Hypoglycemia

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Iatrogenic hypoglycemia causes recurrent physical and recurrent or even persistent psychosocial morbidity, and some mortality, in patients with insulin-dependent diabetes mellitus (IDDM), and in some patients with non-insulin-dependent diabetes mellitus (NIDDM) (1,2). There is now compelling evidence, from the Diabetes Control and Complications Trial (DCCT), that metabolic control delays the development and progression of retinopathy, nephropathy and neuropathy in IDDM, albeit at the expense of an increased frequency of treatment-induced hypoglycemia (3). These findings will almost assuredly provide further impetus to patients and health care providers to attempt to maintain plasma glucose levels as close to the nondiabetic range as possible. If so, hypoglycemia will become an even more common problem for patients with diabetes in the near future.

Clinical hypoglycemia, largely in IDDM, is the focus of this review. We first summarize selected background information. Then, the clinical issues are discussed in more detail. Our intent is to define the current body of knowledge and to point out relevant areas where knowledge is lacking. Obviously, the latter are substantial since hypoglycemia is a major unsolved problem for the diabetes community. However, our intent is to be selective rather than comprehensive. The interested reader is referred to a recently published book on diabetes and hypoglycemia (1) for further details and for other points of view.

LITERATURE REVIEW AND ANALYSIS

BACKGROUND

CNS effects of hypoglycemia

The brain is dependent on a continuous supply of glucose from the circulation (4). The brain depends almost exclusively on glucose for its energy production under physiological conditions. (A frequently cited exception is prolonged fasting, when ketone bodies can provide as much as two-thirds of brain energy metabolism [5], but this is hardly a physiological condition.) Indeed, glucose oxidation normally accounts for almost all of the oxygen consumed by the brain (6), and the brain respiratory quotient approaches 1.0 (4).

The brain cannot synthesize glucose and it can store only a few minutes' supply as glycogen (4). Therefore, it must continuously derive its predominant metabolic fuel from the circulation. Furthermore, the brain cannot quickly increase its extraction of glucose. Normally, the rate of carrier-mediated (GLUT1) facilitated glucose transport across the blood-brain barrier down a concentration gradient exceeds the rate of brain glucose metabolism. Thus, transport is not rate-limiting. However, if the plasma glucose concentration falls below a critical level (or if brain glucose metabolism increases substantially) glucose transport from blood to brain becomes rate-limiting to brain glucose metabolism and, thus, brain function and survival (4).

Hypoglycemia, sensed in the brain itself (7) and in peripheral structures such as the liver (8), triggers a series of central nervous system (CNS) mediated changes (9–11). These include, but are not limited to, changes in hormone secretion, symptoms, cognitive dysfunction, coma and, ultimately, death. The stepped hypoglycemic clamp technique has been used to determine the glycemic thresholds for (i.e., the glucose concentration required to trigger) several of these responses to hypoglycemia (9,10). Mean arterialized venous glycemic thresholds in nondiabetic humans are shown in Fig. 1. Decrements in plasma glucose within the physiological range decrease insulin secretion (9,11). Glucose decrements just below the physiological range increase the secretion of glucose counterregulatory hormones (9,10). Further glucose decrements elicit symptoms of hypoglycemia (9,10), while even further decrements cause cognitive dysfunction (10). As will become apparent later, however, these glycemic thresholds are dynamic rather than static.

Given the survival value of maintenance of the plasma glucose concentration, it is hardly surprising that physiological mechanisms that very effectively prevent or correct hypoglycemia (11) have evolved. Indeed, hypoglycemia is a

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; DCCT, Diabetes Control and Complications Trial; CNS, central nervous system; IQ, intelligence quotient.

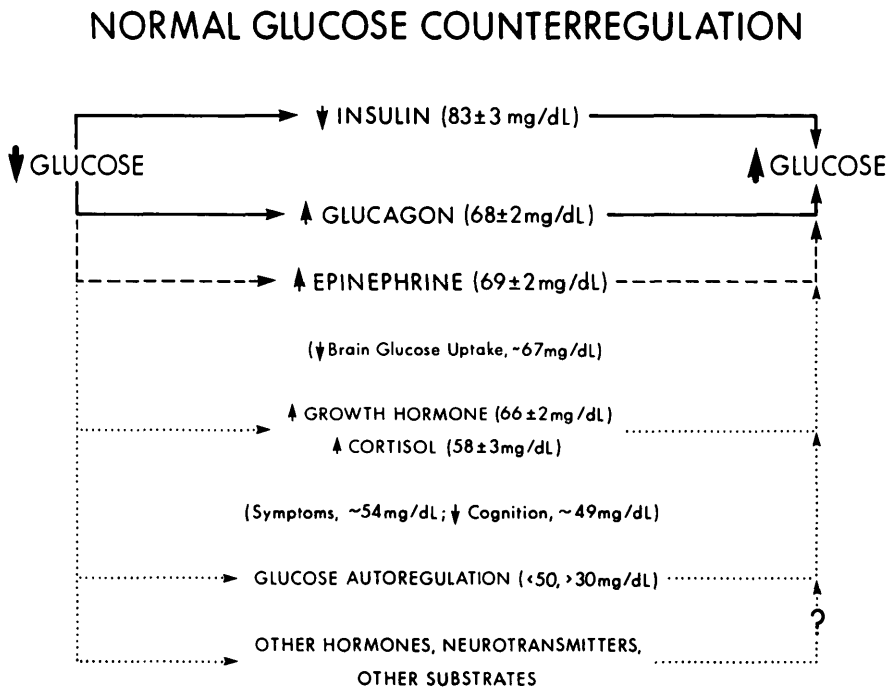

Figure 1—*Schematic representation of the physiology of glucose counterregulation. Mean (±SE) arterialized venous glycemic thresholds for the various responses/changes are also shown (9–11). From Cryer (11).*

distinctly uncommon clinical event except in persons who use drugs, such as insulin or sulfonylureas, that lower the plasma glucose concentration (12). As discussed later, however, it is more than just the use of these glucose-lowering drugs that explains the occurrence of hypoglycemia in patients with diabetes.

Extra-CNS effects of hypoglycemia

Although the effects of hypoglycemia on the brain per se are potentially most devastating, hypoglycemia elicits an array of extra-CNS effects. The vast majority of the recognized responses are, however, CNS mediated. Some are clearly adaptive, some are seemingly maladaptive, and many are teleologically obscure. They include changes in hormone secretion including those relevant to the prevention and correction of hypoglycemia, summarized later, and the autonomic discharge that results in hemodynamic changes and neurogenic (autonomic) symptoms.

The changes in hormone secretion during hypoglycemia include decrements in insulin and increments in glucagon, epinephrine, growth hormone and cortisol (9–12). The physiological relevance of these is summarized shortly. Other hormones—corticotropin-releasing hormone, adrenocorticotropin, prolactin, vasopressin, oxytocin, pancreatic polypeptide, renin, aldosterone, atrial natriuretic hormone, gastrin, and parathyroid hormone, among others—and several neuropeptides have been reported to be released during hypoglycemia (13).

Both the sympathochromaffin (adrenomedullary and sympathetic neural) and parasympathetic components of the autonomic nervous system are activated during hypoglycemia (14). This underlies the hemodynamic changes (15) and the neurogenic (autonomic) symptoms (16). The typical hemodynamic pattern includes an increase in heart rate with widening of the pulse pressure (increments in systolic and decrements in diastolic blood pressure) with no change in mean blood pressure. Increments in cardiac output are the result of increments in stroke volume as well as heart rate. Increased muscle sympathetic nerve activity (14) presumably underlies net vasodilatation, but the sympathetic response is differentiated. Splanchnic blood flow has been reported to be increased (17) or unchanged (18) while renal blood flow is reduced (15). Hypoglycemia also produces lymphocytosis, probably epinephrine mediated, and neutrophilia, at least in part cortisol mediated (19).

Physiology of glucose counterregulation

The physiological mechanisms that normally prevent or correct hypoglycemia have been reviewed (11) and discussed in detail (20) recently and are summarized in Fig. 1.

The principles of glucose counterregulation are three. First, the prevention or correction of hypoglycemia is the result of both dissipation of insulin and activation of glucose counterregulatory (glucose-raising) systems. Second, whereas insulin is the dominant glucose-lowering factor, there are redundant glucose counterregulatory factors. There are multiple glucose-raising factors that collectively constitute a fail-safe system that prevents or minimizes failure of the entire system despite failure of one, or perhaps more, of its components. Third, there is a hierarchy among the glucoregulatory factors. There is a ranked series of counterregulatory factors, some more critical to the effectiveness of the fail-safe system than others, that act in concert with decrements in insulin to prevent or correct hypoglycemia.

