REVIEW ARTICLE

A Biopsychobehavioral Model of Risk of Severe Hypoglycemia

LINDA GONDER-FREDERICK, PHD
DANIEL COX, PHD
BORIS KOVATCHEV, PHD
DAVID SCHLUNDT, PHD
WILLIAM CLARKE, MD

Severe hypoglycemia (SH) is a significant problem for many patients with type I diabetes and presents a major barrier to optimal diabetes control. A critical task facing diabetes research is to understand, predict, and reduce the risk of SH in insulin-treated patients. The purpose of this article is to propose a biopsychobehavioral model of SH risk that integrates and extends previously proposed models. Current biological and psychological models of SH risk, which focus on hormonal counterregulation and symptom awareness, are reviewed. The limitations of these models are also discussed, including their failure to recognize important psychological and behavioral processes that contribute to SH risk. Specifically, the biopsychobehavioral model includes patients' decision-making, judgment, and behavioral responses as significant predictors of SH risk. The proposed model is comprised of seven steps: *1*) physiological and behavioral precursors to low blood glucose (BG), *2*) low BG occurrence, *3*) hormonal and neurological responses to low BG, *4*) awareness of symptoms caused by hormonal and neurological changes, *5*) detection of low BG, *6*) decision-making and judgment, and *7*) behavioral response. The model has several advantages, including the ability to mathematically calculate the transitional probabilities from each step to the next as well as the ability to describe SH risk in both hypoglycemia-aware and hypoglycemia-unaware patients. Research findings supporting the biopsychobehavioral model are presented, and its empirical and clinical implications are discussed.

One of the biggest challenges in contemporary diabetes management is finding ways to achieve optimal diabetes control without increasing the risk of severe hypoglycemia. In both the Diabetes Control and Complications Trial (DCCT) and its European counterpart, intensive therapy and improved metabolic control increased the frequency of severe hypoglycemia at least threefold (1,2). For example, DCCT patients on intensive therapy experienced an average of 62 episodes of severe hypoglycemia per 100 patient-years, while patients using conventional therapy experienced an average of 19 episodes per 100 patient-years. Severe hypoglycemia (SH) is not defined as a specific blood glucose (BG) value, but rather is defined symptomatically. That is, SH occurs when BG becomes so low that neuroglycopenia renders the patient unable to self-treat because of mental confusion, incoordination, lethargy, or unconsciousness. From the patient's perspective, SH has multiple frightening and negative consequences, including unpleasant symptoms, cognitive impairment, social embarrassment, accidents, and even death. Because the threat of these negative sequelae can discourage both patients and clinicians from pursuing intensive therapy, SH has been described as the major barrier to improved diabetes control (3,4).

Thus, our ability to achieve optimal diabetes control depends to a large extent on our ability to identify and reduce those risk factors that increase the likelihood of SH. Current biological and psychological models of SH risk focus on the importance of hormonal counterregulatory processes and the recognition of early warning hypoglycemic symptoms (3–5). However, these models do not consider many other important factors that contribute to the risk of SH. Specifically, they fail to consider the influence of factors such as patient judgment and decision-making processes, behavioral choices and habits, and situational characteristics. The purpose of this review is to propose a biopsychobehavioral model of SH that attempts to integrate the diverse and complex biological, psychological, and behavioral processes that contribute to the generation of SH in type I diabetes. Research findings that support the hypothesized model are also reviewed. In many ways, the biopsychobehavioral model does not differ from previous models of SH risk but rather is an extension and expansion of these perspectives. For this reason, we begin with a brief review of current biological and psychological models.

THE BIOLOGICAL MODEL OF SH RISK

— Research based on the biological model focuses on describing the physiological changes that occur with hypoglycemia and how these determine risk for SH. From this research, we know that SH does not occur randomly, but is associated with several risk factors. These include intensive insulin therapy, tight glycemic control, autonomic neuropathy, a history of SH, frequent mild hypoglycemia, and reduced hypoglycemic symptoms (3,6–9). All of these risk factors appear to be related to what Cryer (3) has termed "hypoglycemia-associated autonomic failure" or a reduction in the hormonal counterregulation response to low BG (3). When counterregulation is compromised, epinephrine secretion in response to low BG is suppressed or delayed, as are its associated autonomic warning symptoms (e.g., trembling and sweating). Thus, BG may fall more precipitously, and symptoms can be dampened or delayed, which significantly reduces the likelihood of early treatment to prevent SH.

Figure 1 presents a simplified illustration of the biological model. In this model, low BG (step 1) can be followed by either adequate or comprised hormonal counter-

From the Departments of Psychiatric Medicine (L.G.-F., D.C., B.K.) and Pediatrics (W.C.), University of Virginia Health Sciences Center, Charlottesville, Virginia; and the Department of Psychology (D.S.), Vanderbilt University, Nashville, Tennessee.

Address correspondence and reprint requests to Linda Gonder-Frederick, PhD, Behavioral Medicine Center, Box 223, University of Virginia Medical Center, Charlottesville, VA 22908.

