaluation of blood glucose awareness training-II. *Diabetes Care* 18: 523–528, 1995
3. Cox DJ, Gonder-Frederick L, Antoun B, Cryer PE, Clarke WL: Perceived symptoms in the recognition of hypoglycemia. *Diabetes Care* 16:519–527, 1993
4. Cox DJ, Clarke WL, Gonder-Frederick L, Pohl S, Hoover C, Snyder A, Zimbelman L, Carter WR, Bobbitt S, Pennebaker J: Accuracy of perceiving blood glucose in IDDM. *Diabetes Care* 8:529–536, 1985
5. Nurick MA, Johnson SB: Enhancing blood glucose awareness in adolescents and young adults with IDDM. *Diabetes Care* 14:1–7, 1991
6. Freund A, Johnson SB, Rosenbloom A, Alexander B, Hansen CA: Subjective symptoms, blood glucose estimation, and blood glucose concentrations in adolescents with diabetes. *Diabetes Care* 9:236–243, 1986
7. Gonder-Frederick LA, Snyder AL, Clarke WL: Accuracy of blood glucose estimation by children with IDDM and their parents. *Diabetes Care* 14:565–570, 1991
8. Cryer PE: Glucose counterregulation: prevention and correction of hypoglycemia in humans. *Am J Physiol* 264:E149–E155, 1993
9. Hepburn DA, Deary IJ, MacLeod KM, Frier BM: Structural equation modeling of symptoms, awareness and fear of hypoglycemia, and personality in patients with insulin-treated diabetes. *Diabetes Care* 17: 1273–1280, 1994
10. Matthews G, Deary IJ: *Personality Traits*. Cambridge, U.K., Cambridge University Press, 1998
11. Watson D, Clark LA: Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull* 96: 465–490, 1984
12. Watson D, Pennebaker JW: Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychol Rev* 96:234–254, 1989
13. Wiebe DJ, Alderfer MA, Palmer SC, Lindsay R, Jarrett L: Behavioral self-regulation in adolescents with type 1 diabetes: negative affectivity and blood glucose symptom perception. *J Consult Clin Psychol* 62: 1204–1212, 1994
14. Gschwend S, Ryan C, Atchinson J, Arslanian S, Becker D: Effects of acute hyperglycemia on mental efficiency and counterregulatory hormones in adolescents with insulin-dependent diabetes mellitus. *J Pediatr* 126:178–184, 1995
15. Jarjour IT, Ryan CM, Becker DJ: Regional cerebral blood flow during hypoglycaemia in children with IDDM. *Diabetologia* 38:1090–1095, 1995
16. Deary IJ, Hepburn DA, MacLeod KM, Frier BM: Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 36: 771–777, 1993
17. Spielberger C, Gorsuch R, Lushene R: *STAI: Manual for the State-Trait Anxiety Inventory*. Palo Alto, Consulting Psychologists Press, 1970
18. Chance RE, Moon NE, Johnson MG: Human pancreatic polypeptide (HPP) and bovine pancreatic polypeptide (BPP). In *Methods of Hormone Radio-Immunoassay*. Jaffe BM, Behrman HR, Eds. New York, Academic Press, 1979, p. 657–672
19. Gonder-Frederick LA, Cox DJ, Bobbitt SA, Pennebaker JW: Blood glucose symptom beliefs of diabetic patients: accuracy and implications. *Health Psychol* 5:327–341, 1986
20. Mokan M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, Gerich J: Hypoglycemia unawareness in insulin-dependent diabetes mellitus. *Diabetes Care* 17:1397–1403, 1994
21. Bjørgaas M, Vik T, Sand T, Birkeland K, Sager G, Vea H, Jorde R: Counterregulatory hormone and symptom responses to hypoglycaemia in diabetic children. *Diabet Med* 14:433–441, 1997
22. Kinsley BT, Widom B, Simonson DC: Differential regulation of counterregulatory hormone secretion and symptoms during hypoglycemia in IDDM. *Diabetes Care* 18: 17–26, 1995
23. Weinger K, Jacobson AM, Draelos MT, Finkelstein DM, Simonson DC: Blood glucose estimation and symptoms during hyperglycemia and hypoglycemia in patients with insulin-dependent diabetes mellitus. *Am J Med* 98:22–31, 1995
24. Hepburn DA, Deary IJ, Munoz M, Frier

BM: Physiological manipulation of psychometric mood factors using acute insulin-induced hypoglycaemia in humans. *Pers Individ Diff* 18:385–391, 1995
25. Amiel SA, Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS: Rate of glucose fall does not affect counterregulatory hormone responses to hypoglycemia in normal and diabetic humans. *Diabetes* 36:518–522, 1987
26. Jones TW, Boulware SD, Kraemer DT, Caprio S, Sherwin RS, Tamborlane WV: Independent effects of youth and poor diabetes control on responses to hypoglycemia in children. *Diabetes* 40:358–363, 1991
27. Amiel SA, Simonson DC, Sherwin RS, Lauritano AA, Tamborlane WV: Exaggerated epinephrine responses to hypoglycemia in normal and insulin-dependent diabetic children. *J Pediatr* 110:832–837, 1987
28. Hepburn DA, Deary IJ, Frier BM, Patrick AW, Quinn JD, Fisher BM: Symptoms of acute hypoglycemia in humans with and without IDDM: factor-analysis approach. *Diabetes Care* 14:949–957, 1991
29. Pennebaker JW: Psychological factors influencing the reporting of physical symptoms. In *The Science of Self-Report: Implications for Research and Practice*. Stone AA, Turklan JS, Bachrach CA, Jobe JB, Kurtzman HS, Cain VS, Eds. Mahwah, NJ, Lawrence Erlbaum Associates, 2000, p. 299–315
30. Gray JA, McNaughton N: *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System*. Oxford, UK, Oxford University Press, 2000
31. Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. *J Clin Invest* 91:819–828, 1993
32. Pennebaker JW: *The Psychology of Physical Symptoms*. New York, Springer-Verlag, 1982
33. Janssen MMJ, Snoek FJ, Heine RJ: Assessing impaired hypoglycemia awareness in type 1 diabetes. *Diabetes Care* 23:529–532, 2000
34. Pohl J, Frohnau G, Kerner W, Fehm-Wolfsdorf G: Symptom awareness is affected by the subjects' expectations during insulin-induced hypoglycemia. *Diabetes Care* 20:796–802, 1997
35. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W: Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 24: 637–642, 2001
36. Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W: A biopsychobehavioral model of risk of severe hypoglycemia. *Diabetes Care* 20:661–669, 1997
37. Polonsky WH, Davis CL, Jacobson AM, Anderson BJ: Correlates of hypoglycemic fear in type I and type II diabetes mellitus. *Health Psychol* 11:199–202, 1992