The first defense against falling plasma glucose concentrations is decreased insulin secretion; this occurs with glucose decrements within the physiological range, normally at a glycemic threshold of ~83 mg/dl (4.6 mM) (9,11). However, biological glucose recovery from hypoglycemia can occur despite an approximately twofold peripheral hyperinsulinemia and in the absence of portal hy-

Table 1—*Range of frequencies (%) of individual symptoms of hypoglycemia reported in eight series of patients with insulin-treated diabetes mellitus*

Sweating	47–84	Dizziness	11–41
Trembling	32–78	Headache	24–36
Weakness	28–71	Anxiety	10–44
Visual disturbance	24–60	Nausea	5–20
Hunger	39–49	Difficulty concentrating	31–75
Pounding heart	8–62	Tiredness	38–46
Difficulty with speaking	7–41	Drowsiness	16–33
Tingling around mouth	10–39	Confusion	13–53

From Hepburn (31).

poinsulinemia (21). Thus, additional (glucose counterregulatory) factors must be involved. Critical glucose counterregulatory systems are normally activated at a glycemic threshold of ~68 mg/dl (3.8 mM), well above the thresholds for symptoms of hypoglycemia (~54 mg/dl [3.0 mM]) and those for cognitive dysfunction (~49 mg/dl [2.7 mM]) (9,10). Among the glucose counterregulatory factors, glucagon plays a primary role. Epinephrine is not normally critical, but it becomes critical to glucose counterregulation when glucagon is deficient. Because hypoglycemia develops or progresses when the secretion of both glucagon and epinephrine is deficient and insulin is present (22–29), these three hormones stand high in the hierarchy of redundant glucoregulatory factors. Other factors, such as growth hormone and cortisol in defense against prolonged hypoglycemia, are known to be involved. Furthermore, glucose autoregulation (hepatic glucose production as an inverse function of ambient glucose levels independent of hormonal and neural glucoregulatory factors) may be operative during severe hypoglycemia, and fatty acid elevations appear to mediate, in part, the effects of epinephrine (11). Other hormones, neurotransmitters, and other metabolic substrate effects may also be shown to be involved. Nonetheless, all of these latter factors must stand low in the hierarchy of redundant glucose counterregulatory factors since, despite their actions, hypoglycemia develops or progresses when both glucagon and epinephrine are deficient and insulin is present.

HYPOGLYCEMIA IN IDDM

Classification

For descriptive purposes treatment-induced hypoglycemia can be divided into three categories: *1*) asymptomatic (biochemical) hypoglycemia, *2*) mild-moderate symptomatic hypoglycemia, and *3*) severe hypoglycemia. Detection of asymptomatic hypoglycemia requires measurement of the plasma/blood glucose concentration. The patient is able to recognize and self-treat mild-moderate symptomatic hypoglycemia. Severe hypoglycemia, as defined in the DCCT protocol, is temporarily disabling and, therefore, requires the assistance of another person (30).

While clinically and pedagogically useful, this classification is arbitrary. Typically, the plasma glucose level falls through asymptomatic and mild-moderate symptomatic phases before reaching levels that produce severe clinical hypoglycemia. As discussed later, however, the absence of symptoms, or the failure of the patient to recognize symptoms or to interpret symptoms as indicative of developing hypoglycemia, is a major determinant of the frequency of severe hypoglycemia (30).

Clinical manifestations

Because treatment-induced hypoglycemia is most often self-diagnosed, there is a critical reliance on symptoms. Spouses, other family members, friends, or coworkers, as well as medical personnel, also use signs to recognize hypoglycemia.

Symptoms. Patients with diabetes report an array of symptoms during hypoglycemic episodes. Many of these, compiled by Hepburn (31) from eight published series (32–39), are listed in Table 1. The variety of reported symptoms and particularly the wide range of their frequencies in the different reports are noticeable. The latter likely represents differences in patient populations, ascertainment methods, and symptom assessment techniques. The difficulty in providing a short list of reliable symptoms is compounded by the fact that symptoms of hypoglycemia are often idiosyncratic (40–42). In a given patient a certain symptom or symptom complex is often reliable for that patient but not for another patient. Thus each individual patient must learn to recognize the individual symptoms that most reliably suggest developing hypoglycemia to him or her.

Although it has been suggested that hypoglycemic symptom patterns may differ in patients with NIDDM treated with oral agents (33), this remains to be established. It appears that the hypoglycemic symptom patterns of insulin-treated NIDDM and IDDM are the same (43).

It is conventional to divide the symptoms of hypoglycemia into two categories (16,44). *1*) Neuroglycopenic symptoms are those that result directly from brain glucose deprivation. Behavioral and cognitive changes are examples, as are coma and seizure. *2*) Neurogenic (or autonomic) symptoms are those that result from perception of physiological changes caused by the autonomic (adrenomedullary, sympathetic neural and parasympathetic neural) discharge triggered by hypoglycemia. It could be reasoned that this division is misleading because the autonomic discharge is ultimately the result of neuroglycopenia. Nonetheless, the division is clinically useful as discussed later. Parenthetically, it is imprecise to refer to neurogenic symptoms as a group as "adrenergic." As discussed later, some are mediated by catecholamines (adrenergic), but others are mediated by acetylcholine (cholinergic).

Table 2—*Neurogenic and neuroglycopenic symptoms of hypoglycemia*

Neurogenic	Neuroglycopenic
Shaky/tremulous	Difficulty thinking/confused
Heart pounding	Tired/drowsy
Nervous/anxious	Weak
	Warm
Sweaty	Difficulty speaking
Hungry	Incoordination
Tingling	Odd behavior
Blood sugar low (awareness of hypoglycemia)	(Coma, seizure, death)

Table is derived largely from Towler et al. (16).

It is conceivable that some might be mediated by peptides (peptidergic). Therefore, the term neurogenic, or autonomic as some prefer (31), is more appropriate (44).

While many symptoms are readily characterized as neurogenic or neuroglycopenic, others have been more difficult to classify, and there has been some debate about these (31). Three approaches to such classification have been taken. *1*) A physiological approach based on the physiological mechanism (neurogenic or non-neurogenic) thought to underlie a given symptom (45). 2) Factor analysis to identify statistical clusters of symptoms coupled with the physiological approach to deduce the mechanism of a given cluster (46–48). 3) A pharmacological approach not unlike that used, in part, to define physiological mechanisms in the past but in this instance using adrenergic and cholinergic antagonists to attempt to block both awareness of and individual symptoms of hypoglycemia (16). With these approaches a consensus, albeit not quite complete, is emerging (16).

Major neurogenic and neuroglycopenic symptoms of hypoglycemia are listed in Table 2. All three methods indicate that the symptoms of "shaky/tremulous," "heart pounding," and "sweaty" are neurogenic (16,45,48). Factor analysis and the pharmacological method indicate that "hungry" is a neurogenic symptom (18,48). The pharmacological method indicates that "nervous/anxious," not assessed with the other methods, is a neurogenic symptom (16). The symptom of "tingling" was found to be neurogenic with the latter method (16); it did not fit in either category by factor analysis (47). As deduced from the pharmacological method and from factor analysis, "difficulty thinking/confused" and "tired/drowsy" are neuroglycopenic symptoms. Variously classified as neurogenic (46) or unclassified (47) by factor analysis, the symptom of "weak" was found to be neuroglycopenic with the pharmacological method (16) as was the symptom of "warm." The latter was classified as neurogenic in one factor analysis report (46) but not included in the others (47,48). The symptom "difficulty speaking" was found to be neuroglycopenic by factor analysis (48); it was not a significant symptom of hypoglycemia in the pharmacological study (16). The symptoms of "incoordination" and "odd behavior" were classified as neuroglycopenic by factor analysis (48); these were not assessed in the pharmacological study (16). Finally, neither "headache" nor "nausea" were found to be significant symptoms of hypoglycemia in the pharmacological study (16), and these did not fall into either the neurogenic or neuroglycopenic categories on factor analysis (48).

The neurogenic symptoms "shaky/tremulous," "heart pounding," and "nervous/anxious" are reduced substantially by adrenergic blockade (with the nonselective α-adrenergic antagonist phentolamine plus the nonselective β-adrenergic antagonist propranolol) during hypoglycemia (16). Thus, these are adrenergic neurogenic symptoms of hypoglycemia. This conclusion is entirely consistent with earlier data (45) indicating that patients with cervical spinal cord transections, and thus no sympathochromaffin system outflow from the CNS, do not exhibit these symptoms (49–51). Since bilaterally adrenalectomized (52,53) and splanchniectomized (54) individuals do not report palpitations during hypoglycemia, these are probably normally mediated by epinephrine secreted from the adrenal medullae. On the other hand, since such patients do report tremor during hypoglycemia (53,54), the latter is probably mediated by norepinephrine released from sympathetic nerves as well as by circulating epinephrine (45,55).

In contrast, the neurogenic symptoms of "sweaty," "hungry," and "tingling" are not reduced by adrenergic blockade during hypoglycemia but are reduced substantially by panautonomic blockade that includes the muscarinic cholinergic antagonist atropine (16). Thus, these are predominantly cholinergic neurogenic symptoms of hypoglycemia. The conclusion that these are neurogenic symptoms is entirely consistent with earlier data (45) indicating that patients with cervical spinal cord transections (49–51) and those who had undergone bilateral adrenalectomy (52,53) or splanchniectomy (54) do not report these symptoms during hypoglycemia. The conclusion that "sweaty" is a cholinergic symptom was expected since the diaphoretic response to hypoglycemia is mediated by cholinergic sympathetic nerves (45,55).