Received for publication 4 June 1996 and accepted in revised form 11 November 1996.

BG, blood glucose; BGAT, blood glucose awareness training; DCCT, Diabetes Control and Complications Trial; SH, severe hypoglycemia.

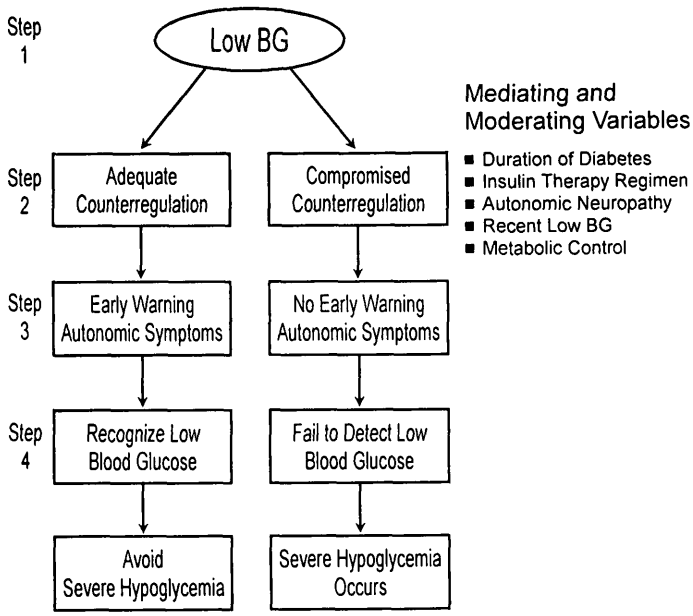

Figure 1—*The biological model of SH risk.*

regulation (step 2). (Note that in the biological model and the remainder of this manuscript, a BG level <3.9 mmol/l [70 mg/dl] is considered to be low.) If counterregulation is not compromised, the biological model assumes that early warning autonomic symptoms will occur (step 3) and be perceived (step 4). Therefore, the patient is likely to recognize their low BG and take appropriate self-treatment action to avoid SH. If counterregulation is compromised and autonomic symptoms are reduced or delayed, the probability of failing to detect and treat low BG increases, as does the probability of SH. As Fig. 1 shows, the probabilities of low BG occurrence and adequate hormonal counterregulation are determined by a number of mediating and moderating variables, such as insulin regimen, metabolic control, and autonomic neuropathy. There are other important biological risk factors, such as insulin sensitivity and the difficulty of matching normal insulin secretion pharmacologically, that are not included in the simplified illustration in Fig. 1.

Thus, in the biological model, integrity of hormonal counterregulatory response is the primary determinant of SH risk. Integrity of hormonal counterregulation was once thought to be relatively static for a given patient, but it has recently been shown to vary across time and situation. For example, the occurrence of even a mildly low BG (<3.9 mmol/l) can dampen or delay epinephrine secretion and autonomic symptoms with subsequent low BG levels for up to 72 h (10,11). Conversely, the scrupulous avoidance of mild hypoglycemia for a few days appears to improve counterregulation and increase symptoms (12–14). These findings suggest that integrity of hormonal counterregulation is not a dichotomous phenomenon as depicted in Fig. 1, but is better described as a continuum.

LIMITATIONS OF THE BIOLOGICAL MODEL

— Although this biological model has greatly advanced the understanding of iatrogenic hypoglycemia, research has also shown that many SH episodes cannot be explained by this model and that SH frequently occurs in the absence of risk factors associated with compromised counterregulation and reduced autonomic symptoms. During the DCCT, for example, 23% of SH episodes occurred in the conventional treatment group, not in the intensive therapy group (6). The best predictors of SH in the DCCT (insulin dose, history of SH, diabetes duration, and glycosylated hemoglobin) accounted for only 8.5% of these episodes. Additionally, the DCCT reported that ~50% of the documented episodes of SH were preceded by perceived symptoms.

Recently, we prospectively tracked SH episodes for 1 year in 78 patients classified as hypoglycemia-aware or -unaware by standard clinical criteria (15). As expected, hypoglycemia-unaware patients had significantly more SH episodes than hypoglycemia-aware patients. However, 16% of the hypoglycemia-unaware patients did not experience SH, while 26% of the hypoglycemia-aware patients did. A recent European study using a similar prospective method found an even higher rate of SH in hypoglycemia-aware patients (9). Thus, there must be other risk factors, in addition to those that alter hormonal counterregulation and autonomic symptomatology, that are important predictors of SH.

SOMATIC SELF-REGULATION THEORY AND THE BIOPSYCHOLOGICAL MODEL

— From a psychological perspective, health care behaviors are viewed within the framework of somatic self-regulation theory (16,17). This theoretical framework emphasizes the fundamental role of symptom perception and attribution in determining self-treatment behavior. Health care behavior is conceptualized as a negative-feedback control system, in which subjective symptoms provide the feedback necessary for self-regulation (17–19). Research shows that even when objective measurement of physiological status is possible (e.g., BG self-tests), people still tend to trust and rely strongly on subjective symptoms to make self-treatment decisions (16,20). For example, patients rarely test their BG to confirm their symptoms before treating themselves for hypoglycemia, even when testing supplies are available (20).

