Hypoglycemia in Type 2 Diabetes

Pathophysiology, frequency, and effects of different treatment modalities

NICOLA N. ZAMMITT, MRCP
BRIAN M. FRIER, MD

The importance of strict glycemic control to limit the risk of diabetic vascular complications is indisputable, but many barriers obstruct its attainment. Hypoglycemia is recognized to be a major limitation in achieving good control in type 1 diabetes (1) but has been considered to be a minor problem of the treatment modalities used for type 2 diabetes (2). This may be a misperception based on inadequate information. The burden of covert hypoglycemia associated with oral antidiabetic agents may be underestimated, and with the increasing use of insulin to treat type 2 diabetes, the actual prevalence of hypoglycemia is likely to escalate.

The frequency and pathophysiology of hypoglycemia in type 2 diabetes and the relationship to different therapies was reviewed by conducting a literature search using the bibliographic database PubMed to identify publications in English from 1984 until 2005 related to hypoglycemia associated with treatment of type 2 diabetes, and the bibliographies of relevant articles were scrutinized for additional citations. Search terms included "type 2 diabetes," "NIDDM," "non-insulin-dependent diabetes," "hypoglycemia," and "hypoglycaemia."

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

Normal physiological responses to hypoglycemia

The human brain primarily uses glucose as its source of energy. Under normal conditions, the brain is unable to synthesize or store glucose and is exquisitely vulnerable to glucose deprivation. To protect the integrity of the brain, several physiological mechanisms have evolved to respond to and limit the effects of hypoglycemia (3–6).

In humans, the initial response to a decline in blood glucose is suppression of endogenous insulin secretion followed by release of counterregulatory hormones, of which glucagon and epinephrine (adrenaline) are the most potent. When blood glucose falls in a nondiabetic adult, the secretion of counterregulatory hormones and the onset of cognitive, physiological, and symptomatic changes occur at reproducible blood glucose thresholds (4,7) within a defined hierarchy (5) (Fig. 1). Subjective recognition of the symptoms of hypoglycemia is fundamental to effective self-management and to prevent progression in severity (9,10). Symptoms are generated at arterialized blood glucose concentrations around 2.8–3.2 mmol/l (50–58 mg/dl) and in young adults have been classified as neuroglycopenic, autonomic, and malaise (11). Hypoglycemic symptoms are idiosyncratic and age specific (10).

The effects of ageing on the responses to hypoglycemia

Despite the increasing incidence of type 2 diabetes in young people, this condition is primarily associated with advancing age. It is pertinent therefore to consider the specific effects of ageing on the responses to hypoglycemia before examining how type 2 diabetes affects these processes.

With increasing age, the symptoms of hypoglycemia may become less intense (12,13) and the symptom profile is modified (9,12,14). In a small British study (12) that compared responses to hypoglycemia in seven (five male) nondiabetic adults, aged 65–80 years, with six (three male) younger people, aged 24–49 years, the symptom scores were significantly lower in the older group; autonomic and neuroglycopenic symptoms were affected equally. A Canadian study (15) comparing symptom responses to hypoglycemia in 10 young (5 male, aged 25–30 years) and 9 older nondiabetic subjects (5 male, aged 67–84 years) implicated attenuation of autonomic activation as the cause of the diminished symptomatic response. A further study (16) by the same group reported that symptomatic responses were similar in 10 elderly people with (7 male, aged 72 ± 1 years) and 10 without (6 male, aged 74 ± 1 years) type 2 diabetes, suggesting that the decreased symptom intensity observed in their first study was associated with increasing age, independent of any effects of diabetes.

In young adults, symptomatic responses to hypoglycemia are generated at a blood glucose level that is higher than the level at which cognitive function becomes impaired. This allows sufficient time to take corrective action before severe neuroglycopenia supervenes (5). The difference between these glycemic thresholds is ~1.0 mmol/l (18 mg/dl). In a study comparing seven healthy older men (aged 65 ± 3 years) with seven younger male control subjects (aged 23 ± 2 years), symptoms and cognitive dysfunction occurred almost simultaneously at 3.0 ± 0.2 mmol/l (54 ± 4 mg/dl) in the older subjects (13) (Fig. 2). The juxtaposition of these thresholds may limit the time available to self-treat and increase the risk of developing incapacitating neuroglycopenia.

Does the ageing process modify the counterregulatory hormonal responses to hypoglycemia? Early studies (17–21) that compared these responses in young and older nondiabetic adults yielded conflicting results, and many of the participants had comorbidities that confounded interpretation of the data. Hypoglycemia was induced mostly with an intravenous bolus injection of insulin, producing variable degrees of hypoglycemia, and principally

From the Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, Scotland, U.K.
Address correspondence and reprint requests to Prof. B.M. Frier, Department of Diabetes, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, Scotland, U.K. E-mail: brian.frier@luht.scot.nhs.uk.
Received for publication 16 May 2005 and accepted in revised form 12 September 2005.
B.M.F. has been a member of an advisory panel for and has received honoraria/consulting fees from Eli Lilly, Sanofi-Aventis, GlaxoSmithKline, and Takeda.
Abbreviations: CSII, continuous subcutaneous insulin infusion.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
© 2005 by the American Diabetes Association.

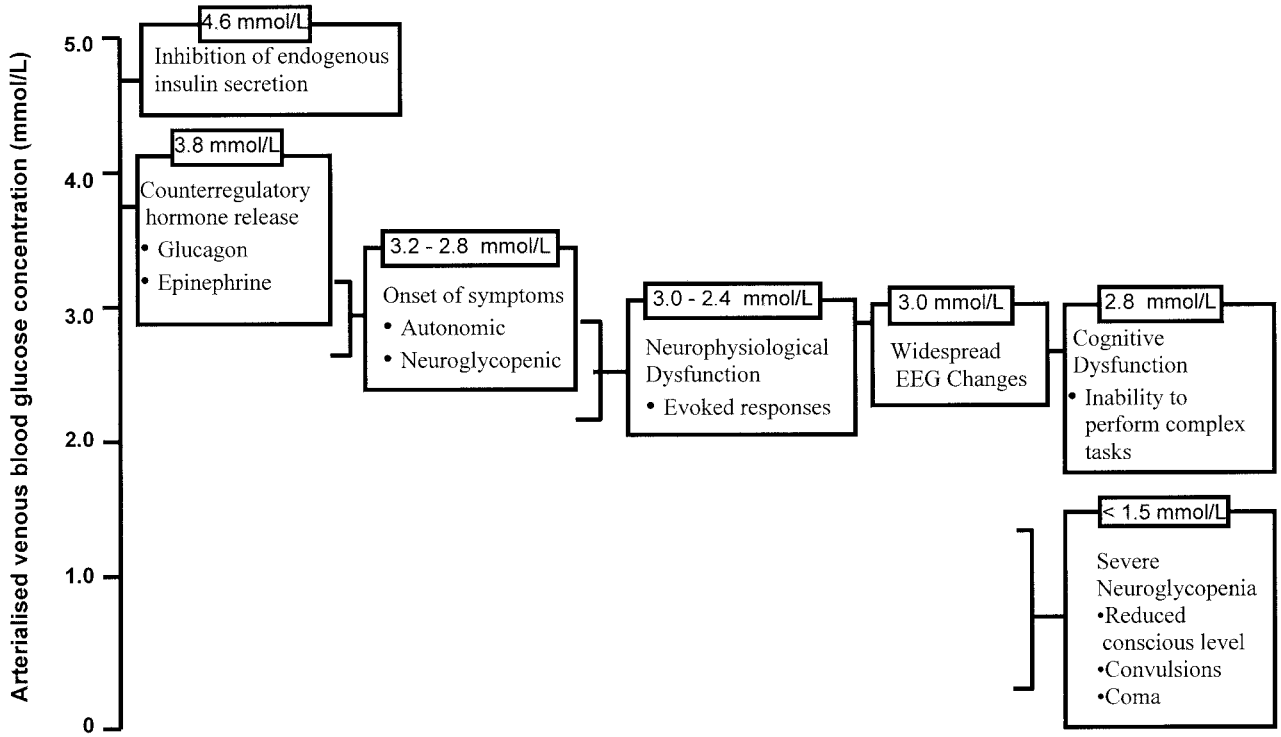

Figure 1—*Glycemic thresholds for secretion of counterregulatory hormones and onset of physiological, symptomatic, and cognitive changes in response to hypoglycemia in the nondiabetic human. Reproduced from Frier and Fisher (8) in* Hypoglycaemia in Clinical Diabetes. *Reproduced with permission of John Wiley and Sons, Chichester, U.K.*

examined cortisol and growth hormone responses (17–21), so these results are of limited value.

A modest attenuation of blood glucose recovery from hypoglycemia may occur in older nondiabetic adults, in whom the rise in plasma epinephrine is slower than in younger subjects (22). The glycemic thresholds for the secretory responses of glucagon and epinephrine to hypoglycemia occurred at a blood glucose of 3.3 mmol/l (59 mg/dl) in 10 young nondiabetic adults (5 male, aged 25–30 years) compared with 2.8 mmol/l (50 mg/dl) in 9 older adults (5 male, aged 67–84 years) (15).

With advancing age, the magnitude of the counterregulatory response may be determined by the hypoglycemic nadir. In clamp studies comparing elderly and young nondiabetic subjects aged (means ± SE) 65 ± 1 and 24 ± 1 years, respectively, the magnitude of the glucagon and epinephrine responses was lower in the elderly group during mild hypoglycemia (blood glucose 3.3 mmol/l; 59 mg/dl), but in both age-groups equivalence was achieved at a lower blood glucose (2.8 mmol/l; 50 mg/dl), indicating preservation of these responses to more profound hypoglycemia (23). The rate of insulin clearance from the circulation declines with age (24–26), which may enhance the risk of hypoglycemia in elderly people.

If symptomatic and counteregulatory responses to hypoglycemia are modified by advancing age, it is not known at what age this occurs and whether the effects differ in male and female subjects. Considerable biological variability between individuals may occur in nondiabetic and diabetic adults with respect to the effects of ageing. This introduces a potentially confounding variable in studies of people with type 2 diabetes, which is not only a heterogeneous disorder but affects a wide age range. Few investigations of hypoglycemia in type 2 diabetes have taken age into account when designing studies and analyzing results, and few studies have included patients aged >70 years (Tables 1 and 2).