Awareness of hypoglycemia is largely, perhaps exclusively, the result of the perception of neurogenic symptoms (16). This finding is relevant to the clinical syndrome of hypoglycemia unawareness as discussed later. Interestingly, awareness is largely the result of the perception of cholinergic, rather than adren-

ergic, symptoms. Towler et al. (16) found that subjects' scoring of the symptom "blood sugar low" during hypoglycemia was not reduced significantly by adrenergic blockade but was reduced substantially (~70%) by panautonomic blockade (phentolamine and propranolol plus atropine).

Signs. In contrast to the patient, who relies on neurogenic cues, behavioral or cognitive changes, which are manifestations of neuroglycopenia, most often prompt recognition of hypoglycemia by observers of the patient. This is done informally by a family member, friend, or co-worker, and by a more formal mental status examination by medical personnel. Diaphoresis and pallor are common findings. Tachycardia and a widened pulse pressure are supportive but are often too subtle to provide strong clues to the diagnosis.

Diagnosis

Hypoglycemia is best documented by Whipple's triad: symptoms compatible with hypoglycemia, a low plasma glucose concentration, and relief of symptoms after the plasma glucose concentrations is raised (56). While devices for self-monitoring of blood glucose are not precise, particularly at low plasma glucose concentrations (57), they are invaluable in the management of IDDM outside of a hospital environment since they permit estimation of the glucose level and thus documentation of hypoglycemia (as well as euglycemia or hyperglycemia). Because of the imprecision of these devices and because the glycemic thresholds for symptoms may lie at higher plasma glucose concentrations in patients with poorly controlled IDDM (58,59) as discussed later, it is not appropriate to use a single glucose value to define hypoglycemia. If suggestive symptoms are present the glucose level should be estimated, if possible. If the glucose level is not elevated it is reasonable to treat (e.g. for the patient to ingest carbohydrate) and see if the symptoms resolve. If it is not practical to estimate or measure the plasma glucose concentration, it is appropriate to treat on the basis of symptoms alone since the risk of untreated hypoglycemia outweighs the risk of transient hyperglycemia.

While rigid definitions of asymptomatic (biochemical) hypoglycemia are useful for epidemiological studies, more flexible definitions should be used in the management of IDDM. In general, a glucose level of 50 mg/dl (2.8 mM) or less is too low and should prompt treatment. However, in a given patient a level of 60 mg/dl (3.3 mM), 70 mg/dl (3.9 mM), or even higher might well prompt a management decision (e.g. food ingestion, deferral of exercise, change in insulin dose).

Treatment

An episode of treatment-induced hypoglycemia requires urgent treatment and short-term measures to prevent recurrence of hypoglycemia followed by consideration of the probable cause of the episode and any adjustments that should be made to reduce the likelihood of subsequent episodes. Because hypoglycemia is so common and usually readily treated in IDDM, it is sometimes taken too lightly by health professionals, particularly physicians (60).

Most hypoglycemic episodes can be treated effectively by ingestion of glucose per se or carbohydrate-containing juices or soft drinks, candy, crackers, or a meal (61–64). The glycemic response is better correlated with the glucose than the carbohydrate content of the feeding (61). Recent data (64) support the earlier recommendation (61) that a 20-g dose of glucose (0.3 g/kg in children) is advisable. In a model of insulin-induced hypoglycemia in patients with IDDM (64), illustrated in Fig. 2, 10 g of oral glucose raised plasma glucose levels from 60 mg/dl (3.3 mM) to only 97 mg/dl (5.4 mM) over 30 min; the levels started to fall after 60 min and reached placebo levels in <2 h. Twenty grams of oral glucose raised plasma glucose levels from 58 mg/dl (3.2 mM) to 122 mg/dl (6.8 mM) over 45 min, with a greater response at 15 min; again, the levels started to fall after 60 min and approached placebo levels in ~2 h. Clearly, oral glucose is an effective but temporary measure; persistent hypoglycemia generally requires subsequent ingestion of a more substantial meal to prevent recurrent hypoglycemia.

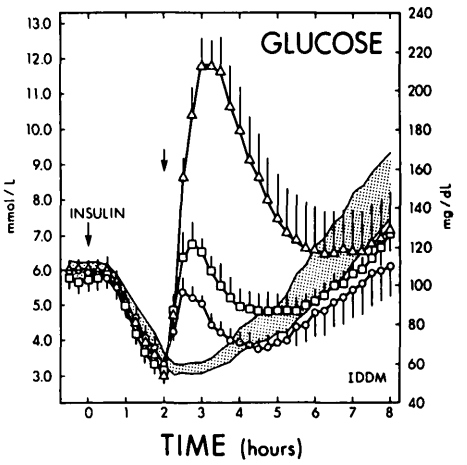

Figure 2—*Mean (±SE) plasma glucose concentrations, in a model of insulin-induced hypoglycemia in patients with IDDM, in response to 10 g (○) and 20 g (□) of oral glucose, 1.0 mg (△) of subcutaneous glucagon, or placebo (stippled area). From Wiethop and Cryer (64).*

When the patient is unable, or unwilling because of neuroglycopenia, to take an oral treatment, glucagon, administered subcutaneously or intramuscularly generally by a spouse, family member, friend or co-worker, is the treatment of choice outside of the hospital setting (60,64–72). Glucagon stimulates hepatic glucose production. It increases both glycogenolysis and gluconeogenesis and is less effective in patients with glycogen depletion. The standard dose is 1.0 mg (15 μg/kg in children), but that can produce substantial hyperglycemia (see Fig. 2). As with oral glucose, the glycemic response is transient; glucose levels begin to fall after ~1.5 h (64). Lower doses would produce less hyperglycemia but would be expected to shorten that interval. Thus, this too is a temporary measure generally requiring subsequent ingestion of food to prevent recurrent hypoglycemia. Vomiting sometimes follows treatment of hypoglycemia with glucagon (60,67).

Glucagon can also be used in the emergency treatment of hypoglycemia by paramedical personnel, although the latter can usually administer glucose intravenously (73). Although the hormone can be used in the emergency room setting (67), intravenous glucose is perhaps more appropriate (60). Intranasal glucagon, with a time course of action comparable to injected glucagon, is a promising practical advance in the out-of-hospital treatment of severe hypoglycemia (74–79).

Intravenous glucose is the standard treatment of severe hypoglycemia in the emergency room setting (60) and, increasingly, by paramedical personnel outside of the hospital (73). The usual dose is 25 g. Aside from occasional difficulty obtaining intravenous access, particularly in an uncooperative neuroglycopenic patient, and instances of phlebitis, there is little to criticize about this rapidly effective therapy. The response, of course, is transient, and subsequent glucose infusion, feeding, or both are required.

Experimental approaches to the treatment of hypoglycemia, based on the pathophysiology of glucose counterregulation in IDDM (2), include oral administration of the amino acid alanine and oral and parenteral administration of the β_2-adrenergic agonist terbutaline (64,80). The glycemic response to alanine is largely attributable to stimulation of endogenous glucagon secretion; the response to terbutaline is attributable to epinephrine-like direct β_2-adrenergic actions as well as stimulation of endogenous norepinephrine release (80). The theoretical advantage of these agents is that, unlike glucose or glucagon, they produce sustained glycemic responses. Therefore, they might be useful in the treatment of mild hypoglycemia or in the prevention of hypoglycemia when food intake is not anticipated over the following several hours (e.g. overnight). However, the clinical utility of these agents remains to be established.

Obviously, as mentioned earlier and discussed later, strategies that reduce the frequency of iatrogenic hypoglycemia are preferable to the treatment of hypoglycemia.

Frequency

Hypoglycemia is a fact of life for people with IDDM. The frequency of severe hypoglycemia can be determined with some precision. That of mild-moderate symptomatic hypoglycemia can be estimated. The frequency of asymptomatic (biochemical) hypoglycemia can only be approximated.

Asymptomatic hypoglycemia. Using seven-point multiple sampling during the day, Thorsteinsson et al. (81) documented the fact that the frequency of hypoglycemia is inversely related to the median plasma glucose concentration regardless of the glucose level used to define biochemical hypoglycemia. At a euglycemic median glucose level of 90 mg/dl (5.0 mM), their data predict glucose levels <54 mg/dl (3.0 mM) ~10% of the time. This prediction is supported by the data of Arias et al. (82). Using continuous blood glucose monitoring throughout a 24-h period, glucose levels <50 mg/dl (2.8 mM) were found in 9 of 10 patients treated to a mean glucose level of 100 mg/dl (5.6 mM). These were not isolated low values. The mean duration of glucose levels <50 mg/dl was ~2.5 h, the longest 7 h. Notably, the patients were aware of only 6 of the 23 episodes (26%).

Asymptomatic hypoglycemia is particularly common during the night (29,83–86). Gale and Tattersall (86) found 22 of 39 patients (56%) with IDDM to have blood glucose levels <36 mg/dl (2.0 mM) during overnight sampling. These episodes lasted >3 h in 17 (77%) of the affected patients. Only 8 (36%) of the 22 patients reported symptoms. Thus, more than one-third of the patients studied had asymptomatic nocturnal hypoglycemia of substantial proportions.