Self-regulatory theory does not assume a one-to-one correspondence between the occurrence of physical symptoms and the accurate interpretation of these symptoms. Rather, symptom perception and attribution are viewed as complex cognitive processes that are mediated by many factors, such as attention mechanisms, knowledge, past experiences, beliefs, and motivation. Because of these individual and situational factors, symptom perception and attribution are not always accurate. For example, a person deeply engaged in an enjoyable activity is far less likely to notice a mild headache than a person engaged in a boring task (17). Similarly, people recently diagnosed with a chronic disease are likely to begin reporting numerous symptoms, even when their condition is asymptomatic (16).

Figure 2 shows the biopsychological model of hypoglycemia, derived from self-regulatory theory, which attempts to inte-

grate the biological and psychological processes that determine the detection of hypoglycemia (5). Briefly, the model states that when low BG occurs, the resulting physiological responses (step 1), including hormonal counterregulation and neuroglycopenia, cause autonomic and neuroglycopenic symptoms (step 2), such as trembling and difficulty concentrating. If these symptoms are detected and interpreted accurately (steps 3 and 4), the probability of avoiding SH increases. As in other self-regulatory models, there is not a one-to-one correspondence among symptom occurrence, symptom awareness, and accurate detection. The probability of accurately recognizing hypoglycemia can be altered at every step of the model by mediating or moderating variables. For example, low BG may produce sweating (step 2), but a person engaged in strenuous manual labor or exercise may not perceive the additional sweating (step 3) or may not attribute the additional sweating to low BG (step 4).

While the model in Fig. 2 expands the biological model, it still fails to consider the many complex psychological and behavioral processes that occur after a patient recognizes that BG is low. Rather, the model assumes that if hypoglycemic symptoms are interpreted accurately, appropriate self-treatment will follow. This, unfortunately, is often not the case. Even if symptoms are recognized, patients may delay or fail to treat their low BG for many reasons, for example, to avoid social embarrassment or stopping an enjoyable activity or because food is not available. If treatment is delayed or neglected, there is increased risk that neuroglycopenia will become so severe that self-treatment is impossible because of mental confusion and disorientation. Thus, judgment and decision-making after symptom perception and low BG detection can determine whether or not SH is avoided. In addition, the model in Fig. 2 does not include the diabetes self-treatment decisions and behaviors that are often the causes or precursors of low BG. For example, skipping meals or snacks greatly increases the likelihood of low BG. In spite of their importance as determinants of SH risk, patient judgments and behaviors have been virtually ignored empirically.

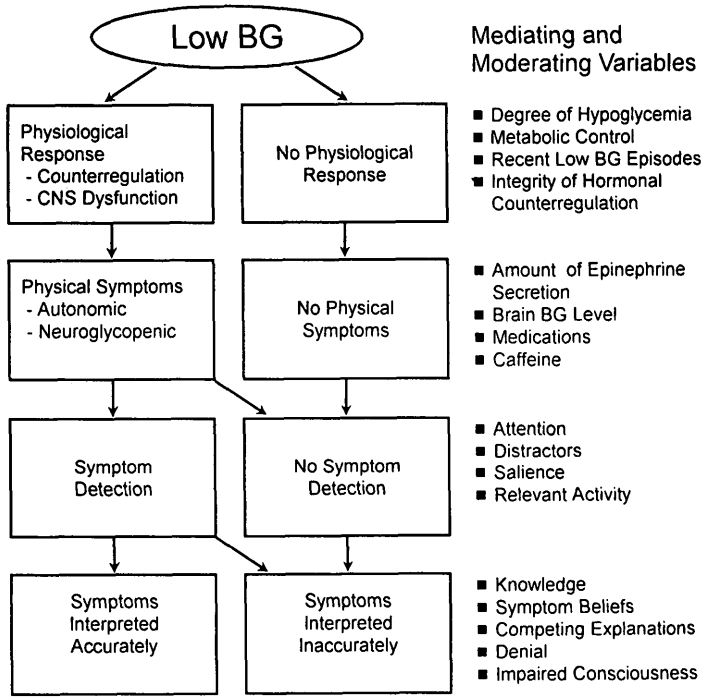

Figure 2—*The biopsychological model of hypoglycemia detection. CNS, central nervous system.*