The effects of type 2 diabetes on the responses to hypoglycemia

Counterregulatory responses to hypoglycemia have been investigated less systematically in type 2 than in type 1 diabetes (1,27,28). Although various counterregulatory hormonal deficiencies have been described in type 2 diabetes, these were mostly mild, and epinephrine secretion was invariably preserved. Interpretation of the early studies is limited by heterogeneity of study design (29), differences in blood glucose nadir between the diabetic and control groups (30,31), a lack of age-matched control subjects (31), and the disparate methods used to induce hypoglycemia (30–35).

Three studies of counterregulatory responses to hypoglycemia in people with type 2 diabetes, treated with either diet or oral medication, have shown that counterregulatory hormonal release occurs at higher blood glucose levels than in nondiabetic control subjects (36,37) and people with type 1 diabetes (38). In one of these studies, the influence of glycemic control on the counterregulatory response to hypoglycemia was assessed in 11 subjects (9 male) with type 2 diabetes (aged 56 ± 7 years), who were either diet treated or were taking sulfonylureas, and compared with 10 subjects (5 male) with type 1 diabetes (aged 27 ± 6 years) and 2 nondiabetic control groups matched for age and body weight (38). Hypoglycemia was induced using a stepped glucose clamp. Counterregulatory hormones were secreted at higher blood glucose levels in the subjects with type 2 than in those with type 1 diabetes (Fig. 3). Two potential confounding factors in this study merit discussion. First, male sub-

Table 1—*Epidemiological data on hypoglycemia in type 2 diabetes, expressed as incidence*

Study	VA CSDM, 1995 (ref. 74)	Gurlek, Erbas, and Gedik, 1999 (ref. 78)*	Henderson et al., 2003 (ref. 82)	Leese et al., 2003 (ref. 79)*	Donnelly et al., 2005 (ref. 81)*
Design	Prospective multicentre, randomized clinical trial of standard vs. intensive insulin regimen	Retrospective, medical records examined	Retrospective questionnaire	Population-based dataset analysis	Prospective
n	150	165	215	160	267
Subjects	All have type 2 diabetes	All insulin treated: 114 type 2 and 51 type 1 diabetic subjects	All insulin-treated type 2 diabetic subjects	Type 1 (69) and type 2 diabetic subjects on sulfonylurea (22) or insulin (66)	94 with type 1 diabetes; 173 with type 2 diabetes
Age (years)	60 ± 6	59 ± 10	68 (27–87)	mean 53.8 (50.8–56.9)	66 (34–86)
A1C (%)	Conventional: 9.0%, intensive: 7.0%	Not specified	8.6 ± 1.5	7.85 (7.57–8.14)	8.9 ± 1.41
HbA1 (%)	—	—	—	—	—
Duration	18–35 months	3.3 years	1 year	1 year	1 month
Definition of severe hypoglycemia	Need for third party assistance or loss of consciousness or seizure	Need for third party assistance and attendance at hospital	Need for third party assistance	Need for parenteral treatment by emergency services	Need for third party assistance
Oral antidiabetic agents: all hypoglycemia	NA	NA	NA	NA	NA
Oral antidiabetic agents: severe hypoglycemia	NA	NA	NA	Sulfonylureas: 0.009 episodes/patient/year; metformin: 0.0005 episodes/patient/year	NA
Insulin: all hypoglycemia	1.5 (standard therapy) and 16.5 (intensive therapy)	NA	NS	NA	16.4
Insulin: severe hypoglycemia	0.02 events/patient/year	0.15 events/patient/year	0.28 events/patient/year	0.12 events/patient/year (both type 1 and type 2 diabetes)	0.35 events/patient/year
Main criticisms	All male intensively managed group	Only assessed severe hypoglycemia; incidence underestimated as included only events requiring hospital admission	Recall bias for mild hypoglycemia	Only assessed hypoglycemia requiring emergency service	Short duration

Data are means ± SD or median (range), unless otherwise indicated. NA, not applicable; VA CSDM, Veterans Affairs Cooperative Study in Type 2 Diabetes. *Only figures for type 2 diabetes given.

Table 2—*Epidemiological data on hypoglycemia in type 2 diabetes, expressed as prevalence*

Study	Jennings, Wilson, and Ward, 1989 (ref. 75)	U.K. Prospective Diabetes Study 33, 1998 (ref. 2)	Hepburn, 1993 (ref. 83)*	VA CSDM, 1995 (ref. 74)	Miller et al., 2001 (ref. 76)	Henderson et al., 2003 (ref. 82)*	Leese et al., 2003 (ref. 79)	Donnelly et al., 2005 (ref. 81)*
Design	Retrospective, structured interview	Prospective multicentre randomized clinical trial	Retrospective, questionnaire	Prospective multicenter randomized clinical trial	Retrospective, interview	Retrospective questionnaire	Population-based dataset analysis	Prospective
Subjects	Type 2 diabetes, oral antidiabetic agents only	Type 2 diabetes, oral antidiabetic agents and insulin	Types 1 and 2 diabetes, insulin only	All type 2 diabetes	Type 2 diabetes	Insulin-treated type 2 diabetes	Mixed type 1 and type 2 diabetic subjects, oral antidiabetic agents and insulin	Insulin-treated type 1 and type 2 diabetic subjects
Number	219 (sulfonylurea 203, metformin 16)	3,935	104 type 1 and 104 type 2 diabetic subjects	153	1,055	215	160	94 type 1 and 173 type 2 diabetic subjects
Age	59 (40–65)	54 ± 8	63 ± 9	60 ± 6	60.9 ± 0.4 (means ± SE)	68 (27–87)	53.8 (50.8–56.9)	66 (34–86)
A1C %	—	6.2 ± 1.2	—	9.3 ± 1.8	7.6 ± 0.1 (means ± SE)	8.6 ± 1.5	7.85 (7.57–8.14)	8.9 ± 1.41
HbA1%	Subjects with hypoglycemia 9.5 ± 9, subjects without hypoglycemia 11.4 ± 3.0	—	10.3 ± 2	—	—	—	—	—
Duration	6 months	10 years	1 year	18–35 months	7 months	1 year	1 year	1 month
Definition of severe hypoglycemia	NA	Third party assistance	Third party assistance	Third party assistance/ LOC/fit	Third party assistance	Third party assistance	Need for parenteral treatment by emergency services	Third party assistance
Oral antidiabetic agents: all hypoglycemia	Metformin 0%, sulfonylurea 20.2% (glyburide 31.3%, chlorpropamide 13.6%, gliclazide 13.1%)	Glyburide 17.0%, chlorpropamide 11.0%	NA	NA	16%	NA	NA	NA
Oral antidiabetic agents: severe hypoglycemia	—	Glyburide 0.6%, chlorpropamide 0.4%	NA	NA	0%	NA	0.8%	NA
Insulin: all hypoglycemia	NA	36.5%	82.7%	56% (conventional), 93% (intensive)	30%	64%	NA	45%
Insulin: severe hypoglycemia	NA	2.3%	10%	NA	0%	15%	7.3%	3%
Main criticisms	Recall bias for mild hypoglycemia	Atypical intensively managed group. Under-recording of events	—	All male, intensively managed	Recall bias. Mainly female African Americans	Recall bias for mild hypoglycemia	Only assessed hypoglycemia requiring emergency services	Short duration

Data are means ± SD or median (range), unless otherwise indicated. LOC, loss of consciousness; NA, not applicable; VA CSDM, Veterans Affairs Cooperative Study in Type 2 Diabetes. *Only figures for type 2 diabetes given.

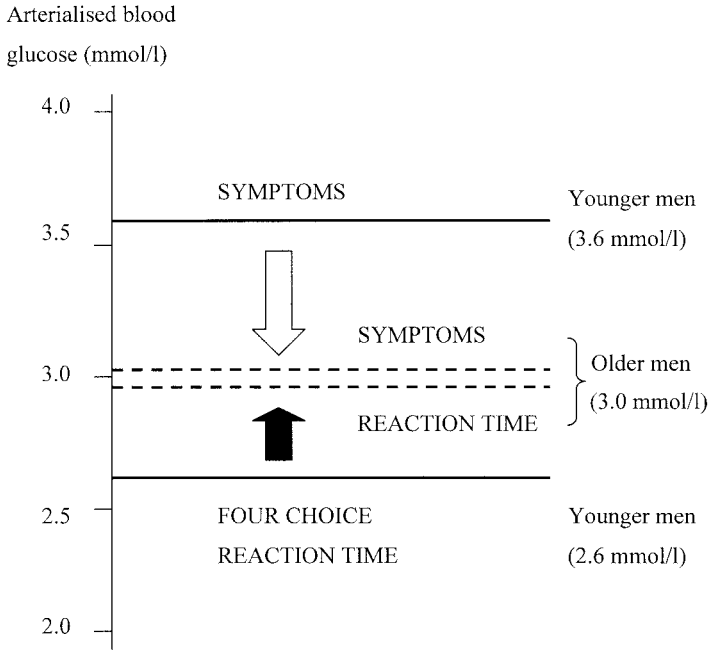

Figure 2—*Glycemic thresholds for subjective symptomatic awareness of hypoglycemia and for the onset of cognitive dysfunction in young and elderly nondiabetic males. Based on data derived from Matyka et al. (13). Figure reproduced from McAulay and Frier in* Diabetes and Old Age *(57), with permission of John Wiley and Sons, Chichester, U.K.*

jects were overrepresented in the group with type 2 diabetes, which may have influenced the magnitude of hormonal response. In both nondiabetic and type 1 diabetic subjects, female subjects have lower counterregulatory responses to hypoglycemia than male subjects (39–42), although no information is available in type 2 diabetes. Secondly, six of the subjects with type 2 diabetes required a high rate of insulin infusion (3–6 mU · kg^{-1} · min^{-1}) to achieve hypoglycemia. Evidence exists in nondiabetic and type 1 diabetic subjects to implicate hyperinsulinemia per se in suppressing the release of glucagon in response to hypoglycemia (43–46) while increasing catecholamine and cortisol release (47), although this has been disputed (48). This putative effect of hyperinsulinemia is undetermined in type 2 diabetes.