In general, plasma glucose concentrations during the night are directly related to the bedtime (as well as the morning) glucose levels (84,85,87–90). For example, in a study of 135 pediatric patients with IDDM, Shalwitz et al. (90) found that the 10:00 P.M. glucose level was 100 mg/dl (5.6 mM) or less on 48% of nights with subsequent 2:00 A.M. glucose levels of 60 mg/dl (3.3 mM) or less. The risk of hypoglycemia at 2:00 A.M. was about one in four when the 10:00 P.M. glucose level was 100 mg/dl or less. Using hourly sampling during the night, Pramming et al. (84) found even higher rates of nocturnal hypoglycemia in a study of 58 adults with IDDM. They calculated that if the bedtime glucose level was <108 mg/dl (6.0 mM) the risk of nocturnal hypoglycemia was 80%.

Clearly, asymptomatic iatrogenic hypoglycemia is extraordinarily common in patients with IDDM.

Mild-moderate symptomatic hypoglycemia. The best estimates of the frequency of mild-moderate symptomatic hypoglycemia, i.e. symptomatic hypoglycemia not requiring the assistance of another person, are based on data from the Steno Memorial Hospital in Denmark. Pramming et al. (91) studied 411 insulin-treated patients and found that they suffered an average of 1.8 episodes of symptomatic hypoglycemia per week. Extrapolated over a lifetime of IDDM, these data suggest that a given patient suffers several thousand episodes of symptomatic hypoglycemia. While these patients may have been treated aggressively, at a hospital dedicated to the management of diabetes, they were not, as a group, being treated intensively by current criteria. Approximately 75% of the patients were using a "split/mixed" insulin regimen (intermediate and rapid-acting insulin twice daily). Thus, the frequency of mild-moderate symptomatic hypoglycemia might well be even higher in intensively treated IDDM.

Severe hypoglycemia. Reported frequencies of severe treatment-induced hypoglycemia range from 4.5 to 44% of patients per year and from 5 to 140 episodes per 100 patient-years (92). The reasons for the widely discrepant results in these reports (68,91,93–109) are not entirely clear. One suspects factors such as differ-

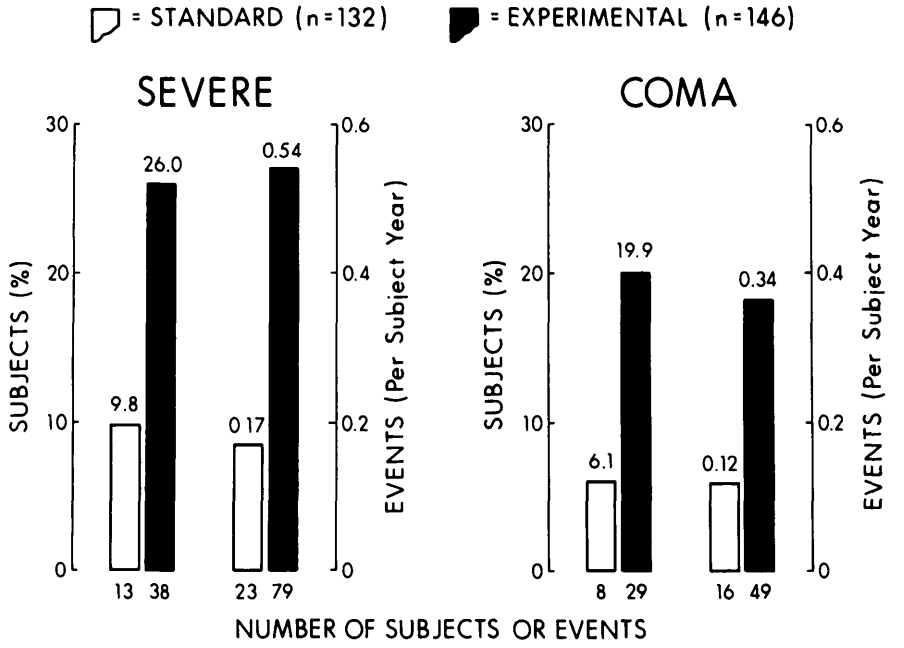

Figure 3—*Proportion of patients affected and event rates for severe hypoglycemia and hypoglycemic coma in the feasibility phase of the Diabetes Control and Complications Trial (DCCT). Data from Ref. 100.*

ent definitions of severe hypoglycemia (one study [99] required loss of consciousness), incomplete ascertainment of severe hypoglycemia (in 1 study [91] only 6% of severe episodes were treated in a hospital emergency room), and wide variance in the degree of metabolic control achieved. In any event, this heterogeneity precludes meaningful meta-analysis of these published data.

The Diabetes Control and Complications Trial (DCCT) provided informative data on the frequency of severe hypoglycemia in IDDM (3,30,100). The DCCT was a large, prospective, randomized trial designed to compare the effects of conventional and intensive therapies on the development and progression of the early vascular and neurological complications of IDDM. In the 1-year feasibility phase of the DCCT (96) 10% of 132 conventionally treated patients suffered at least one episode of severe hypoglycemia; 26% of 146 intensively treated suffered severe hypoglycemia (Fig. 3); 6 and 20%, respectively, suffered hypoglycemic coma. There were 17 and 54 episodes of severe hypoglycemia (and 12 and 34 episodes of hypoglycemic coma) per 100 patient-years in the conventionally and intensively treated groups respectively. In the full scale trial (3)—1,441 patients followed for a mean of 6.5 years with a broadened definition of severe hypoglycemia that included episodes requiring assistance even if treatment was only oral carbohydrate—the event rates were slightly higher, 19 and 62 episodes of severe hypoglycemia per 100 patient-years in the conventionally and intensively treated groups respectively. Thus on average a patient treated intensively to a mean plasma glucose level of 155 mg/dl (8.6 mM) can be projected to suffer an episode of severe, temporarily disabling hypoglycemia, often with coma or seizure, once every 1.6 years. A patient treated conventionally to a mean plasma glucose level of 231 mg/dl (12.8 mM) can be projected to suffer such an episode once every 5 years. These should be viewed as minimum estimates since, based on the experience in the feasibility phase (100), patients with a history of recurrent severe hypoglycemia were excluded from the DCCT. As discussed later, such a history is a major risk factor for subsequent severe hypoglycemia (30). Obviously, these projections obscure the fact that there is heterogeneity among patients. Some suffer repeated episodes of severe hypoglycemia, others suffer none. Nonetheless, the data document a high frequency of severe iatrogenic hypoglycemia in patients with IDDM, especially those attempting to keep plasma glucose levels as close to the nondiabetic range as possible.

Aggressive treatment of IDDM is particularly important before and during pregnancy. However, intensive therapy during pregnancy results in a frequency of severe hypoglycemia comparable to, or even greater than, that in the nonpregnant patient with IDDM (110,111). Indeed, evidence from studies in rats suggests that pregnancy per se impairs physiological defenses against developing hypoglycemia (112).

Impact/Outcome

Physical morbidity. The physical morbidity of an episode of hypoglycemia is largely neurological. It ranges from an array of unpleasant symptoms (Table 2) to impairment of cognitive function, behavioral changes, seizure, and coma. Reversible focal neurological deficits (113) and decerebrate posturing (114) can occur. Generally, these symptoms and signs clear promptly after the plasma glucose concentration is raised. Sometimes recovery is delayed because of cerebral edema (60). Rarely, there are permanent generalized or focal neurological deficits (115). In one such patient a temporal lobe abnormality, perhaps reflecting hypoglycemic brain damage, was found on magnetic resonance imaging (115). Both the depth and duration of hypoglycemia are probably determinants of neurological damage. In monkeys, 5–6 h at a blood glucose of <20 mg/dl (1.1 mM) were re-

quired for the regular production of neurological damage (116).

A major unresolved issue is the extent to which recurrent iatrogenic hypoglycemia produces permanent impairment of brain function over time in patients with IDDM (117,118). There are several reports suggesting that children with early-onset IDDM are at risk for development of cognitive impairment (119–123). In some reports this impairment was associated with previous recurrent hypoglycemia (121,123). Even if one assumes a cause and effect relationship between recurrent iatrogenic hypoglycemia and cognitive impairment in young children, whose brains are still developing, it would be inappropriate to extrapolate that to adults.

There are also several reports suggesting a relationship between recurrent hypoglycemia and cognitive impairment in adults with diabetes (124–129). Langan et al. (127), in a study of 100 adults with IDDM using a retrospective measure of premorbid cognition, found a relationship between recurrent hypoglycemia and lower intelligence quotients (IQ). A relationship between recurrent hypoglycemia and lower verbal IQ was also found when this group of patients was contrasted with a nondiabetic control group (128). On the other hand, despite an increased frequency of severe hypoglycemia in the intensively treated patients in the 5-year Stockholm study (130), no differences in cognitive function between this group and the conventionally treated group were detected. Apparently, that was also the case in the DCCT (3), although the detailed data from the latter have not yet been published. Although the statistical power of the Stockholm study can be questioned, the DCCT data should have sufficient power to detect a meaningful effect.

Psychosocial morbidity. Treatment-induced hypoglycemia can produce recurrent or even persistent psychological morbidity in IDDM (2,91,131–133). That includes both fear of developing hypoglycemia and guilt about that fear (2) and can be a major but unrecognized impediment to achieving glycemic control (132). Pramming et al. (91) found their patients to be as concerned about the development of an episode of severe hypoglycemia as they were about the development of blindness or renal failure. Wredling et al. (133) found patients with recurrent severe hypoglycemia to have higher levels of anxiety and lower levels of happiness on psychological testing. One patient put it poignantly when she wrote, "Being fearful of hypoglycemia, is it wrong to be afraid? If so, I am" (2). Not only was she afraid of hypoglycemia, but she also had been made to feel guilty about that rational fear.