A BIOPSYCHOBEHAVIORAL MODEL OF SH RISK— Figure 3 illustrates the biopsychobehavioral model of SH risk, which attempts to provide a more comprehensive description of the biological, psychological, and behavioral processes that interact to determine SH risk. The model includes seven steps and describes the possible transitions from one step to the next, which are indicated by arrows. Steps 2–5 of the biopsychobehavioral model are identical to the steps proposed in previous biological and psychological models. As Fig. 3 shows, however, this model also includes precursor self-treatment behaviors that increase the probability of low BG episodes, as well as the judgment and behavioral processes that follow hypoglycemia detection. Briefly, the model proposes that when behavioral and/or biological precursors (step 1) lead to low BG (step 2), physiological responses, such as hormonal counterregulation and neuroglycopenia, either occur or do not occur (step 3). If physiological responses occur and cause symptoms, a person may or may not detect them (step 4) and, even if symptom awareness occurs, detection of hypoglycemia may or may not occur (step 5). If hypoglycemia is recognized, then a patient may or may not make appropriate decisions (step 6). Finally, even if a patient decides to take appropriate action, behavioral implementation may or may not occur (step 7).

Although Fig. 3 does not list mediating and moderating variables, it is assumed that the transition to each step of the model depends on a number of biological, psychological, social, and situational factors. For example, it is assumed that any of the mediating and moderating variables in Figs. 1 and 2 can determine the outcome of steps 2–5 in Fig. 3. The biopsychobehavioral model also assumes that personality variables play a pivotal role in determining SH risk. Certainly, we would expect that personality tendencies would influence diabetes management decisions (step 1), processes of risk appraisal (step 6), and appropriateness of behavioral response to low BG (step 7). One well-documented personality determinant is fear of hypoglycemia (21), defined as the extent to which an individual *1*) worries about the occurrence of hypoglycemia and its negative consequences and *2*) engages in behavior to avoid hypoglycemia and its negative consequences. Fear of hypoglycemia tends to be higher in patients who have experienced frequent or traumatic hypoglycemic episodes, as well as in patients who score high on measures of neuroticism and general anxiety (21–23). Fear of hypoglycemia can influence SH risk at several steps of the biopsychobehavioral model. For example, patients with high levels of fear may alter their diabetes treatment to minimize the likelihood of hypoglycemia (step 1),

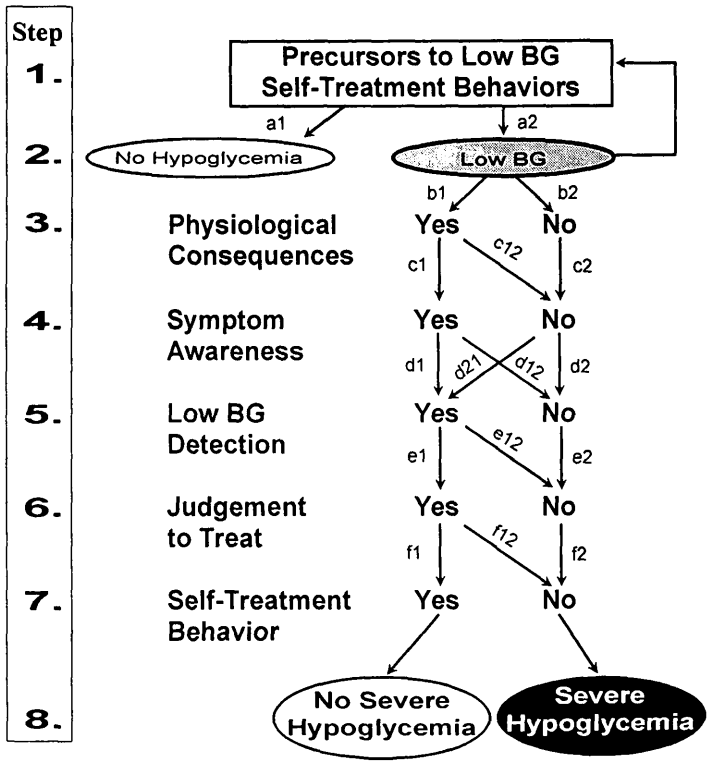

Figure 3—*The biopsychobehavioral model.*

including maintaining higher BG levels in certain situations. They may also treat low BG levels prematurely or overtreat themselves (steps 6 and 7). In contrast, patients with little or no fear may make riskier decisions, such as delaying treatment until BG is quite low or undertreating (steps 6 and 7). Fear of hypoglycemia and neuroticism can also influence hypoglycemic symptom awareness and low BG detection (steps 4 and 5). Patients with decreased symptom awareness worry more about hypoglycemia, and patients who worry more have more difficulty distinguishing symptoms of anxiety from those caused by low BG (23; A.E. Gold, K.M. MacLeod, B.M. Frier, I.J. Deary, unpublished observations).