Type 2 diabetes may therefore confer greater protection against hypoglycemia, particularly when glycemic control is suboptimal, because the counterregulatory responses commence at higher blood glucose levels than observed in the nondiabetic state or in people with type 1 diabetes (37,38). However, improving glycemic control with insulin therapy shifts the threshold for the counterregulatory response to a lower blood glucose level (37,38) (Fig. 3); a similar phenomenon is observed in type 1 diabetes when glycemic control is intensified (1,8,49).

In type 1 diabetes, deficiency of the secretory response of glucagon to hypoglycemia is an early acquired abnormality of counterregulation. The catecholamine response compensates for several years but declines with time (1). In type 2 diabetes, the glucagon response to hypoglycemia has been diversely reported as being either modestly diminished (16, 30,50) or preserved (33,34,37,38). People with type 2 diabetes constitute a disparate group, within which the ability of an individual to secrete glucagon in response to hypoglycemia may be related to the degree of insulin deficiency. Most investigators reporting preservation of the glucagon response have studied people with type 2 diabetes who were unlikely to be insulin deficient (33,34,36,38), and, with one exception (16), all of these studies have examined counterregulatory responses in middle-aged subjects in their 5th or 6th decade. However, most people with type 2 diabetes are aged >60 years, and these studies have therefore neglected to consider or account for the effect of ageing on counterregulation. The counterregulatory responses to hypoglycemia were examined in 15 nondiabetic control subjects (7 male, aged 50 ± 6 years) and in 13 people with type 2 diabetes, 7 of whom were receiving treatment with oral antidiabetic agents (3 male, aged 56 ± 6 years), while 6 had been treated with insulin for at least 5 years and were insulin deficient as demonstrated by C-peptide measurements (3 male, aged 57 ± 6 years) (51). The glucagon response to hypoglycemia was intact in the tablet-treated patients and in the nondiabetic control subjects but was almost absent in the insulin-deficient patients (Fig. 4), demonstrating the presence of acquired counterregulatory abnormalities in association with insulin deficiency.

A condition labeled HAAF (hypoglycemia-associated autonomic failure) has been described in type 1 diabetes (52,53), whereby recurrent hypoglycemia provokes failure of the centrally mediated sympatho-adrenal response so causing counterregulatory deficiency and impaired awareness of hypoglycemia. Are people with insulin-deficient type 2 diabetes at risk of developing HAAF? In the study by Segel, Paramore, and Cryer (51), a hypoglycemic clamp performed on the 1st day of the study was followed by another period of hypoglycemia later in the day. When these subjects with type 2 diabetes were exposed to further hypoglycemia on the following day, the plasma

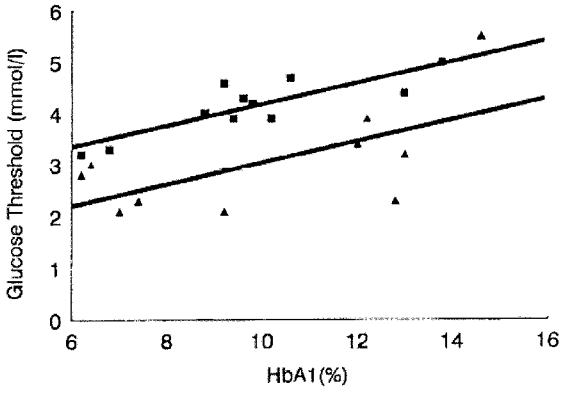

Figure 3—*Relationship between blood glucose threshold (mmol/l) for epinephrine secretion in response to hypoglycemia and total HbA1 (%) in type 2 (■) and type 1 (▲) diabetes. Type 2 diabetes:* r = *0.82,* P < *0.01; type 1 diabetes:* r = *0.63,* P < *0.05;* P = *0.05 between groups. Reproduced from Levy et al. 1998 (38) with permission of the American Diabetes Association.*

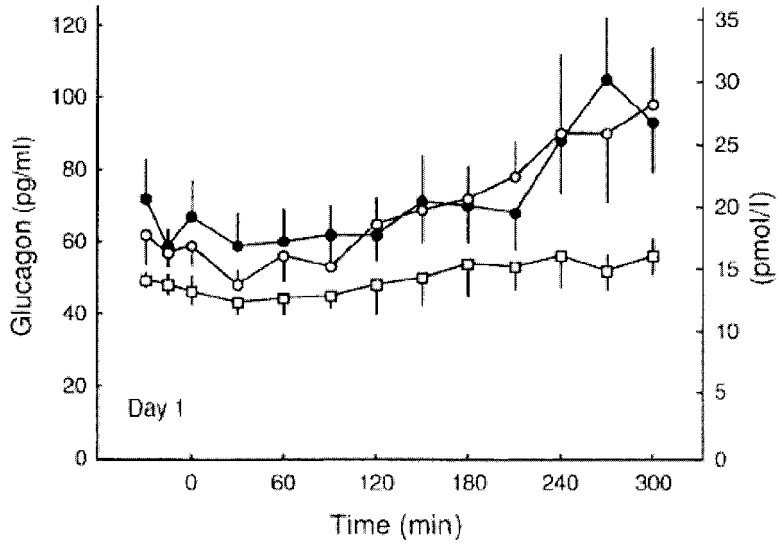

Figure 4—*Mean (±SE) plasma glucagon concentrations during hyperinsulinemic stepped hypoglycemic clamps in nondiabetic subjects (●) (n = 15) and in patients with type 2 diabetes treated with oral antidiabetic agents (○) (n = 7) and with insulin (□) (n = 6). P = 0.0252 for nondiabetic vs. type 2 diabetic subjects treated with insulin therapy. Reproduced from Segel, Paramore, and Cryer (51) with permission of the American Diabetes Association.*

glucose levels required to activate the glucagon, catecholamine, and symptomatic responses were lower than in the first hypoglycemic clamp (51). Thus, antecedent hypoglycemia can modify the glycemic thresholds for responses to hypoglycemia in type 2 diabetes and may promote HAAF (53).

In many people with type 2 diabetes who have insulin resistance, the lipolytic effects of epinephrine outweigh the effects of insulin on adipose tissue (50). Plasma free fatty acids increase in response to hypoglycemia in type 2 diabetes (30,33,50) but do not in type 1 diabetes (54). Epinephrine secretion during hypoglycemia may therefore have a greater protective effect in insulin-resistant patients by promoting metabolic substrate release rather than storage. Epinephrine also stimulates release of glucose from the kidney, and, in people who have a deficient glucagon response to hypoglycemia, this may compensate for their impaired hepatic glucose output (55). Thus, in type 2 diabetes, defensive mechanisms to hypoglycemia may be more effective than in type 1 diabetes.

Morbidity of hypoglycemia in type 2 diabetes and in the elderly

Hypoglycemia may cause serious morbidity, provoking major vascular events such as stroke, myocardial infarction, acute cardiac failure, and ventricular arrhythmias (56–58). When the patient receives treatment, the precipitating role of hypoglycemia may not be recognized, particularly if medical attendants are unfamiliar with the age-related differences in the manifestations of hypoglycemia. In a 7-year review of 102 cases of hypoglycemic coma secondary to either insulin or glyburide (glibenclamide), 92 patients had type 2 diabetes, 7 sustained physical injury, 5 died, 2 suffered myocardial ischemia, and 1 patient had a stroke as a consequence of severe hypoglycemia (59). The morbidity associated with hypoglycemia, such as impaired consciousness and convulsions, can be particularly debilitating in the elderly, who are at increased risk of injury and bone fractures because of general frailty and the presence of comorbidities, such as osteoporosis (57).

In elderly people of either sex who have diabetes, unsteadiness and weakness are commonly reported symptoms of hypoglycemia (60), and a group of neurological symptoms affecting vision and coordination have been identified in addition to autonomic and neuroglycopenic symptoms (10,14). Consequently, the manifestations of hypoglycemia in elderly people may be mistaken for other conditions, such as transient ischemic attacks or vaso-vagal episodes. Many elderly people with type 2 diabetes possess little knowledge of the symptoms and treatment of hypoglycemia (60,61). This lack of knowledge extends to their relatives and caregivers (62). Inadequate retention of information may be a consequence of age-related cognitive decline, but irrespective of age, knowledge of diabetes and its treatment decreases with time (63), so regular educational reinforcement is required.

FREQUENCY OF HYPOGLYCEMIA IN TYPE 2 DIABETES

— Mild hypoglycemia is usually defined by the ability to self-treat, while episodes requiring external assistance are defined as severe. The frequency of hypoglycemia has been examined most extensively in people with type 1 diabetes, in whom mild hypoglycemia occurs on average around twice weekly (64,65). In studies in northern Europe of unselected populations with type 1 diabetes, the estimated incidence of severe hypoglycemia ranges from 1.0 to 1.7 episodes per patient per year (65–67). The annual prevalence is between 30% (66,68,69) and 40% (67). These unselected cohorts included people at high risk of severe hypoglycemia, such as those with impaired awareness of hypoglycemia (70). They differ from the atypical participants of the Diabetes Control and Complications Trial (68), who had been selected because they had a low risk of severe hypoglycemia (71) and in whom the observed incidence of severe hypoglycemia was lower, ranging from 0.19 to 0.62 episodes per patient per year.

It is difficult to derive equivalent figures for people with type 2 diabetes because of the heterogeneity of this disorder. Most people with type 2 diabetes are middle aged or elderly; accurate measures of the frequency of hypoglycemia are probably underestimated in the latter (57). Definitions of hypoglycemia differ between studies, hindering comparison, and most studies have reported retrospective data. In people with type 1 diabetes, recall of severe hypoglycemia is relatively robust over a period of 1 year, but recall of mild hypoglycemia is unreliable after an interval of 1 week (64,72). In people with insulin-treated type 2 diabetes, recall of severe hypoglycemia also appears to be preserved over a period of 1 year (73), but reliability of their recall of mild hypoglycemia is unknown. Data from various epidemiological studies are shown in Tables 1 and 2.