Patients with IDDM are barred from many forms of employment, and hypoglycemia is said to be a major concern of prospective employers (134). Driving performance is demonstrably impaired during hypoglycemia (135). Motor vehicle accidents attributable to iatrogenic hypoglycemia have been documented (3,136–138). Interestingly, however, most studies do not indicate higher accident rates in people with diabetes (137–139). A small age-adjusted increase has, however, been reported (140). The management required to prevent hypoglycemia as well as hypoglycemia itself can intrude on other routine activities such as exercise, sports, and social events (134). At best, an episode of hypoglycemia is a nuisance and a distraction. It can also be embarrassing, and even lead to ostracism or be mistaken for disorderly or unlawful behavior.

Mortality. Unless the event is witnessed and hypoglycemia documented before death, establishing treatment-induced hypoglycemia as a cause of death is extraordinarily difficult (141). Thus, the true iatrogenic mortality rate from hypoglycemia in IDDM is not known. Estimates from large retrospective series range from 2 to 13% of deaths of patients with IDDM (142–147); 4% (143,145) is a commonly quoted figure. Higher (148, 149) and lower (150) rates have been reported in smaller studies. In an analysis of 35 deaths of patients using continuous subcutaneous insulin infusion, Teutsch et al. (151) concluded that hypoglycemia was the probable cause of death in 3; however, the relationship seemed clear in only 1 patient. On the other hand, several others died without a clear explanation. The latter problem was highlighted by an investigation of 50 deaths of patients with IDDM by Tattersall and Gill (152). Two patients had hypoglycemic brain damage, but 22 patients, most of whom retired to bed in apparent good health, were found dead in bed the following morning. The relationship of this phenomenon to hypoglycemia, if any, is unknown.

Regardless of the precise frequency, it is clear that some patients with IDDM die from hypoglycemia. There is an iatrogenic mortality rate.

Pathophysiology and clinical risk factors

Conventional risk factors. Conventional risk factors for treatment-induced hypoglycemia in IDDM are based on the premise that absolute or relative insulin excess is the sole determinant of risk. Because of the imperfections of current insulin replacement regimens, absolute or relative insulin excess must occur from time to time in patients with IDDM. It occurs, for example, when:

1. Insulin doses are excessive, ill-timed, or of the wrong type.
2. The influx of exogenous glucose is decreased, as following a missed meal or snack or during an overnight fast.
3. Insulin-independent glucose utilization is increased (with or without increased insulin absorption), as during exercise.
4. Endogenous glucose production is decreased, as following alcohol ingestion.
5. Sensitivity to insulin is increased, as during effective intensive therapy or after exercise or in patients with hypopituitarism or primary adrenocortical insufficiency.

6. Insulin clearance is decreased, as with progressive renal insufficiency.

However, the extensive experience of the DCCT indicates clearly that these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia in IDDM (30).

The DCCT investigators analyzed 714 episodes of severe hypoglycemia in 216 patients with IDDM (30). Fifty-five percent of the episodes occurred during sleep. Warning symptoms were absent in 36% of the episodes that occurred while the patients were awake. Although 75% of the affected patients were in the intensive therapy group, the proportions of episodes during sleep and without warning symptoms were similar in the two groups. To identify risk factors, the DCCT investigators first compared the frequency of several conventional risk factors on the hypoglycemia day with that on a randomly selected nonhypoglycemia day. Of the factors examined, only a missed meal was more frequent ($P < 0.05$) on the hypoglycemia day. Using a time-dependent proportional hazards statistical model, they then identified five significant risk factors (relative risk, with 95% confidence intervals, shown):

1. Previous severe hypoglycemia 2.5 (1.7–3.9).
2. Duration of IDDM 9–12 years 1.7 (1.1–2.9).
3. Recent hemoglobin A_{1c} 1% lower 1.4 (1.2–1.8).
4. Baseline hemoglobin A_{1c} 1% higher 1.2 (1.0–1.4).
5. Baseline insulin dose 0.1 units/kg higher 1.1 (1.0–1.2).

No other variables added to the risk. The identified factors explained only 8.5% of the variance in episodes of severe hypoglycemia. The conventional risk factors were noticeably absent.

Clearly, we must look beyond the conventional risk factors if we are to understand the pathogenesis of most episodes of severe treatment-induced hypoglycemia in IDDM. The finding that a history of prior severe hypoglycemia was the most powerful predictor of subsequent severe hypoglycemia in the DCCT (30) suggests that there are unique features of patients at high risk. These features likely include those that compromise physiological and behavioral defenses against hyperinsulinemia and developing hypoglycemia (2). Thus, it appears that iatrogenic hypoglycemia is the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in IDDM (2).

Syndromes of compromised glucose counterregulation.

Defective glucose counterregulation. The glucagon secretory response to hypoglycemia becomes deficient in the first few years of IDDM (153,154). This is a selective defect; glucagon responses to other stimuli are largely, if not entirely, intact. Therefore, it cannot be attributed to a structural abnormality of the α-cells per se and must represent a signaling abnormality. The mechanism of this defect is not known, but it is tightly linked to absolute insulin deficiency (155). The deficient glucagon response appears to be absolute; even substantial hypoglycemia does not elicit a glucagon response (156). Because glucagon is normally the primary glucose counterregulatory hormone, as discussed earlier, and a deficient glucagon response to falling plasma glucose concentrations is the rule in patients with IDDM, glucose counterregulation is altered in patients with established IDDM. Yet it appears to be adequate in the first few years of IDDM, perhaps because epinephrine compensates, at least in part.

A reduced epinephrine secretory response to hypoglycemia develops somewhat later in the course of IDDM (154,156). This, too, is selective; epinephrine secretory responses to other stimuli are intact (157). Therefore, the reduced epinephrine response cannot be attributed to a structural lesion of the adrenal medullae or the sympathochromaffin reflex arc that mediates all epinephrine secretory responses, and must represent a regulatory abnormality. In contrast to the reduced glucagon response, the reduced epinephrine response to a given degree of hypoglycemia represents, at least in part, a shift to a higher glycemic threshold. Epinephrine responses can be elicited but lower plasma glucose concentrations are required (156). Thus, after 5–10 years of IDDM most patients have no glucagon responses to hypoglycemia and reduced epinephrine (as well as pancreatic polypeptide) responses to a given degree of hypoglycemia (64, 156).

The semantics of the glycemic threshold concept warrant comment. The rationale for the terms used in this review and elsewhere (156) is as follows. If a lower plasma glucose concentration is required to elicit a given response, the glycemic threshold for that response is elevated, or higher, since a more intense hypoglycemic stimulus is required to elicit that response. Conversely, if a given response occurs at a higher plasma glucose level the threshold for that response is reduced, or lower, since a less intense hypoglycemic stimulus elicits the response.

In the setting of absent glucagon responses, the development of deficient epinephrine responses is a critical event in the pathophysiology of glucose counterregulation in IDDM. Patients with combined deficiencies of their glucagon and epinephrine responses to falling plasma glucose concentrations have defective glucose counterregulation (2, 158–160). When compared with those with deficient glucagon but intact epinephrine responses, they have been shown, in prospective studies, to be at 25-fold or greater increased risk for severe iatrogenic hypoglycemia, at least during intensive therapy (158,159), as illustrated in Fig. 4.

Hypoglycemia unawareness. As many as 50% of patients with very longstanding (>30 years) IDDM (91) and an estimated 25% of patients overall (161) have the clinical syndrome of hypoglycemia unawareness (162–167). Affected patients no longer have the warning neurogenic symptoms that previously allowed them

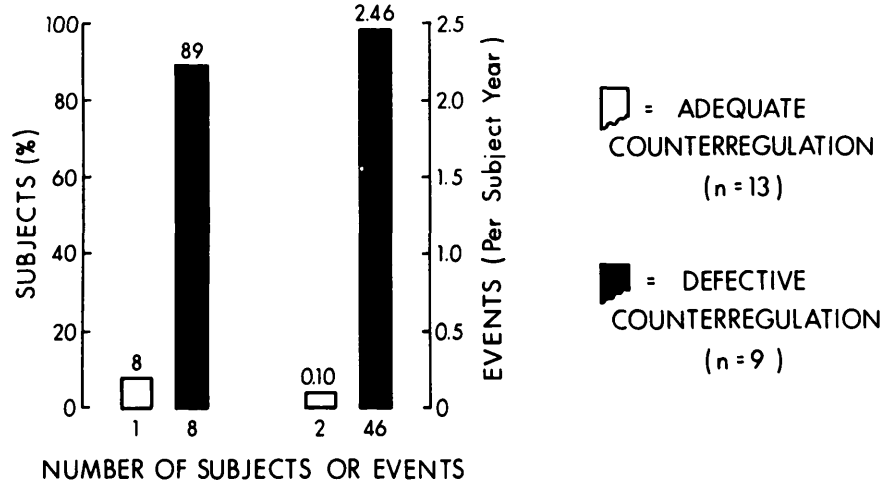

Figure 4—*Proportion of patients affected and event rates for severe hypoglycemia during intensive therapy of patients with IDDM and adequate or defective glucose counterregulation. Data from White et al. (158).*

to recognize developing hypoglycemia and act (e.g. eat) to prevent its progression to severe hypoglycemia. Therefore, the first symptoms are those of neuroglycopenia, and it is often too late for the patients to treat themselves. Patients with hypoglycemia unawareness have elevated glycemic thresholds (lower plasma glucose concentrations required) for autonomic, including epinephrine, as well as symptomatic responses to hypoglycemia (165,167). Patients with histories of hypoglycemia unawareness have been shown, in a prospective study, to be at about sevenfold increased risk for severe iatrogenic hypoglycemia (168), as illustrated in Fig. 5.