The example of fear of hypoglycemia and its potential impact on transition from each step to the next points out an important feature of the biopsychobehavioral model. SH risk can increase or decrease at any step of the model, depending on the influence of relevant mediating or moderating factors on the transitions from each step to the next. This reflects the clinical reality that there is no single cause of SH, but rather numerous pathways that can lead patients to "get into trouble" because of hypoglycemia. Although counterregulation and symptom awareness are still considered critical, the ultimate occurrence or avoidance of SH is also determined by patient judgment and behavior. For this reason, the model can be used to describe SH risk in both hypoglycemia-aware patients and those with reduced symptoms. Another important feature of the biopsychobehavioral model is that it is a mathematical model. This means that each step can be operationalized and measured and that the transitions from one step to the next can be described as mathematical probabilities. Thus, the model can be tested empirically. From a clinical perspective, the primary goal of the biopsychobehavioral model is to minimize the probability of SH with one very important constraint: SH risk should be decreased without jeopardizing metabolic control.

EMPIRICAL SUPPORT FOR THE BIOPSYCHOBEHAVIORAL MODEL

— In this section, we will explore each step of the biopsychobehavioral model in more detail and examine research findings that support the hypothesized model. Many of these findings come from recent studies conducted by our research group, which included 78 type I patients, half of whom were classified as hypoglycemia-aware and half of whom were classified as hypoglycemia-unaware by standard clinical criteria (15). In that study, patients used a Psion-250 handheld computer that included a programmed assessment procedure. Patients completed this computerized assessment during their normal routines, several times each day, over a period of 3–4 weeks for a total of 50 entries. Figure 4 shows a flow chart of the computer's programmed assessment, which required patients to *1*) complete a symptom rating scale; 2) perform four neuropsychological tests (mental math, verbal fluency, visual vigilance, and reaction time); *3*) rate their perceived performance impairment on each test; 4) record whether they had recently had more, less, or their usual amount of insulin, food, and exercise; 5) estimate their current BG level; *6*) indicate whether they would currently raise their BG or drive a car based on their estimate; and 7) enter their measured BG.

The handheld computer also contained an internal calendar and clock, which recorded the date and time of each trial and the time that elapsed between the prompt to "measure BG" and data entry. These "validity checks" help to identify invalid data, such as numerous trials done in a short period of time. The handheld-computer data allow us to test many of the steps of the proposed biopsychobehavioral model. For example, the data provide information about precursors to low BG at step 1 (changes in insulin, food, and exercise), low BG occurrence at step 2 (measured BG), autonomic and neuroglycopenic symptoms at step 4 (symptom ratings, neuropsychological tests, impairment ratings), low BG detection at step 5 (estimated BG), and judgment at step 6 (decision to drive or to raise BG).

Step 1

As Fig. 3 indicates, most precursors to low BG are self-treatment behaviors that result in an excess of insulin relative to food intake and metabolic demand. For example, one common precursor is performing vigorous exercise without decreasing insulin and/or increasing food intake. In addition to self-treatment behaviors, there are also physiological precursors, such as insulin sensitivity, that influence the likelihood of low BG. However, our research indicates that behavioral precursors play a key role in the majority of hypoglycemic episodes.

We recently examined the extent to which frequency of low BG could be predicted by diabetes management behaviors (25). The 78 patients described above, who were classified as hypoglycemia-aware or -unaware, experienced an average of 6.9 low BG levels (<3.9 mmol/l) over a 3- to 4-week period, with the number of episodes ranging from 1 to 24 across patients. As expected, hypoglycemia-aware patients had fewer low BG readings than did hypoglycemia-unaware patients. However, in both patient groups low BG episodes were likely to be preceded by changes in routine diabetes management, such as taking more insulin, eating less food, or doing more exercise. Logistic regressions showed that each of these precursor behaviors significantly predicted ($P < 0.001$) the number of low BG levels experienced by individual patients. In fact, taken together, these behaviors predicted 86.5% of the hypoglycemic episodes.