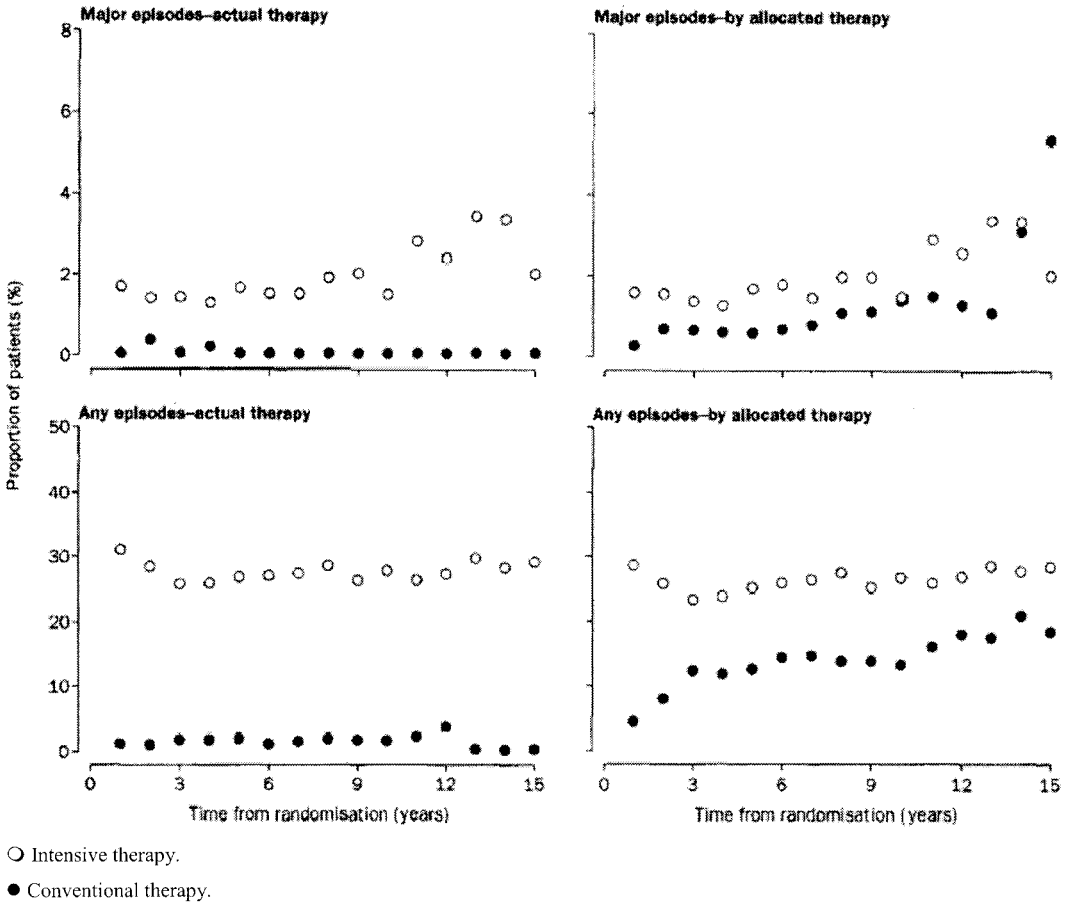

Figure 5—*Major and any hypoglycemic episodes per year by intention-to-treat analysis and actual therapy for intensive and conventional treatment. Reproduced from the U.K. Prospective Diabetes Study 33 (2), with permission of the* Lancet.

Epidemiological data from interventional trials

The U.K. Prospective Diabetes Study (2) reported the prevalence of hypoglycemia in different treatment groups of people with type 2 diabetes, ranging in age from 25 to 65 years. A higher frequency of hypoglycemia was associated with intensive, compared with conventional, treatment with either sulfonylureas or insulin. With intensive treatment, hypoglycemia occurred most frequently in the insulin-treated patients, and the prevalence of hypoglycemia was lower in the 1st decade of the study than in later years (2) (Fig. 5). The prevalence of hypoglycemia was lower when the groups were analyzed on an "intention-to-treat" basis because an increasing number of patients in the conventional treatment groups required the addition of treatment with sulfonylureas or insulin as their glycemic control deteriorated. Although patients were questioned about the occurrence of hypoglycemia at every 4-monthly review, only the most severe episode was documented, so underestimating the overall frequency. The lack of accurate information on the incidence of hypoglycemia is an unfortunate lacuna among the wealth of material provided by this large study.

In the U.S., the Veterans Affairs Cooperative Study in Type 2 Diabetes, examining glycemic control and complications, compared a simple ("standard") insulin regimen administered once daily with an intensive ("stepped") regimen (74). The participants in this trial differed from those of the U.K. Prospective Diabetes Study in that they had diabetes of shorter duration ([mean ± SD] 7.8 ± 4 years), they were all insulin-treated male subjects, and they were followed-up for only 18–35 months. The overall incidence of severe hypoglycemia was 0.02 episodes per patient per year, and no significant difference was observed between the standard and stepped treatment groups. The frequency of mild hypoglycemia was significantly higher in the intensively treated group (stepped vs. standard: 16.5 vs. 1.5 episodes per patient per year), but in the standard treatment group blood glucose was monitored less frequently so mild hypoglycemia may have been underreported (74).

Data obtained in clinical trials in which treatment has been applied in an unconventional manner should not be extrapolated to the wider diabetic population. Thus, the U.K. Prospective Diabetes Study and Veterans Affairs Cooperative Study in Type 2 Diabetes trials, while frequently cited, are not representative of current treatment regimens and do not demonstrate the true frequency and risk of hypoglycemia.

Epidemiological data from observational studies

Several observational studies have recorded (mostly retrospectively) the frequency of hypoglycemia in the setting of a hospital outpatient clinic. A study (75) in England of 219 people with type 2 diabetes treated with sulfonylureas and/or metformin observed that 20% of those taking sulfonylureas had experienced symptoms of hypoglycemia in the preceding 6 months. In Atlanta, a 6-month, retrospec-

tive, cross-sectional survey of 1,055 predominantly female, African-American patients with type 2 diabetes, treated with oral antidiabetic drugs or insulin, completed serial questionnaires to estimate the frequency of hypoglycemia (76). A quarter of the group had experienced at least one episode of hypoglycemia during the study period. The prevalence of hypoglycemia rose with escalating therapeutic requirements, with the highest rate being associated with insulin. Severe hypoglycemia occurred in 0.5% of patients, all of whom had been treated with insulin. The study is limited by its reliance on patient recall of hypoglycemia and the ethnicity and sex of the study group. A population-based study in Tennessee examined episodes of hypoglycemia retrospectively over a 4-year period in 19,932 Medicaid patients, aged ≥65 years, who had type 2 diabetes (77). This study reported incidences of 1.23 episodes per 100 person-years of "serious" hypoglycemia with sulfonylureas and 2.76 episodes per 100 person-years with insulin treatment, but the strict definition of "serious" hypoglycemia (an episode having a fatal outcome or requiring hospital treatment) may have underestimated the frequency of severe events.

A retrospective study in Turkey examined 165 patients treated with insulin, 114 of whom had type 2 diabetes (78). Hospital case notes were examined for a record of hypoglycemia requiring assistance or hospital admission. This historical approach is likely to have substantially underestimated the overall frequency of severe hypoglycemia, and the incidence of severe hypoglycemia was only 0.15 episodes per patient per year, both in type 1 and insulin-treated type 2 diabetes (78). The authors interpreted these findings as indicating that severe hypoglycemia occurred with a similar magnitude in insulin-treated type 2 diabetic patients as in type 1 diabetes. Although the low incidence of severe hypoglycemia suggests incomplete data collection, particularly in type 1 diabetes, it is possible that the incidence of severe hypoglycemia necessitating emergency medical intervention is similar in these groups. This was certainly true in a population survey in a region of Scotland, in which all episodes of severe hypoglycemia that were attended by the emergency medical services were identified over a 12-month period (79). A total of 244 episodes of severe hypoglycemia had been treated in 160 patients with diabetes. Severe hypoglycemia had required emergency treatment in 7.1% of patients with type 1 diabetes, in 7.3% of patients with insulin-treated type 2 diabetes, and in 0.8% of patients taking oral antidiabetic agents. In type 1 diabetes, severe hypoglycemia is often treated at home, and less than one-third of episodes are thought to need the assistance of the emergency medical services (80). People with insulin-treated type 2 diabetes who suffer severe hypoglycemia may be more likely to require emergency assistance than people with type 1 diabetes, and this was confirmed by a prospective survey in the same region, where the occurrence of hypoglycemia was monitored in a cohort of 267 people with insulin-treated diabetes (both type 1 and type 2) over a period of 1 month (81). The prevalence of all hypoglycemia (mild and severe) in the group with insulin-treated type 2 diabetes was 45% with an incidence of 16.4 episodes per patient per year (42.9 episodes per patient per year in type 1 diabetes). Their incidence of severe hypoglycemia was 0.35 episodes per patient per year (1.15 episodes per patient per year in type 1 diabetes). In the group with type 1 diabetes, only 1 in 10 of those experiencing severe hypoglycemia required emergency service treatment compared with 1 in 3 of the group with type 2 diabetes (81). Although the annual incidence in this study (81) was extrapolated from prospective data collected over a short period of 1 month, the calculated annual rates for people with type 1 diabetes are consistent with those recorded in other European studies (64–67). However, the frequency of severe hypoglycemia recorded in people with type 2 diabetes was higher than anticipated (81). Although plasma C-peptide levels were not measured, it is likely that most of these subjects with insulin-treated type 2 diabetes were insulin deficient and were therefore at greater risk of hypoglycemia than people treated with oral antidiabetic agents.