Elevated glycemic thresholds during intensive therapy. The first clue that glycemic thresholds for autonomic and symptomatic responses to hypoglycemia are dynamic rather than static was the clinical impression that intensively treated patients with IDDM often tolerate low plasma glucose levels without symptoms. This impression has been amply supported by objective data. During intensive therapy of IDDM that effectively lowers overall plasma glucose levels, glycemic thresholds for autonomic responses and symptoms are elevated (169,170). These responses can be elicited, but lower plasma glucose concentrations are required. Conversely, glycemic thresholds are reduced in patients with poorly controlled IDDM (171). The mechanism(s) of these shifts in glycemic thresholds is not known. However, prolonged (days) hypoglycemia has been shown to increase fractional extraction of glucose into the brain in rats (172). Recent data indicate that 56 h of hypoglycemia of ~50 mg/dl (2.8 mM) between meals is associated with increased glucose extraction into the human brain at a given level of hypoglycemia (173).

It is well established, from the large prospective experience of the DCCT (3,100), that effective intensive therapy results in a threefold increase in the incidence of severe treatment-induced hypoglycemia. However, the extent to which elevated glycemic thresholds for autonomic and symptomatic responses to hypoglycemia contribute to this is not clear. A major as yet unresolved issue is whether glycemic thresholds for cognitive dysfunction during hypoglycemia are also elevated (lower plasma glucose levels required) during intensive therapy. Data on both sides of this issue are available. If the glycemic thresholds for cognitive dys-

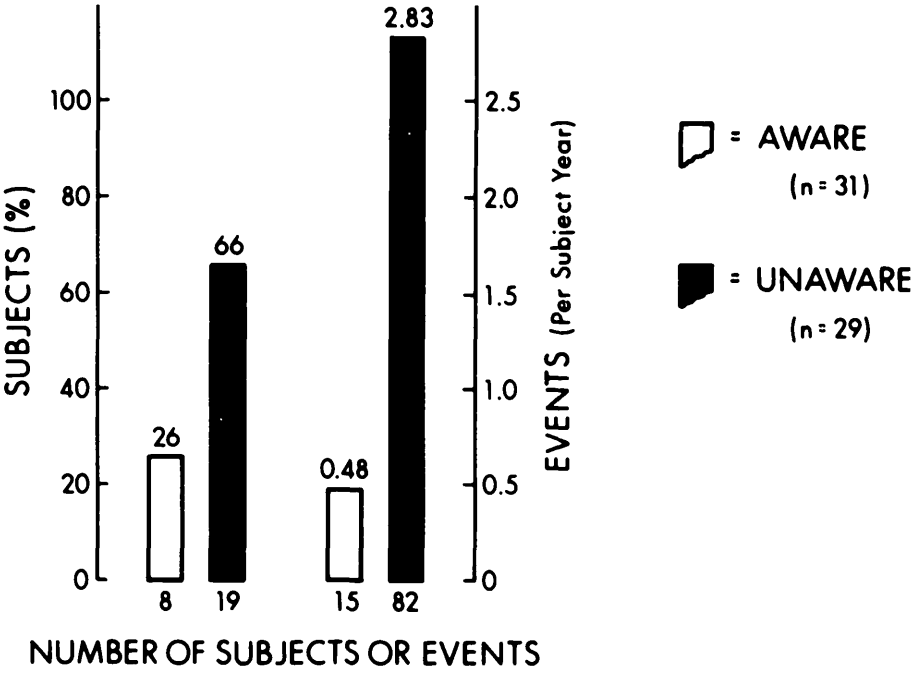

Figure 5—*Proportion of patients affected and event rates for severe hypoglycemia in patients with IDDM and normal or reduced awareness of hypoglycemia. Data from Gold et al. (168).*

function are not elevated, as suggested by some data (174–176), it would be reasonable to suggest that elevated glycemic thresholds for autonomic and symptomatic responses are a major risk factor for iatrogenic hypoglycemia, since neuroglycopenia might precede neurogenic symptoms. If the glycemic thresholds for cognitive dysfunction are also elevated, as suggested by other data (166,177,178), elevated thresholds for autonomic and symptomatic responses might be less detrimental.

Elevated glycemic thresholds following recent hypoglycemia. Recent antecedent hypoglycemia reduces autonomic and symptomatic responses to hypoglycemia in nondiabetic humans (179–181) and patients with IDDM (156,182,183). For example, Heller and Cryer (179) found that a single <2 h episode of afternoon hypoglycemia reduced autonomic (including epinephrine and pancreatic polypeptide) and symptomatic (both neurogenic and neuroglycopenic) responses to hypoglycemia the following morning in nondiabetic subjects. Similarly, Dagogo-Jack et al. (156) found such an episode of afternoon hypoglycemia to cause both elevated glycemic thresholds for autonomic (including epinephrine and pancreatic polypeptide) and symptomatic (both neurogenic and neuroglycopenic) responses and impaired physiological defense against hyperinsulinemia the following morning in patients with IDDM. The potential clinical impact of these findings is discussed later (see *Hypoglycemia-associated autonomic failure*). This effect may explain the observation of Gulan et al. (184) that epinephrine responses to hypoglycemia were reduced after 3 months of intensive therapy of IDDM with subcutaneous compared with intravenous insulin since there were fewer hypoglycemic episodes with the latter.

Elevated glycemic thresholds during β-adrenergic blockade. By blocking the β_2-adrenergic actions of epinephrine, β-adrenergic antagonists impair glucose recovery from experimental hypoglycemia in patients with IDDM (185). This class of drugs also elevates the glycemic threshold (lower plasma glucose levels required) for symptoms in IDDM (186). Since both the counterregulatory effects of epinephrine and awareness of a given level of hypoglycemia are reduced, it is reasonable to suspect that administration of a β-adrenergic antagonist might increase the frequency of iatrogenic hypoglycemia in patients with IDDM. Compelling clinical support for this expectation is lacking, but this issue has not been examined critically in the setting of intensive therapy of IDDM.

Hypoglycemia-associated autonomic failure. As discussed in detail elsewhere (187), the syndromes of defective glucose counterregulation, hypoglycemia unawareness, and elevated glycemic thresholds during intensive therapy (perhaps a result of recent antecedent hypoglycemia) segregate together clinically, are associated with a high frequency of severe treatment-induced hypoglycemia, and share several pathophysiological features. The latter include elevated glycemic thresholds for autonomic responses to hypoglycemia: adrenomedullary (epinephrine), parasympathetic (pancreatic polypeptide), and sympathetic (neurogenic symptoms) responses to a given level of hypoglycemia are reduced (156,187). In the setting of absent glucagon responses, reduced epinephrine responses compromise physiological defense against developing hypoglycemia. Reduced symptomatic responses compromise awareness of developing hypoglycemia and thus the appropriate behavioral response. This line of reasoning led one of us (P.E.C.) to propose the concept of hypoglycemia-associated autonomic failure, of which these three clinical syndromes are examples (187).

The pathogenesis of hypoglycemia-associated autonomic failure is not known, need not necessarily be the same in all of the clinical syndromes of compromised glucose counterregulation, and could be multifactorial even in a given syndrome. Indeed, at a clinical level it is probably best to consider each of the component syndromes summarized earlier as separate, albeit often overlapping, entities, given current lack of a clear understanding of the pathogenesis of each syndrome. However, at an investigative level some insight has been gained. The status of this incomplete puzzle is summarized in the following paragraphs.

Recent antecedent iatrogenic hypoglycemia may well be one factor in the pathogenesis of hypoglycemia-associated autonomic failure. The hypothesis, illustrated in Fig. 6, is that recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure in IDDM and hypoglycemia-associated autonomic failure, by reducing both physiological defense against and symptoms of developing hypoglycemia, results in recurrent severe hypoglycemia thus creating a vicious cycle (187). As mentioned earlier, recent data support two key elements of this hypothesis: Recent antecedent hypoglycemia elevates glycemic thresholds for autonomic and symptomatic responses to subsequent hypoglycemia and impairs physiological defense against hyperinsulinemia in patients with IDDM (156). Furthermore, the phenomenon has been shown to be specific for the stimulus of hypoglycemia; autonomic responses to standing, exercise, and a mixed meal are unaltered by recent antecedent hypoglycemia (188). The phenomenon is not simply the result of prior activation of the system since prior sympathochromaffin system activation (by exercise 90 min earlier) does not reduce the response of that system to subsequent hypoglycemia (188). Finally, hypoglycemia-associated autonomic failure is distinct from classical diabetic autonomic neuropathy (156,187).