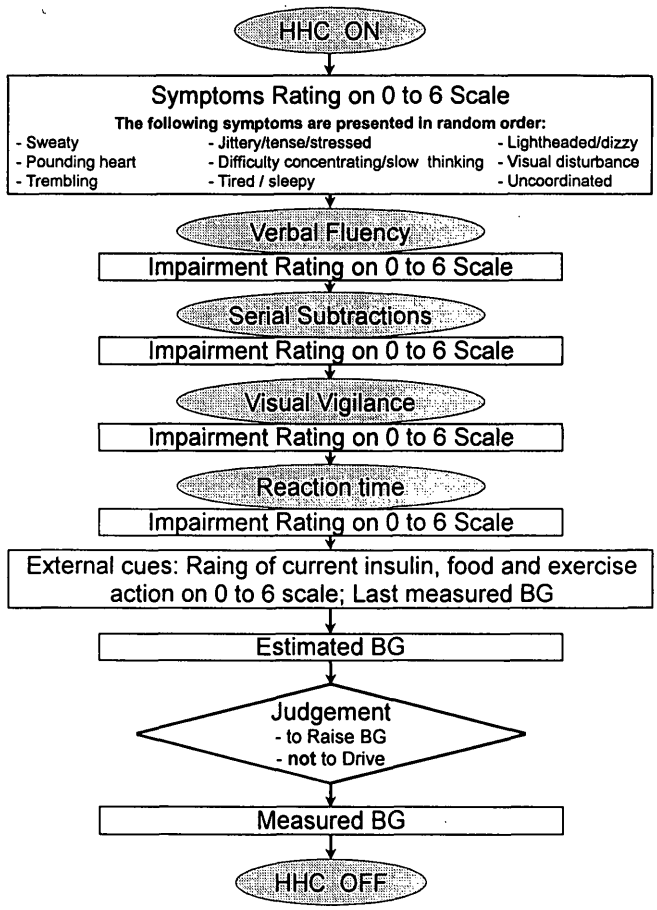

Figure 4—*Handheld-computer (HHC) survey program.*

Step 2

Although precursors do not always cause low BG at step 2, as indicated by the a1 arrow, they greatly increase its probability (a2 arrow). Even if low BG does not lead to SH immediately, it can increase the probability of future SH. In the above study, frequency of SH in both hypoglycemia-aware and hypoglycemia-unaware patients could be predicted by the number of low BG levels experienced and the variability of BG fluctuations (26). As discussed earlier, findings from several recent studies suggest that the occurrence of even mildly low BG can decrease or delay hormonal counterregulation and autonomic symptoms for several days afterward (3,10–12). The biopsychobehavioral model takes into account the fact that low BG is both the outcome of precursor events and a risk factor for future hypoglycemia in and of itself. The arrow from step 2 to step 1 in Fig. 3 reflects this dual function.

Step 3

The occurrence of low BG at step 2 can produce numerous physiological changes at step 3, as shown by the b1 arrow. For the purposes of describing SH risk, the most important are hormonal counterregulation and neuroglycopenia. It is also possible for low BG to occur and not produce these physiological changes (b2 arrow); for example, if counterregulation is compromised, significant epinephrine increase may not occur. Unlike the other steps of the model, step 3 can only be tested in an inpatient setting, where blood hormone levels and other physiological parameters can be measured frequently. Numerous inpatient studies have demonstrated that in patients with compromised counterregulation, epinephrine secretion is delayed or absent, BG falls more rapidly, and BG nadir is lower (7,8,27–29). Hypoglycemia's impact on brain function can also vary across patients and appears to be determined, in part, by repeated exposure to low BG levels and mechanisms in the central nervous system that adapt to frequent hypoglycemia (30,31).

Step 4

Whether or not symptoms are perceived at step 4 obviously depends largely, but not entirely, on the physiological responses that occur at step 3. A patient who adequately counterregulates clearly has an increased probability of perceiving symptoms, as indicated by the c1 arrow, while the patient with compromised counterregulation is less likely to perceive early warning symptoms (c2 arrow). Both hormonal counterregulation and neuroglycopenia have widespread physiological effects, and for this reason, hypoglycemic symptoms tend to be highly idiosyncratic (5,32,33). Thus, two patients, both of whom adequately counterregulate, can perceive different symptoms; for example, one may feel nervous while the other feels trembly. As in the model in Fig. 2, physiological changes are a prerequisite to symptoms but are not necessarily followed by symptom awareness (c12 arrow). The patient who is watching television, for example, may be less likely to recognize mild cognitive impairments.

The proposed biopsychobehavioral model diverges somewhat from other models of hypoglycemic risk in that mild neuroglycopenia and its symptoms are seen as important contributors to low BG detection and the avoidance of SH. Most biological models do not consider neuroglycopenic symptoms to be useful cues to mild hypoglycemia, primarily because they are

believed to occur only when BG becomes very low. Therefore, by the time neuroglycopenic symptoms occur, mental function is assumed to be so compromised that patients are unable to recognize or respond to their hypoglycemia. In contrast to this perspective, our research shows that *1*) measurable deterioration in task performance can occur with very mild (3.6 mmol/l) hypoglycemia (34), *2*) patients can subjectively recognize their impairment (5), *3*) neuroglycopenic and autonomic symptoms begin at similar BG thresholds (5,28), and 4) neuroglycopenic symptoms are just as likely to be empirically related to hypoglycemia as are autonomic symptoms (5,28,35). Symptoms of early neuroglycopenia include difficulty concentrating, slowed thinking, incoordination, and lightheaded or dizzy feelings. Subjectively, patients notice that they are slower and have to exert more effort than usual to perform mental and motor tasks. These early neuroglycopenic symptoms may be especially important for patients with reduced autonomic symptoms. In addition, unlike autonomic symptoms, neuroglycopenic symptoms may not be dampened or delayed after low BG episodes (36).

One final assumption about symptom awareness in this model is that hypoglycemia awareness is not viewed as an "all or none" phenomenon but rather on a continuum. Our research has demonstrated that while patients classified as hypoglycemia-unaware have fewer symptoms than hypoglycemia-aware patients, it is not the case that they have no symptoms. Rather, most of these patients have what we term "reduced hypoglycemic awareness" (15). In addition, as we discussed above, hypoglycemic awareness can vary across time and situations for a given individual not only because of recent antecedent low BG but also because of factors such as caffeine and alcohol consumption (37,38).