A retrospective Scottish survey in Edinburgh of 215 people with insulin-treated type 2 diabetes observed that the frequency of hypoglycemia increased with duration of insulin therapy and of diabetes and was inversely proportional to HbA_{1c} (A1C) concentration (82). The annual prevalence of severe hypoglycemia was 15% with an overall incidence of 0.28 episodes per patient per year. A retrospective study performed a decade earlier in Edinburgh had assessed the incidence of severe hypoglycemia in 600 unselected insulin-treated diabetic patients. The incidence in the 56 people with type 2 diabetes was 0.73 episodes per patient per year compared with 1.7 episodes per patient per year in the 544 with type 1 diabetes (66). A further survey in the same center compared the frequency of severe hypoglycemia in 86 people with insulin-treated type 2 diabetes with 86 people with type 1 diabetes, matched for duration of insulin treatment and dose (83). The frequency of severe hypoglycemia was comparable in the two groups, and a direct relationship was found between increasing frequency of severe hypoglycemia and increasing duration of treatment with insulin ($r = 0.39$, $P < 0.001$).

Moderators of hypoglycemia in type 2 diabetes

There is no evidence to suggest that in type 2 diabetes the principal causes of hypoglycemia (too much insulin or insulin secretagogue, physical exertion or inadequate carbohydrate consumption) differ from type 1 diabetes. Several factors such as sleep, consumption of alcohol, caffeine and various medications, and the timing of exercise, that are known to affect the risk of hypoglycemia in type 1 diabetes, are an unknown quantity in type 2 diabetes. Treatment with insulin for >10 years is an important predictor of increased risk of severe hypoglycemia in type 2 diabetes (81). When people with type 2 diabetes become insulin deficient, their frequency of severe hypoglycemia approaches that experienced by people with type 1 diabetes (83).

Impaired awareness of hypoglycemia is a major risk factor for severe hypoglycemia in type 1 diabetes (70) but is less common in people with type 2 diabetes (83). One retrospective survey of 215 individuals with insulin-treated type 2 diabetes showed that only 8% had impaired awareness estimated by a validated scoring system (70), but those so affected had a ninefold greater incidence of hypoglycemia than those with intact awareness (82). Continuous glucose monitoring systems have been used to detect asymptomatic hypoglycemia in type 1 diabetes, but to date their use in type 2 diabetes has been limited. In a prospective study (84), asymptomatic hypoglycemia <3 mmol/l (<60 mg/dl) was detected in 47% of 30 individuals (17 male, aged 58 ± 11 years) with type 2 diabetes (9 on oral agents, 21 on intensive insulin therapy) compared with 63% of 40 patients with

type 1 diabetes (18 male, aged 36.5 ± 12 years). An Australian study examined the frequency of hypoglycemia over two 72-h periods using continuous monitoring in 25 patients treated with sulfonylureas (21 male, aged 73.9 ± 4.4 years). Readings of <2.2 mmol/l (<40 mg/dl) for at least 15 min were recorded in 56% of subjects and none were perceived (85). Impaired awareness of hypoglycemia may be more prevalent in type 2 diabetes than is appreciated.

The Diabetes Outcomes in Veterans Study in the U.S. was a prospective observational trial (86) designed to validate a statistical model for predicting hypoglycemia. The model was tested on a predominantly male cohort of people with insulin-treated type 2 diabetes. Participants performed blood glucose profiles for 8 weeks, and episodes of hypoglycemia were prospectively reported over 1 year. The probability of all hypoglycemia was greater in those who had a low mean blood glucose with a high SD, suggesting that the variability of blood glucose values is as important as A1C values in predicting the risk of hypoglycemia in insulin-treated type 2 diabetes.

Compared with the nondiabetic state, people with type 2 diabetes have a normal rate of exercise-related skeletal muscle glucose uptake but an impaired hepatic glucose output (87), which can result in hypoglycemia during physical exertion. Exercise in type 2 diabetes results in improved insulin sensitivity (88) and reduced postprandial plasma glucose levels (89,90). Improvements in insulin resistance persist for up to 16 h after the period of activity (91), thus exposing the individual to a continuing risk of hypoglycemia. The combination of moderate exercise and ingestion of alcohol did not result in acute hypoglycemia, either after a light meal or after fasting in 12 (8 male) untrained middle-aged subjects with type 2 diabetes who were C-peptide positive (92). Alcohol impairs counterregulatory responses to hypoglycemia in type 1 diabetes (93) but does not appear to delay recovery from hypoglycemia in type 2 diabetes (94).

Risk factors for severe hypoglycemia in people with type 2 diabetes treated with sulfonylureas include age, a past history of vascular disease, renal failure, reduced ingestion of food, alcohol consumption, and interactions with other drugs (59,73,95–102).

FREQUENCY OF HYPOGLYCEMIA WITH DIFFERENT TREATMENT MODALITIES

Oral antidiabetic agents

Hypoglycemia with oral antidiabetic agents is predominantly associated with the insulin secretagogues. Hypoglycemia is not a common side effect of treatment with metformin, thiazolidinediones, or α-glucosidase inhibitors, although it has been occasionally reported in association with metformin when food intake is limited (2,103). The frequency of hypoglycemia is lower in people treated with sulfonylureas than in those treated with insulin (2,76,79) but is probably underestimated (104).

The risk of hypoglycemia of each sulfonylurea relates to its pharmacokinetic properties (104–108) and is highest with long-acting sulfonylureas such as chlorpropamide, glyburide (glibenclamide), and long-acting glipizide (101,109–111). Glyburide is associated with significantly more episodes of severe hypoglycemia than gliclazide (112) because its hypoglycemic effects last for 24 h (111) as a consequence of the presence of active metabolites (111,113). Glyburide also impairs the glucagon response to hypoglycemia in nondiabetic volunteers (114) and in people with type 2 diabetes (56,115).

Although glipizide is associated with fewer episodes of hypoglycemia, over a 7-year period the Swedish Adverse Drug Reactions Advisory Committee reported 19 cases of severe hypoglycemia that presented with coma or reduced consciousness, with two fatalities (116). Renal impairment and advanced age were identified as risk factors for severe hypoglycemia. In most cases, the severe hypoglycemia had occurred within 1 month of commencing the drug and was not related to dose, suggesting that the response was idiosyncratic.

Efforts have been made to find a sulfonylurea that provides good glycemic control with a low risk of hypoglycemia. Glimepiride, a long-acting sulfonylurea, may partly fulfil this role as it has a lower affinity for the β-cell receptor than glyburide (117), and its insulin secretory capacity is lower in both the fasting (118) and postprandial (119) states. A population-based study in Germany examined the incidence of hypoglycemia in patients with type 2 diabetes who had attended a hospital emergency department over a 4-year period (120). A total of 145 episodes of severe hypoglycemia were treated, and 45 of these patients were receiving treatment with sulfonylureas. Although glimepiride had been prescribed more frequently than glyburide, it was implicated in 6 episodes of severe hypoglycemia, compared with a total of 38 severe events associated with glyburide. In patients with renal impairment, glimepiride can cause prolonged hypoglycemia (121), but it is thought to be safer than other sulfonylureas (122).

A modified release preparation of gliclazide may have a lower risk of hypoglycemia than glimepiride. A multicenter, double-blind, controlled trial in Europe compared the efficacy and safety of modified release gliclazide with glimepiride over a 6-month period (123). The study included people at greater risk of hypoglycemia, such as those aged >65 years (35%) and people with renal impairment. Both groups achieved a reduction of A1C of around 1.0%, with fewer patients reporting hypoglycemia with modified release gliclazide (3.7%) compared with glimepiride (8.9%). Severe hypoglycemia did not occur.

The oral glucose prandial regulators, repaglinide and nateglinide, are insulin secretagogues that have a rapid onset of action but do not stimulate insulin secretion in the fasting state and provoke less hypoglycemia than the sulfonylureas (124–127). Repaglinide has been compared with glipizide, gliclazide, and glyburide in separate double-blind, randomized, 1-year studies (125–127). Mean A1C concentrations did not differ between any of the treatment groups, and in all sulfonylurea groups the prevalences of hypoglycemia (3.3%) were comparable. In the repaglinide group the prevalence of hypoglycemia was 1.3% with equivalent glycemic control. In a randomized multicenter trial comparing repaglinide with nateglinide, slightly lower A1C values were achieved after 16 weeks on repaglinide, but 7% of patients had experienced mild hypoglycemia compared with none in the nateglinide group (128).

Alternative insulin regimens

Basal insulins can be used safely in combination with oral antidiabetic agents in people with type 2 diabetes. In a systematic review of randomized controlled trials comparing insulin monotherapy and combination therapy with oral agents, 13 of 14 studies did not show any significant difference in hypoglycemia rates between

the different regimens (129). In an observational study in our own center of 41 people with type 2 diabetes treated with bedtime NPH (isophane) insulin and oral antidiabetic drugs, 49% had experienced infrequent mild hypoglycemia since commencing insulin, with an incidence of four episodes per patient per year and no episodes of severe hypoglycemia (130). Insulin analogs appear to limit hypoglycemia. In some studies, the risk of hypoglycemia has been reported to be lower with long-acting insulin glargine (131–134) and insulin detemir (135) when compared with NPH insulin. Glargine was also associated with a lower frequency of hypoglycemia than premixed insulins (136,137). Rapid-acting insulin analogs, such as lispro and glulisine, were also associated with a lower frequency of hypoglycemia in people with type 2 diabetes when compared with short-acting (soluble) regular insulins (138–140).

While continuous subcutaneous insulin infusion (CSII) is beneficially used in selected participants with type 1 diabetes, at present this method of insulin delivery is not commonly employed in people with type 2 diabetes. In a randomized trial of 121 male participants with type 2 diabetes, CSII was compared with multiple dose insulin. Comparable glycemic control was obtained with both regimens, with a lower incidence of mild hypoglycemia in the CSII group (28.4 vs. 9.5 events per patient-year, $P < 0.001$) (141), although no effect was observed on the incidence of severe hypoglycemia. A 12-month prospective randomized study in 107 adults with insulin-treated type 2 diabetes showed no significant difference between CSII and multiple dose insulin in the rates of mild or severe hypoglycemia (142).

Studies of alternative formulations of insulin, which can be administered by inhalation, include a 6-month randomized trial of 299 participants with type 2 diabetes in which inhaled insulin was compared with subcutaneous insulin. Glycemic control was comparable and inhaled insulin was associated with a relative risk of all hypoglycemia of 0.89 (95% CI 0.82–0.97) when compared with subcutaneous insulin (143).