Many of these phenomena have also been demonstrated in a study of nondiabetic and diabetic BB/Wor rats (189). It was shown that *1*) antecedent hypoglycemia causes reduced counterregulatory hormone (glucagon and epinephrine) responses to subsequent hypoglycemia in rats, as it does in humans (156, 179–183); 2) the reduced responses induced

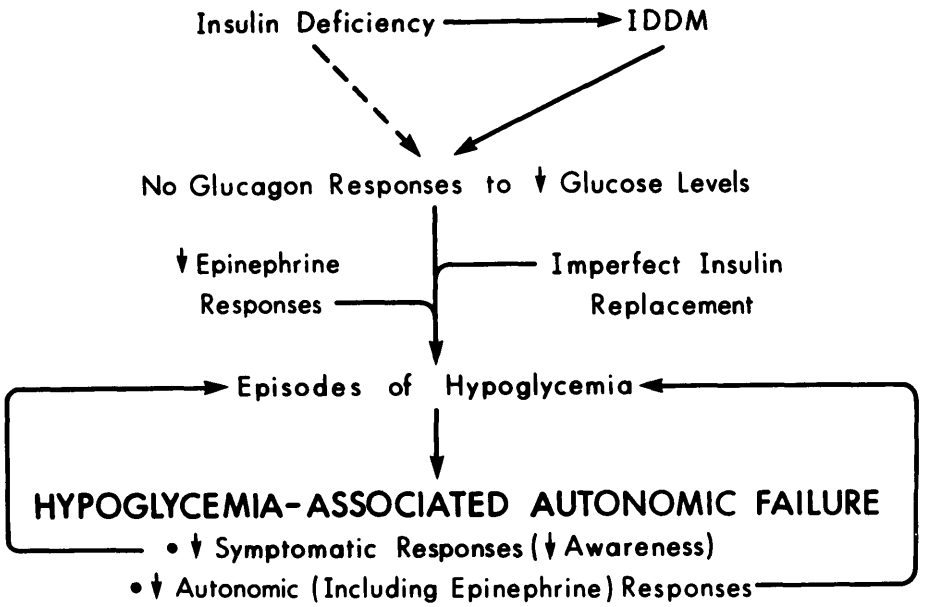

Figure 6—*Schematic diagram of the concept of hypoglycemia-associated autonomic failure in IDDM. From Cryer (187).*

by antecedent hypoglycemia are specific for the stimulus of hypoglycemia in rats, as they are in humans (188); and 3) diabetes per se, in the absence of antecedent hypoglycemia, causes reduced counterregulatory responses to hypoglycemia in rats, as it does in humans (156).

To the extent that recent antecedent hypoglycemia is a causal factor in the pathogenesis of hypoglycemia unawareness, defective glucose counterregulation, or both, relatively short-term scrupulous avoidance of iatrogenic hypoglycemia should reduce the frequency of subsequent iatrogenic hypoglycemia (187). Indeed, a similar phenomenon—elevated glycemic thresholds for counterregulatory hormone responses, symptoms and deterioration of cognitive function—occurs in nondiabetic patients with an insulinoma and is completely reversed following removal of the tumor (190). Furthermore, Fanelli et al. (191) have reported that raising glycemic goals coupled with vigorous attempts to avoid hypoglycemia in intensively treated patients with relatively short-duration IDDM resulted in increased symptomatic, epinephrine, and perhaps glucagon responses to a given level of hypoglycemia 2 weeks and 3 months later. The frequency of hypoglycemic episodes was also reduced. Glycemic control was compromised, but not greatly. These data suggest that, at least in some patients, the syndrome of hypoglycemia unawareness is reversible (191,192). If so, it follows that relatively short periods of scrupulous avoidance of iatrogenic hypoglycemia might reduce the overall frequency of iatrogenic hypoglycemia substantially (192). However, this plausible extrapolation remains to be systematically explored.

Dagogo-Jack et al. (193) confirmed the finding of Fanelli et al. (191) that awareness of hypoglycemia can be restored by scrupulous avoidance of iatrogenic hypoglycemia in patients selected initially for hypoglycemia unawareness. However, they found no change in the (reduced) glucagon, epinephrine, and pancreatic polypeptide responses to hypoglycemia during reversal of unawareness. Thus, it appears that while the syndrome of hypoglycemia unawareness is reversible, that of defective glucose counterregulation may not be reversible (192).

It has also been suggested that treatment with human compared with animal insulin might cause hypoglycemia unawareness in patients with IDDM (194–197). As reviewed elsewhere (198), there are some additional reports seemingly consistent with that suggestion (199–201). However, the bulk of the evidence does not support it (202–210). Notably, Colagiuri et al. (210) performed a prospective, randomized, double-blind, cross-over comparison of treatment with human and porcine insulin in 50 patients who had previously reported reduced awareness of hypoglycemia after transfer from porcine to human insulin. They found no differences in the frequency of hypoglycemia, or in that of hypoglycemia with reduced or absent awareness, during treatment with human or porcine insulin. Thus, it does not appear that treatment with human compared with animal insulin produces clinically important hypoglycemia unawareness.

In summary, although insulin excess of sufficient magnitude can be expected to produce hypoglycemia under any condition, the integrity of the glucose counterregulatory systems, including their effects to both defend against and warn of developing hypoglycemia, determines whether or not therapeutic hyperinsulinemia results in iatrogenic hypoglycemia. Since the risk of treatment-induced hypoglycemia is the result of the interplay of insulin excess and compromised glucose counterregulation, it follows that both of these should be considered in attempts to minimize the frequency of hypoglycemia in IDDM.

HYPOGLYCEMIA IN NIDDM

Hypoglycemia also occurs in patients with NIDDM treated with a sulfonylurea or with insulin. Most of the issues just discussed in relation to IDDM also apply to NIDDM. However, there are some differences. These are pointed out in the paragraphs that follow.

While it has been said that older patients with NIDDM have fewer neurogenic symptoms of hypoglycemia (211),

Hepburn et al. (43) found the symptom patterns to be similar in NIDDM and IDDM patients.

Iatrogenic hypoglycemia appears to be a less frequent problem among patients with NIDDM than those with IDDM (211,212). In one study 20% of sulfonylurea-treated NIDDM patients reported at least one episode of symptomatic hypoglycemia in the preceding 6 months, and 6% reported monthly episodes (213). Rates of sulfonylurea-induced severe hypoglycemia of 1.9–2.5 per 100 patient-years in NIDDM (212,214,215) contrast with those of 19–62 per 100 patient-years in IDDM in the DCCT (3). However, these figures may be misleading. In a preliminary report from a prospective study in which patients whose NIDDM was not controlled with diet were randomly assigned to insulin or sulfonylurea therapy and which included the glycemic goal of a fasting plasma glucose concentration of <144 mg/dl (8.0 mM), the frequencies of symptomatic hypoglycemia over 3 years were 35% in those treated with insulin, 29% in those treated with glyburide, and 12% in those treated with chlorpropamide (216). The frequencies of severe hypoglycemia were 6.6%, 3.7%, and 2.0% respectively. These data suggest that there is a higher risk of severe hypoglycemia with aggressive insulin treatment of NIDDM, and that the frequency of severe hypoglycemia in aggressively treated NIDDM may be higher than previously thought. Nonetheless, the rate of about 1–2% per year (216) is considerably lower than that of ~25% per year in the intensively treated IDDM patients in the DCCT (100). However, Hepburn et al. (43) found the frequency of severe hypoglycemia to be similar in insulin-treated NIDDM and IDDM matched for duration of insulin therapy. Furthermore, with respect to the impact of iatrogenic hypoglycemia, it should be recalled that the number of patients with NIDDM, and thus at risk, is many fold greater than the number of those with IDDM.

Taken together, the data raise the possibility that while iatrogenic hypoglycemia is a less frequent problem in NIDDM as a whole, it approaches that of IDDM in those patients who reach the insulin-deficient end of the spectrum of NIDDM. This possibility warrants further investigation.

In addition to short-term morbidity, it has been estimated that sulfonylurea-induced severe hypoglycemia results in permanent neurological deficits in ~5% of survivors (217) and has a morality rate of ~10% (214,215,217–222).

While it is reasonable to consider many of the risk factors for iatrogenic hypoglycemia in IDDM, discussed earlier, to be relevant to NIDDM, these have been little studied in NIDDM. With respect to the pathophysiology of glucose counterregulation in NIDDM there has been considerable controversy, much of it based on methodological considerations, as nicely reviewed by Heller (223). In a study of predominantly insulin requiring NIDDM, Bolli et al. (224) found a significantly reduced, but certainly not absent, glucagon secretory response to hypoglycemia produced by subcutaneous insulin injection. Growth hormone and cortisol secretory responses were also slightly reduced, the epinephrine response was not different from control values, and the norepinephrine response was slightly increased. Although the burst of glucose production that normally occurs early during hypoglycemia was reduced in the patients with NIDDM, glucose recovery from hypoglycemia was only slightly reduced because of limited glucose utilization. The net result was only a moderate prolongation of hypoglycemia. Thus, although subtle abnormalities are demonstrable, glucose counterregulation does not appear to be markedly defective in patients with NIDDM. It is, of course, conceivable that studies of patients at the insulin-deficient extreme of the spectrum of NIDDM might disclose more substantive defects in glucose counterregulation.