Step 5

As Fig. 3 shows, the transitional relationships between symptom awareness and low BG detection can be complex, with several possible outcomes. Our research has consistently found that patients on average fail to detect ~50% of their low BG episodes (15,39–41). Obviously, symptom awareness increases the probability of accurately detecting low BG, as shown by the d1 arrow. In fact, our data indicate that when symptoms are perceived, patients recognize that their BG is low ~74% of the time (38). However, this also means that even when symptoms are perceived, patients fail to recognize that their BG is low 26% of the time. The fact that symptom awareness does not guarantee low BG detection is shown by the d12 arrow. Failure to recognize low BG in these instances can occur because of misattribution of symptoms, i.e., attributing hypoglycemic symptoms to some other cause. For example, a patient who experiences mild hypoglycemia after exercise may attribute dizziness and sweating to physical exertion and not to low BG. Other factors can lead to misattribution of symptoms, for example, lack of knowledge about symptoms, inaccurate symptom beliefs, and psychological denial (5,42).

Failure to perceive symptoms at step 4 dramatically decreases the probability of detecting low BG (d2 arrow). Our data show that in the absence of perceived symptoms, patients fail to detect low BG levels 70% of the time. It is also possible for low BG detection to occur in the absence of patient symptom awareness (d21 arrow). This happens when other sources of feedback are available, such as self-testing or other people who recognize hypoglycemic symptoms. Clinical experience suggests that a significant number of hypoglycemic episodes are first recognized by family members. However, the detection of hypoglycemia by family members and others does not necessarily lead to accurate detection by the patient. Family members report that patients often deny that they are symptomatic or hypoglycemic. This can occur secondary to neuroglycopenia, which interferes with the perceptual and cognitive processes involved in symptom recognition. However, other personality and psychological processes may contribute to this type of symptom denial, such as unwillingness to admit either to treatment "mistakes" that caused hypoglycemia or to inability to recognize symptoms. Interpersonal processes may also contribute, as when patients and family members "act out" other unresolved conflicts and power struggles within the context of hypoglycemic episodes.

Step 6

The recognition that BG is low—whether by symptoms, self-testing, or feedback from others—sets into motion a variety of judgment and decision-making processes. When hypoglycemia is accurately detected, the probability that a patient will decide that immediate treatment is needed increases (e1 arrow). However, it is also possible for patients to recognize low BG but fail to decide to take appropriate action (e12 arrow). Judgments about whether and how to respond to hypoglycemia depend largely on cognitive processes of risk assessment. The patient must ask: "Do I need to self-treat? How quickly do I need to respond? Is my BG likely to continue falling?" Patients must also weigh perceived risk against the perceived costs or consequences of immediate treatment (e.g., embarrassment, inconvenience, weight gain). Handheld-computer data have shown that even when patients accurately detect low BG, 15.5% of the time the patients indicate that they do not intend to take any action (B.K., D.C., L.G.-F., W.C., unpublished observations). Patients vary greatly in the degree of hypoglycemia they will tolerate before considering themselves to be at risk and in need of treatment. In our studies, target BG levels for self-treatment range from 2.5 to 6.4 mmol/l.

After assessing their current risk level, patients must decide what actions to take, such as what type and amount of food to eat. However, patients also need to make important risk assessments about their current or planned activities, for example whether or not to continue driving or to pick up the crying baby from its crib. Poor judgment at this step of the model can have tragic results, including fatal automobile accidents or other physical injury. Nonetheless, our data show that when patients recognize that their BG is low, they would still choose to drive 25.6% of the time (B.K., D.C., L.G.-F., W.C., unpublished observations). These preliminary data support our hypothesis that even if symptom awareness and low BG detection occur, judgment and decision-making play a pivotal role in determining risk for SH and its negative sequelae.

As discussed earlier, the outcome of this process of risk assessment and judgment making will be determined in part by intrapersonal variables, such as personality traits, coping styles, and past experiences. For example, highly anxious patients or patients with a high level of fear of hypoglycemia should make more conservative risk appraisals and may even overestimate risk level, leading to premature or overtreatment. In contrast, other patients, such as those who have never experienced SH or its negative consequences or those who engage in high-risk behaviors in others areas of life,

might underestimate risk and make decisions that increase the probability of SH.

Step 7

Once a patient decides to self-treat, the probability of implementing this plan of action behaviorally and the probability of successfully avoiding SH increase (f1 arrow). It is also possible for a patient to decide that treatment is needed but be unable to carry out that decision behaviorally (f12 arrow). For example, there may be no readily available carbohydrate, or the patient may become too neuroglycopenic to respond effectively. In those instances when patients underestimate their current risk and fail to self-treat (f2 arrow), the likelihood of SH greatly increases. For obvious methodological reasons, it is extremely difficult to assess patients' behavioral responses to specific hypoglycemic episodes empirically. However, we are currently attempting to do this in an inpatient study in which subjects drive a sophisticated driving simulator during insulin infusion. As their BG level is lowered from 4.5 to 2.6 mmol/l over a 20- to 30-min period, subjects are given the option to stop driving and/or treat themselves whenever they feel they should.