New agents for the treatment of type 2 diabetes

A detailed discussion of new treatment modalities for type 2 diabetes is beyond the scope of this review. Analogs of glucagon-like peptide-1 are associated with improvements in glycemic control (144–148). Although they may provoke reactive hypoglycemia in nondiabetic volunteers (149), they do not appear to cause hypoglycemia in people with type 2 diabetes (150,151).

CONCLUSIONS — Few studies of hypoglycemia in people with type 2 diabetes have addressed the potential effects of ageing per se, but the available evidence suggests that it modifies the counterregulatory and symptomatic responses to hypoglycemia. In older people, effective self-treatment of hypoglycemia may be compromised by the juxtaposition of the glycemic thresholds for onset of symptoms and cognitive dysfunction, which occur almost simultaneously, and these age-related changes will be relevant to many people with type 2 diabetes. Most studies that have examined the responses to hypoglycemia in type 2 diabetes have overlooked the potential effects of ageing on counterregulation by selecting middle-aged subjects. The paucity of data from elderly people is of concern, as this age-group is at greatest risk from the morbidity of hypoglycemia, particularly as their presenting features are often misinterpreted and they may not receive prompt treatment. In type 2 diabetes, counterregulatory responses to hypoglycemia commence at higher blood glucose levels than those observed in nondiabetic adults or in people with type 1 diabetes, and this may have a protective effect. Blood glucose thresholds are influenced by glycemic control, and when A1C is reduced with insulin therapy, they are shifted to lower blood glucose levels. With progressive insulin deficiency, people with type 2 diabetes develop counterregulatory deficiencies and impaired symptomatic awareness, similar to type 1 diabetes.

Hypoglycemia has been considered to be a mild and infrequent side effect of treatment in type 2 diabetes, but insufficient and misleading information may have encouraged this misperception. It occurs most frequently with insulin therapy, but sulfonylurea-induced hypoglycemia is also a significant problem. Hypoglycemia is less frequent with the second generation sulfonylureas. Glimepiride, modified release gliclazide, and the prandial glucose regulators may also limit hypoglycemia risk.

Variations in study design, heterogeneity of study populations, and differing definitions of hypoglycemia have confounded attempts to derive accurate overall figures for the frequency of hypoglycemia in type 2 diabetes. Although less common than in type 1 diabetes, the frequency of hypoglycemia in insulin-treated type 2 diabetes progressively rises with increasing duration of insulin treatment. The use of insulin analogs may limit, but does not eradicate, the risk of hypoglycemia. In insulin-treated type 2 diabetes, the frequency of hypoglycemia must not be underestimated, particularly in the elderly, in whom the morbidity of hypoglycemia poses particular problems, and the mortality may be unrecognized.

Acknowledgments — N.N.Z. was supported by a grant from the Juvenile Diabetes Research Foundation.

References

1. Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002
2. United Kingdom Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–852, 1998
3. Cryer PE: Glucose counterregulation in man. *Diabetes* 30:261–264, 1981
4. Schwartz NS, Clutter WE, Shah SD, Cryer PE: Glycemic thresholds for activation of glucose counterregulatory systems are higher than the thresholds for symptoms. *J Clin Invest* 79:777–781, 1987
5. Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J: Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms and cerebral dysfunction. *Am J Physiol* 266:E67–E74, 1991
6. King P, Macdonald IA: Normal glucose metabolism and response to hypoglycaemia. In *Hypoglycaemia in Clinical Diabetes*. Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley and Sons, 1999, p. 29–54
7. Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Di Vincenzo A, Modarelli F, Ciofetta M, Lepore M, Annibale B, Torlone E, Periello G, De Feo P, Santeusanio F, Brunetti P, Bolli GB: Long term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia following institution of rational intensive therapy in IDDM. *Diabetologia* 37:1265–1276, 1994

8. Frier BM, Fisher BM: Impaired hypoglycaemia awareness. In *Hypoglycaemia in Clinical Diabetes.* Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley and Sons, 1999, p. 111–146
9. Deary IJ: Symptoms of hypoglycaemia and effects on mental performance and emotions. In *Hypoglycaemia in Clinical Diabetes.* Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley and Sons, 1999, p. 29–54
10. McAulay V, Deary IJ, Frier BM: Symptoms of hypoglycaemia in people with diabetes. *Diabet Med* 18:690–705, 2001
11. Deary IJ, Hepburn DA, MacLeod KM, Frier BM: Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 36:771–777, 1993
12. Brierley EJ, Broughton DL, James OFW, Alberti KGMM: Reduced awareness of hypoglycaemia in the elderly despite an intact counterregulatory response. *Q J Med* 88:439–445, 1995
13. Matyka K, Evans M, Lomas J, Cranston I, Macdonald I, Amiel SA: Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. *Diabetes Care* 20:135–141, 1997
14. Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM: Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. *Diabet Med* 15:398–401, 1998
15. Meneilly GS, Cheung E, Tuokko H: Altered responses to hypoglycemia of healthy elderly people. *J Clin Endocrinol Metab* 78:1341–1348, 1994
16. Meneilly GS, Cheung E, Tuokko H: Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. *Diabetes* 43:403–410, 1994
17. Hochstaedt BB, Shneebaum M, Shadel M: Adrenocortical responsivity in old age. *Gerontologia Clinica* 3:239–246, 1961
18. Friedman M, Greeb M, Shraland DE: Assessment of hypothalamo-pituitary-adrenal function in the geriatric age group. *J Gerontol* 24:292–297, 1969
19. Kalk WJ, Virik AI, Pimstone BL, Jackson WPU: Growth hormone response to insulin hypoglycemia in the elderly. *J Gerontol* 28:431–433, 1973
20. Muggeo M, Fedele D, Tiengo A, Molinari M, Crepaldi G: Human GH and cortisol response to insulin stimulation in the aged. *J Gerontol* 30:546–551, 1975
21. Schramm VA, Pusch HJ, Franke H, Haubitz I: Hormonal adaptive capacity in old age: behaviour of hormonal parameters after insulin hypoglycaemia in young and old patients. *Fortschr Med* 99: 1255–1260, 1981
22. Marker JC, Cryer PE, Clutter WE: Attenuated glucose recovery from hypoglycemia in the elderly. *Diabetes* 41:671–678, 1992
23. Ortiz-Alonso FJ, Galecki A, Herman WH, Smith MJ, Jacquez JA, Halter JB: Hypoglycemia counterregulation in elderly humans: relationship to glucose levels. *Am J Physiol* 267:E497–E506, 1994
24. Reaven GM, Greenfield MS, Mondon CE, Rosenthal M, Wright D, Reaven EP: Does insulin removal rate from plasma decline with age? *Diabetes* 31:670–673, 1982
25. Minaker KL, Rowe JW, Torino R, Pallotta JA: Influence of age on clearance of insulin in man. *Diabetes* 31:851–855, 1982
26. Fink RI, Revers RR, Kolterman OG, Olefsky JM: The metabolic clearance of insulin and the feedback inhibition of insulin secretion are altered with ageing. *Diabetes* 34:275–280, 1985
27. Gerich JE: Glucose counterregulation and its impact on diabetes mellitus. *Diabetes* 37:1608–1617, 1988
28. Gerich JE, Bolli GB: Counterregulatory failure. In *Hypoglycaemia and Diabetes: Clinical and Physiological Aspects.* Frier BM, Fisher BM, Eds. Edward Arnold, London, 1993, p. 253–267
29. De Galan BE, Hoekstra JBL: Glucose counterregulation in type 2 diabetes mellitus. *Diabet Med* 18:519–527, 2001
30. Bolli G, Tsalikian E, Haymond M, Cryer P, Gerich JE: Defective glucose counterregulation after subcutaneous insulin in noninsulin dependent diabetes mellitus: paradoxical lack of compensatory increase in glucose production, roles of insulin resistance, abnormal neuroendocrine responses and islet paracrine interactions. *J Clin Invest* 73:1532–1541, 1984
31. Campbell LV, Kraegen EW, Meler H, Lazarus L: Hormonal responses to insulin infusion in diabetes mellitus. *Diabetologia* 16:359–364, 1979
32. Levitt NS, Vinik AJ, Sive AA, Child P, Jackson WP: Studies on plasma glucagon concentration in maturity-onset diabetics with autonomic neuropathy. *Diabetes* 28:1015–1021, 1979
33. Heller SR, Macdonald IA, Tattersall RB: Counterregulation in type II (non-insulin-dependent) diabetes mellitus: normal endocrine and glycaemic responses up to 10 years after diagnosis. *Diabetologia* 30:924–929, 1987
34. Boden G, Soriano M, Hoeldtke RD, Owen OE: Counterregulatory hormone release and glucose recovery after hypoglycemia in non-insulin-dependent patients. *Diabetes* 32:231–237, 1983
35. Laager R, Keller U: Effects of recombinant human insulin-like growth factor I and insulin on counterregulation during acute plasma glucose decrements in normal and type 2 (non-insulin-dependent) diabetic subjects. *Diabetologia* 36:966–971, 1993
36. Spyer G, Hattersley A, Macdonald IA, Amiel S, MacLeod KM: Hypoglycemic counterregulation at normal blood glucose concentrations in patients with well controlled type 2 diabetes. *Lancet* 356: 1970–1974, 2000
37. Korzon-Burakowska A, Hopkins D, Matyka K, Lomas J, Pernet A, Macdonald I, Amiel S: Effects of glycemic control on protective responses against hypoglycemia in type 2 diabetes. *Diabetes Care* 21: 283–290, 1998
38. Levy CJ, Kinsley BT, Bajaj M, Simonson DC: Effect of glycemic control on glucose counterregulation during hypoglycemia in NIDDM. *Diabetes Care* 21: 1330–1338, 1998
39. Amiel SA, Maran A, Powrie JK, Umpleby AM, Macdonald IA: Gender differences in counterregulation to hypoglycaemia. *Diabetologia* 36:460–464, 1993
40. Davis SN, Fowler S, Costa F: Hypoglycemic counterregulatory responses differ between men and women with type 1 diabetes. *Diabetes* 49:56–72, 2000
41. Davis SN, Shavers C, Costa F: Differential gender responses to hypoglycemia are due to alterations in CNS drive and not glycemic thresholds. *Am J Physiol* 279:E1054–E1063, 2000
42. Sandoval DA, Ertl AC, Richardson MA, Tate DB, Davis SN: Estrogen blunts neuroendocrine and metabolic responses to hypoglycemia. *Diabetes* 52:1749–1755, 2003
43. Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Ciofetta M, Modarelli F, Di Vincenzo A, Annibale B, Lepore M, Lalli C, Del Sindaco P, Brunetti P, Bolli GB: Relative roles of insulin and hypoglycaemia on induction of neuroendocrine responses to, symptoms of and deterioration of cognitive function in hypoglycaemia in male and female humans. *Diabetologia* 37:797–807, 1994
44. Diamond MP, Hallerman L, Starick-Zych K, Jones TW, Connolly-Howard M, Tamborlane WV, Sherwin RS: Suppression of counterregulatory hormone response to hypoglycemia by insulin per se. *J Clin Endocrinol Metab* 72:1388–1390, 1991
45. Liu D, Moberg E, Kollind M, Lins PE, Adamson U: A high concentration of circulating insulin suppresses the glucagon response to hypoglycemia in normal man. *J Clin Endocrinol Metab* 73:1123–1128, 1991
46. Liu DT, Adamson UC, Lins PE, Kollind ME, Moberg EA, Andreasson K: Inhibitory effect of circulating insulin on glucagon secretion during hypoglycemia in type I diabetic patients. *Diabetes Care* 15: 59–65, 1991
47. Davis SN, Goldstein RE, Jacobs J, Price L, Wolfe R, Cherrington AD: The effects