Additional risk factors for iatrogenic hypoglycemia in NIDDM include advancing age, poor nutrition, drug interactions with sulfonylureas, and hepatic or renal disease leading to altered metabolism and excretion of the drugs (211). Among the sulfonylureas, chlorpropamide and glyburide are associated with a higher frequency of hypoglycemia (215,225).

Finally, the treatment of sulfonylurea-induced hypoglycemia in NIDDM differs from that of severe insulin-induced hypoglycemia in some important ways. Because sulfonylurea-induced hypoglycemia can be prolonged and can recur (226,227), hospitalization, with intravenous glucose infusion following initial treatment with glucose injection, is strongly recommended. Glucagon probably should be avoided because it can stimulate endogenous insulin secretion in NIDDM (228). Drugs that inhibit insulin secretion such as diazoxide (229,230) or octreotide (231,232) might be considered, in conjunction with glucose infusion as necessary.

CONCLUSIONS AND CLINICAL PRACTICE RECOMMENDATIONS

THE PROBLEM

Iatrogenic hypoglycemia is a major unresolved problem for many patients with IDDM and some patients with NIDDM. It is, in fact, the limiting factor in the management of diabetes mellitus (2). With documentation of the fact that effective glycemic control makes a difference with respect to long-term complications (3), it is likely that hypoglycemia will become an even more common problem in the future. From this it follows that *1*) this problem should be acknowledged and addressed by all concerned—patients, health care professionals, and the diabetes community as a whole—and 2) research relevant to hypoglycemia, ranging from the study of basic mechanisms to that of applied clinical strategies, should be encouraged.

RELATIVE RISK

The management of diabetes mellitus is empirical in the sense that one ideally attempts to hold plasma glucose concentrations as close to the nondiabetic range as possible as long as one can do so safely in a given patient. Given the currently limited clinical strategies to consistently minimize the frequency of iatrogenic hypoglycemia without compromising glycemic control to a greater or lesser extent, judgments based on relative risk must be made. Some episodes of asymptomatic or mild-moderate symptomatic hypoglycemia are a fact of life, at least in IDDM. However, recurrent episodes of severe, temporarily disabling hypoglycemia are not acceptable. The very real short-term risks outweigh the likely long-term benefits. The ultimate responsibility for guiding patients in this judgment lies with the physician.

MANAGEMENT TECHNIQUES

General

The issue of treatment-induced hypoglycemia, along with other aspects of diabetes care, should be raised in all patient contacts. The patient's views and concerns about hypoglycemia should be sought explicitly by the physician or other health care provider involved.

Therapeutic goals

In the authors' opinion, in many patients application of the principles of intensive therapy coupled with prudent and individualized glycemic targets can minimize the frequency of treatment-induced hypoglycemia without compromising glycemic control completely. It should be recalled that the DCCT data indicate a direct relationship between glycemic control and long-term complications (as well as an inverse relationship with hypoglycemia) (3). Any improvement in glycemic control would be expected to reduce the risk of long-term complications. Indeed, although there is not a clear threshold, the relationship is curvilinear with the greatest complications risk reduction by moderate compared with poor glycemic control. Thus, the risk of treatment-induced hypoglycemia should not be used as an excuse for not attempting to achieve the best control possible in a given patient at a given point in that patient's life. Clearly, however, glycemic targets must be individualized.

Principles of therapy

Application of the principles of intensive therapy, albeit with individualized and generally higher glycemic targets, is just as important in a patient suffering recurrent hypoglycemia as it is in a patient able to achieve near euglycemia safely. These principles include extensive education, self-monitoring of blood glucose, and professional support.

Patients with diabetes, particularly those with IDDM or severe, insulin-requiring NIDDM, must manage their diabetes effectively themselves if they are to achieve glycemic control. Health professionals provide guidance and support, but self-management is the key to success. Therefore, the patient must be educated about the nuances as well as the basics of diabetes and become an expert in the management of his or her diabetes. With respect to hypoglycemia, they must be taught how to recognize developing hypoglycemia and to treat it effectively. They must keep glucose containing treatments with them at all times, at home, at work, at all other activities, and in between. The last of these warrants emphasis; whether the distance is long or short glucose must be available to the patient while traveling including, particularly, in the automobile when the patient is driving. Self-monitoring of blood glucose is particularly important for patients with hypoglycemia unawareness. They must measure their glucose level frequently, and without fail before performing a critical task such as driving. Spouses, family members, friends, and coworkers should also be educated about the recognition of hypoglycemia and its treatment. The latter includes the use of parenteral glucagon when the patient is unable to take glucose orally.

Therapeutic regimens

As mentioned earlier, all current insulin replacement regimens are imperfect compared with insulin secretion from normal pancreatic β-cells. In a patient suffering from recurrent hypoglycemia, use of a more flexible insulin replacement regimen such as a "basal-bolus" approach (intermediate- or long-acting insulin plus preprandial regular insulin) or continuous subcutaneous insulin infusion should be considered (233). The goal here is relative glycemic stability, at least initially at a somewhat higher than optimal glucose level, rather than near euglycemia. Again, the key issue is the selection of prudent glycemic goals for a given patient.

Risk factor reduction

Given that the risk of treatment-induced hypoglycemia, at least in IDDM, is determined by the interplay of absolute or relative insulin excess and compromised glucose counterregulation, it is reasonable to consider each aspect of both components to attempt to reduce risk factors for hypoglycemia (Table 3).

With respect to the conventional risk factor category, absolute or relative insulin excess: can the insulin regimen (doses, timing, type) be optimized? Particularly if a fixed insulin regimen is used, is the meal plan, including snacks, appropriate to the regimen and to the patient's lifestyle, preferences, and cultural background? Does the patient understand and follow it? Does the patient prepare for exercise (food ingestion, decreased insulin, or both), avoid exercise at times of peak insulin action, and cover unanticipated exercise wisely? Are there relevant drug interactions, including alcohol? Is there a reason, such as improved glycemic control, weight loss, or physical training, to suspect increased sensitivity to insulin and dictate regimen adjustments? Is there a reason, such as progressive renal insufficiency, to suspect decreased clearance of administered insulin? In addition, the un-

Table 3—*Risk factor reduction in the patients with recurrent hypoglycemia*

Absolute or relative insulin excess	+	Compromised glucose counterregulation
Insulin doses, timing, and type		History of severe hypoglycemia
Meals and snacks		Defective glucose counterregulation
Exercise		Hypoglycemia unawareness
Drug interactions, including alcohol		Effective intensive therapy
Sensitivity to insulin		Recent antecedent hypoglycemia
Insulin clearance (renal disease)		(β-Adrenergic antagonists)

common causes of hypoglycemia independent of diabetes and its treatment (12) should be considered.

With respect to compromised glucose counterregulation, recall that a history of severe hypoglycemia is a well-established predictor of subsequent severe hypoglycemia (30) and is probably indicative of the presence of defective glucose counterregulation (158,159). While it is possible to test for the latter with an insulin infusion test (158,159), that is probably neither cost-effective nor clinically worthwhile. A positive test might lead to a more cautious approach to therapy, but management would still be empirical and there is no known therapy for defective glucose counterregulation. On the other hand, the history should be probed for evidence of partial or complete hypoglycemia unawareness and its relation to effective glycemic control/recent antecedent hypoglycemia. Hypoglycemia unawareness has management implications, including the critical need for frequent self-monitoring of blood glucose as mentioned earlier. Furthermore, recent data suggest that a relatively short period (e.g., 2 weeks) of scrupulous avoidance of hypoglycemia might reverse this syndrome (190–193) as discussed earlier. At least the clinician should point out that even "mild" episodes of hypoglycemia may have a long-term impact on the development of compromised glucose counterregulation. Finally, although compelling clinical data indicating a detrimental effect are lacking, it would seem prudent to avoid β-adrenergic antagonists on theoretical grounds if an alternative drug is available. If not, a relatively selective β_1-adrenergic antagonist is probably preferable to a nonselective antagonist.

SUGGESTIONS FOR FUTURE RESEARCH

— As mentioned earlier, given the magnitude of the problem, research relevant to hypoglycemia, ranging from the study of basic mechanisms to applied clinical strategies, should be encouraged. While a great deal has been learned about IDDM, we need to know more about the impact of NIDDM on defenses against developing hypoglycemia. With respect to IDDM, as well as NIDDM, critical issues include the following. *1*) Does the glycemic threshold for cognitive dysfunction shift with those for autonomic and symptomatic responses in relation to antecedent glycemia? 2) What is the mechanism(s) of these shifts in glycemic thresholds? 3) Do recurrent episodes of iatrogenic hypoglycemia cause permanent cognitive impairment? 4) What clinical strategies will minimize iatrogenic hypoglycemia without compromising glycemic control? Fundamentally, we need to learn to replace insulin in a much more physiological fashion or to prevent, correct, or compensate for compromised glucose counterregulation if we are to achieve euglycemia safely in the majority of patients with diabetes mellitus.

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