SUMMARY AND IMPLICATIONS

— In spite of its graphic presentation in Fig. 3, the biopsychobehavioral model is not conceptualized as a linear and unidirectional process. Steps in the model may be repeated or may occur out of order. For example, symptoms (step 4) may continue to be perceived after treatment (step 7), which could result in a decision (step 6) to perform a self-test (step 5) or repeat self-treatment (step 7). In fact, patients will ideally perform a self-test soon after self-treatment to ensure that they are out of danger. We should also emphasize that the model describes a recurrent cyclical process in which the ultimate occurrence or avoidance of one SH episode determines, to some extent, the likelihood of future low BG precursors and SH. For example, a patient who exercises without eating extra carbohydrate and becomes severely hypoglycemic may change future behavior, thereby reducing the likelihood of exercise-induced hypoglycemia.

The research findings we have reviewed clearly support our hypothesis that patient decision-making, judgment, and behavior should be included in models attempting to predict and explain SH risk. For example, our data indicate that most hypoglycemic episodes occur because patients have changed their diabetes management routine in such a way that overinsulinization is more likely. While symptom awareness increases the likelihood of avoiding SH, our data demonstrate that patients often fail to recognize that their BG is low, even when symptoms occur. Even when patients recognize their low BG, they may decide not to self-treat because of personality and situational factors that influence risk assessment and judgment. Thus, it appears that it is not uncommon for patients to make self-treatment decisions that increase their risk for SH and negative consequences. The patient population participating in these studies should be taken into consideration when interpreting these results. These patients, who were willing to participate in an extended and demanding research protocol, may have been more motivated and committed to improving their diabetes management than a random sample of the type I diabetic population. Given this, we might expect to find an even higher rate of high-risk decisions and behaviors in other patient groups.

The biopsychobehavioral model has important implications for research and clinical efforts aimed at reducing SH risk. First, the model highlights the importance of diabetes education as an intervention to reduce SH risk. Education should decrease the frequency of high-risk diabetes management behaviors (step 1), increase the likelihood of accurately recognizing low BG symptoms (steps 4 and 5), and improve self-treatment decisions and behavioral responses (steps 6 and 7). Treatment regimens designed to virtually eliminate low BG episodes appear to improve counterregulation and increase symptom awareness, which should decrease SH risk (13,14). It remains to be seen, however, whether such regimens can be maintained over the long term without sacrificing optimal diabetes control. From our model's perspective, these regimens intervene to reduce SH risk at steps 1–4. In addition, continuous subcutaneous insulin infusion appears to reduce the frequency of SH, perhaps because insulin delivery is more flexible and predictable and better mimics normal insulin secretion (43,44). Thus, continuous subcutaneous insulin infusion intervenes at step 1 of our model, reducing the likelihood of overinsulinization.

Another clinical intervention that significantly decreases the frequency of SH is blood glucose awareness training (BGAT). BGAT is a behavioral program that improves patients' ability to recognize BG symptoms (steps 4 and 5), as well as their ability to predict and avoid (steps 1 and 7) hypo- and hyperglycemia (44,46). BGAT, which does not jeopardize metabolic control, also reduces the frequency of automobile accidents and diabetic ketoacidosis and improves psychological status.

In our clinic, we use the biopsychobehavioral model as a guide for assessing individually relevant problem areas in patients who experience recurrent SH. Following the model, we assess *1*) regimen characteristics and self-treatment behaviors likely to lead to hypoglycemia, *2*) frequency of low BG, *3*) awareness of autonomic and neuroglycopenic symptoms, *4*) ability/willingness to recognize low BG episodes (including frequency of self-monitoring of blood glucose), *5*) risk appraisal and decision-making tendencies, and *6*) typical behavioral responses to low BG. We encourage other clinicians to use similar assessment procedures, for example, structured interviews with patients after episodes of SH to determine which risk factors contributed to that particular episode. From an empirical perspective, the biopsychobehavioral model more accurately reflects the complex and multifactorial nature of SH risk. Although by no means comprehensive, the model offers a systematic framework for integrating and interpreting research from different disciplines. The model may also encourage scientists to consider a wider range of risk factors in their experimental designs. We believe that taking a broader conceptual and interdisciplinary approach to the problem of hypoglycemia, such as the proposed biopsychobehavioral model, will enhance our ability to understand, predict, and reduce SH risk.

Acknowledgments — This manuscript was supported in part by National Institutes of Health Grants DK28288 and RR00847.

We wish to acknowledge the valuable contributions of Cheralee Phillips, BA; Diana Julian, MA; William Polonsky, PhD; and the nursing staff of the General Clinical Research Center of the University of Virginia Medical Center.

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