of differing insulin levels on the hormonal and metabolic response to equivalent hypoglycemia in normal humans. *Diabetes* 42:263–272, 1993
48. Davis SN, Goldstein RE, Price L, Jacobs J, Cherrington AD: The effects of insulin on the counterregulatory response to equivalent hypoglycemia in patients with insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 77:1300–1307, 1993
49. Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 26: 1902–1912, 2003
50. Shamoon H, Friedman A, Canton C, Zacharowicz L, Hu M, Rossetti L: Increased epinephrine and skeletal muscle responses to hypoglycemia in non-insulin-dependent diabetes mellitus. *J Clin Invest* 93:2562–2571, 1994
51. Segel SA, Paramore DA, Cryer PE: Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 51: 724–733, 2002
52. Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a vicious cycle. *Diabetes* 41:255–260, 1992
53. Cryer PE: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350:2272–2279, 2004
54. Maggs DG, Jacob R, Rife F, Caprio S, Tamborlane WV, Sherwin RS: Counterregulation in peripheral tissues: effect of systemic hypoglycemia on levels of substrates and catecholamines in human skeletal muscle and adipose tissue. *Diabetes* 46:70–76, 1997
55. Woerle HJ, Meyer C, Popa EM, Cryer PE, Gerich JE: Renal compensation for impaired hepatic glucose release during hypoglycemia in type 2 diabetes: further evidence for hepatorenal reciprocity. *Diabetes* 52:1386–1392, 2003
56. Landstedt-Hallin L, Adamson U, Lins P-E: Oral glibenclamide suppresses glucagon secretion during insulin-induced hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab* 84:3140–3145, 1999
57. McAulay V, Frier BM: Hypoglycaemia. In *Diabetes in Old Age*. 2nd ed. Sinclair AJ, Finucane P, Eds. Chichester, U.K., John Wiley and Sons, 2001, p. 133–152
58. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V: Association of hypoglycemia and cardiac ischemia. *Diabetes Care* 26:1485–1489, 2003
59. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y: Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med* 159:281–284, 1999
60. Thomson FJ, Masson EA, Leeming JT, Boulton AJM: Lack of knowledge of symptoms of hypoglycaemia by elderly diabetic patients. *Age Ageing* 20:404–406, 1991
61. Pegg A, Fitzgerald D, Wise D, Singh BM, Wise PH: A community-based study of diabetes-related skills and knowledge in elderly people with insulin-requiring diabetes. *Diabet Med* 8:778–781, 1991
62. Mutch WJ, Dingwall-Fordyce I: Is it a hypo? Knowledge of the symptoms of hypoglycaemia in elderly diabetic patients. *Diabet Med* 2:54–56, 1985
63. Lawrence PA, Cheely J: Deterioration of diabetic patients' knowledge and management skills as determined during out-patient visits. *Diabetes Care* 3:214–218, 1980
64. Pramming S, Thorsteinsson B, Bendtson I, Binder C: Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabet Med* 8:217–222, 1991
65. Pedersen-Bjergaard U, Pramming S, Heller SR Wallace TM, Rasmussen AK, Jorgensen HV, Matthews DR, Hougaard P, Thorsteinsson B: Severe hypoglycemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. *Diabetes Metab Res Rev* 20: 479–486, 2004
66. MacLeod KM, Hepburn DA, Frier BM: Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. *Diabet Med* 10:238–245, 1993
67. ter Braak EWMT, Appelman AMMF, van de Laak M, Stolk RP, van Haeften TW, Erkelens DW: Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia. *Diabetes Care* 23:1467–1471, 2000
68. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
69. Stephenson J, Fuller JH, the EURODIAB IDDM Complications Study Group: Microvascular and acute complications in IDDM patients: the EURODIAB IDDM complications study. *Diabetologia* 37: 278–285, 1994
70. Gold AE, MacLeod KM, Frier BM: Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 17:697–703, 1994
71. Frier BM: Intensive glycaemic management in type 1 diabetes. In *The Evidence Base for Diabetes Care*. Williams R, Herman W, Kinmonth AL, Wareham NJ, Eds., Chichester, U.K., John Wiley and Sons, 2002, p. 317–332
72. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B: Recall of severe hypoglycemia and self-estimated state of awareness in type 1 diabetes. *Diabetes Metab Res Rev* 19:232–240, 2003
73. Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B: Recall of severe hypoglycaemic episodes and course of hypoglycaemia awareness in insulin treated type 2 diabetes in one year follow-up (Abstract). *Diabetologia* 46 (Suppl. 2):A304, 2003
74. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, Emanuele NV, Levin SR, Henderson W, Lee HS: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM): results of the feasibility trial. *Diabetes Care* 18:1113–1123, 1995
75. Jennings AM, Wilson RM, Ward JD: Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care* 12:203–207, 1989
76. Miller CD, Philips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM: Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 161:1653–1659, 2001
77. Shorr RI, Ray WA, Daugherty JR, Griffin MR: Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 157:1681–1686, 1997
78. Gurlek A, Erbas T, Gedik O: Frequency of severe hypoglycaemia in type 1 and type 2 diabetes during conventional insulin therapy. *Exp Clin Endocrinol Diabetes* 107:220–224, 1999
79. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD, the DARTS/MEMO Collaboration: Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 26:1176–1180, 2003
80. Frier BM: Hypoglycaemia in the diabetic adult. *Baillieres Clin Endocrinol Metab* 7:567–623, 1993
81. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese GP, the DARTS/MEMO Collaboration: Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population based study. *Diabet Med* 22:449–455, 2005
82. Henderson JN, Allen KV, Deary IJ, Frier BM: Hypoglycaemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med* 20: 1016–1021, 2003
83. Hepburn DA, MacLeod KM, Pell ACH, Scougal IJ, Frier BM: Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med* 10:231–237, 1993
84. Chico A, Vidal-Rios P, Subira M, Novials A: The continuous glucose monitoring system is useful for detecting unrecognised hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic

control. *Diabetes Care* 26:1153–1157, 2003
85. Hay LC, Wilmhurst EG, Fulcher G: Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: the results of continuous glucose monitoring. *Diab Technol Therap* 5:19–26, 2003
86. Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC: A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus. *Arch Intern Med* 164:1445–1450, 2004
87. Chipkin SR, Klugh SA, Chasan-Taber L: Exercise and diabetes. *Cardiol Clin* 19: 489–505, 2001
88. Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Lucchina PG, Fiocchi F, Emanuelli G, Lenti G: Influence of physical training on blood glucose control, glucose tolerance, insulin secretion and insulin action in non-insulin-dependent diabetic patients. *Diabetes Care* 7:416–420, 1984
89. Larsen JJ, Dela F, Kjaer M, Galbo H: The effect of moderate exercise on postprandial glucose homeostasis in NIDDM patients. *Diabetologia* 40:447–453, 1997
90. Minuk HL, Vranic M, Marliss EB, Hanna AK, Albisser AM, Zinman B: Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes. *Am J Physiol* 240:E458–E464, 1981
91. Devlin JT, Hirshman M, Horton ED, Horton ES: Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes* 36:434–439, 1987
92. Rasmussen BM, Christiansen C, Rasmussen OW, Hansen C, Hermansen K: Alcohol and postexercise metabolic responses in type 2 diabetes. *Metabolism* 48:597–602, 1999
93. Avogaro A, Beltramello P, Gnudi L, Maran A, Valerio A, Miola M, Marin N, Crepaldi C, Confortin L, Costa F: Alcohol intake impairs glucose counterregulation during acute insulin-induced hypoglycemia in IDDM patients: evidence for a critical role of free fatty acids. *Diabetes* 42:1626–1634, 1993
94. Rasmussen BM, Orskov L, Schmitz O, Hermansen K: Alcohol and glucose counterregulation during acute insulin-induced hypoglycaemia in type 2 diabetic subjects. *Metabolism* 50:451–457, 2001
95. Asplund K, Wilholm B-E, Lithner F: Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia* 24:412–417, 1983
96. Hartling SG, Faber OK, Wegmann M-L, Wahlin-Boll E, Melander A: Interaction of ethanol and glipizide in humans. *Diabetes Care* 10:683–686, 1987
97. Seltzer HS: Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 18:163–183, 1989
98. Campbell IW: Hypoglycaemia and type 2 diabetes: sulphonylureas. In *Hypoglycaemia and Diabetes: Clinical and Physiological Aspects*. Frier BM, Fisher BM, Eds. London, Edward Arnold, 1993, p. 387–392
99. Campbell IW, Chalmers J, Herlihy OM: Sulphonylurea-induced hypoglycaemia in elderly people with diabetes. *Practical Diabetes* 11:102–103, 1994
100. Burge MR, Zeise T-M, Sobhy TA, Rassam AG, Schade DS: Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care* 22:2037–2043, 1999
101. Tattersall RB: Frequency, causes and treatment of hypoglycaemia. In *Hypoglycaemia in Clinical Diabetes*. Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley and Sons, 1999, p. 55–88
102. Harrigan RA, Nathan MS, Beattie P: Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity and treatment. *Ann Emerg Med* 38:68–78, 2001
103. United Kingdom Prospective Diabetes Study Group: A 6 year randomised controlled trial comparing sulfonylurea, insulin and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy (UKPDS 24). *Ann Intern Med* 128:165–175, 1998
104. Ferner RE, Neil HAW: Sulphonylureas and hypoglycaemia. *Br Med J* 296:949–950, 1988
105. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281–303, 1999
106. Davis TM, Daly F, Walsh JP, Ilett KF, Beilby JP, Dusci LJ, Barrett PH: Pharmacokinetics and pharmacodynamics of gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. *Br J Clin Pharmacol* 49:223–230, 2000
107. Harrower A: Gliclazide modified release: from once-daily administration to 24-hour blood glucose control. *Metabolism* 49 (Suppl. 2):7–11, 2000
108. Schernthaner G: Gliclazide modified release: a critical review of pharmacodynamic, metabolic and vasoprotective effects. *Metabolism* 52 (Suppl. 1):29–34, 2003
109. Stahl M, Berger W: Higher incidence of severe hypoglycaemia leading to hospital admission in type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. *Diabet Med* 16:586–590, 1999
110. Del Prato, Aragona M, Coppelli A: Sulfonylureas and hypoglycaemia. *Diabetes Nutr Metab* 15:444–451, 2002
111. Rendell M: The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 64:1339–1358, 2004
112. Tessier D, Dawson K, Tetrault JP, Bravo G, Meneilly GS: Glibenclamide versus gliclazide in type 2 diabetes of the elderly. *Diabet Med* 11:974–980, 1994
113. Jonsson A, Chan JC, Rydberg T, Vaaler S, Hallengren B, Cockram CS, Critchley JA, Melander A: Pharmacodynamics and pharmacokinetics of intravenous glibenclamide in Caucasian and Chinese patients with type-2 diabetes. *Eur J Clin Pharmacol* 55:721–727, 2001
114. ter Braak EWMT, Appelman AMMF, van Der Tweel I, Erkelens DW, van Haeften TW: The sulfonylurea glibenclamide induces impairment of glucagon and growth hormone responses during mild insulin-induced hypoglycemia. *Diabetes Care* 25:107–112, 2002
115. Banarer S, McGregor V, Cryer PE: Intraislet hyperinsulinemia prevents the glucagon response to hypoglycemia despite an intact autonomic response. *Diabetes* 51:958–965, 2002
116. Asplund K, Wilholm B-E, Lundman B: Severe hypoglycaemia during treatment with glipizide. *Diabet Med* 8:726–731, 1991
117. Muller G, Hartz D, Punter J, Okonomopulos R, Kramer W: Differential interaction of glimepiride and glibenclamide with the β-cell-sulfonylurea receptor: binding characteristics. *Biochim Biophys Acta* 1191:267–277, 1994
118. Draeger KE, Wernicke-Panten K, Lomp H-J, Schuler E, Rosskamp R: Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl): a double-blind comparison with glibenclamide. *Horm Metab Res* 28:419–425, 1996
119. Raptis SA, Hatziagelaki E, Dimitriadis G, Draeger KE, Pfeiffer C, Raptis AE: Comparative effects of glimepiride and glibenclamide on blood glucose, C-peptide and insulin concentrations in the fasting and postprandial state in normal man. *Exp Clin Endocrinol Diabetes* 107:350–355, 1999
120. Holstein A, Plaschke A, Egberts E-H: Lower incidence of severe hypoglycemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev* 17:467–473, 2001
121. Veitch PC, Clifton-Bligh RJ: Long-acting sulphonylureas: long-acting hypoglycemia. *Med J Australia* 180:84–85, 2004
122. Rosenkranz B, Profozic V, Metalko Z, Mrzljak V, Lange C, Malerczyk V: Pharmacokinetics and safety of glimepiride at clinical doses in diabetic patients with renal impairment. *Diabetologia* 39: 1617–1624, 1996
123. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, Novials A, Rottiers R, Rutten GEHM, Shaw KM, the GUIDE Study: Double blind comparison of once-daily glicla-

zide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 34:535–542, 2004
124. Strange P, Schwartz SL, Graf RJ, Polvino W, Weston I, Marbury TC, Huang WC, Goldberg RB: Pharmacokinetics, pharmacodynamics, and dose-response relationship of repaglinide in type 2 diabetes. *Diabetes Technol Ther* 1:247–256, 1999
125. Kristensen JS, Frandsen KB, Bayer T, Muller P: Compared with repaglinide, sulfonylurea treatment in type 2 diabetes is associated with a 2.5-fold increase in symptomatic hypoglycemia with blood glucose levels <45 mg/dl (Abstract). *Diabetes* 49 (Suppl. 1):A131, 2000
126. Kristensen JS, Frandsen KB, Bayer T, Muller P: Repaglinide treatment is associated with significantly less severe hypoglycemic events compared to sulphonylurea. *Diabetologia* 42 (Suppl. 1):A4, 1999
127. Culy CR, Jarvis B: Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 61:1625–1660, 2001
128. Rosenstock J, Hassman DR, Madder RD Brazinsky, Farrell J, Khutoryansky N, Hale PM: Repaglinide versus nateglinide monotherapy. *Diabetes Care* 27:1265–1270, 2004
129. Goudswaard A, Furlong NJ, Rutten G, Stolk R, Valk G: Insulin monotherapy vs. combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus (Cochrane review). *Cochrane Database of Systematic Reviews* 4:CD003418, 2004
130. Allen KV, McAulay V, Sommerfield AJ, Frier BM: Hypoglycaemia is uncommon with a combination of antidiabetic drugs and bedtime NPH insulin for type 2 diabetes. *Pract Diab Int* 21:179–182, 2004
131. Yki-Järvinen H, Dressler A, Ziemen M, the HOE 901/3002 Study Group: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23:1130–1136, 2000
132. Rosenstock J, Schwartz SL, Clark CM, Park GD, Donley DW, Edwards MB: Basal insulin therapy in type 2 diabetes. *Diabetes Care* 24:631–636, 2001
133. Rosenstock J, the HOE 901/204 Study Investigators Group: Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in type 2 diabetic patients. *Diabet Med* 20:545–551, 2003
134. Riddle MC, Rosenstock J, Gerich J, the Insulin Glargine 4002 Study Investigators: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086, 2003
135. Hermansen K, Derezinski T, Kim H, Gall M-A: Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycaemia and less weight gain than NPH insulin at comparable levels of glycaemic improvement in people with type 2 diabetes (Abstract). *Diabetologia* 47 (Suppl. 1):A273, 2004
136. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial therapy for type 2 diabetes. *Diabetes Care* 28:254–259, 2005
137. Raskin P, Allen E, Hollander P, Gabay RA, Hu P, Bode B, Garber A, the INITIATE Study Group: Initiating insulin theapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 26:260–265, 2005
138. Bastyr EJ, Huang Y, Brunelle RL, Vignati L, Cox DJ, Kotsamos JG: Factors associated with nocturnal hypoglycemia among patients with type 2 diabetes new to insulin therapy. *Diabetes Obes Metab* 2:39–46, 2000
139. McAulay V, Frier BM: Insulin analogues and other developments in insulin therapy for diabetes. *Expert Opin Pharmacother* 4:1141–156, 2003
140. Dailey G, Rosenstock J, Moses RG, Ways K: Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care* 27:2363–2368, 2004
141. Saudek CD, Duckworth WC, Giobie-Hurder A, Henderson WG, Henry RR, Kelley DE, Edelman SV, Zieve FJ, Adler RA, Anderson JW, Anderson RJ, Hamilton BP, Donner TW, Kirkman MS, Morgan NA: Implantable insulin pump versus multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomised clinical trial: Department of Veterans Affairs Implantable Insulin Pump Study Group. *JAMA* 276:1322–1327, 1996
142. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, AL Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P: A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 28:1568–1573, 2005
143. Hollander PA, Blonde L, Rowe R, Mehta AE, Milburn JL, Hershon KS, Chaisson J-L, Levin SR, the Exubera Phase III Study Group: Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes. *Diabetes Care* 27:2356–2362, 2004
144. Zander M, Madsbad S, Madsen JL, Holst JJ: Effect of 6-week course of glucagon-like peptide 1 on glycemic control, insulin sensitivity and beta-cell function in type 2 diabetes: a parallel group study. *Lancet* 359:824–830, 2002
145. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD: Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 26:2370–2377, 2003
146. Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bisack TA, Taylor K, Kim D, Aisporna M, Want Y, Baron AD: Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 88:3082–3088, 2003
147. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR, the NN2211–1310 International Study Group: Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog Liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 27:1335–1342, 2004
148. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O: One week's treatment with the long-acting glucagon-like peptide-1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and α- and β-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53:1187–1194, 2004
149. Meier JJ, Nauck MA: Glucagon-like peptide 1 (GLP-1) in biology and pathology. *Diabetes Metab Res Rev* 21:91–117, 2005
151. Vilsbøll T, Krarup T, Madsbad S, Holst JJ: No reactive hypoglycemia in type 2 diabetic patients after subcutaneous administration of GLP-1 and intravenous glucose. *Diabetes Care* 18:144–149, 2001
151. Knop FK, Vilsbøll T, Larsen S, Madsbad S, Holst J, Krarup T: No reactive hypoglycemia after subcutaneous administration of glucagon-like peptide-1 in lean type 2 diabetic patients and in patients with diabetes secondary to chronic pancreatitis. *Diabetes Care* 26:2581–2587, 2003