Altered Hierarchy of Protective Responses Against Severe Hypoglycemia in Normal Aging in Healthy Men

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OBJECTIVE — To investigate the effect of normal aging on the protective responses against hypoglycemia, in view of the fact that type II diabetes is primarily a disease of aging, and its treatment is associated with risk of hypoglycemia with cognitive impairment.

RESEARCH DESIGN AND METHODS — Plasma glucose was lowered stepwise from 5 to 2.4 mmol/l and restored by manipulation of an infusion of 20% glucose during 220-min intravenous infusion of 1.5 mU · kg^{-1} · min^{-1} soluble insulin in 14 men; 7 were aged 60–70 years and the other 7 were 22–26 years. Changes in neurohumoral responses, subjective awareness, and choice reaction time were assessed.

RESULTS — Hormonal responses were similar in the two groups, but symptoms began earlier in the younger men (at a plasma glucose of 3.6 ± 0.1 vs. 3.0 ± 0.2 mmol/l, $P = 0.02$) and were more intense ($P = 0.03$). Four-choice reaction time, a measure of psychomotor coordination, deteriorated earlier in the older men (at a plasma glucose of 3.0 ± 0.1 vs. 2.6 ± 0.1 mmol/l, $P = 0.07$) and to a greater degree. The difference between the glucose level for subjective awareness of hypoglycemia and the onset of cognitive dysfunction was lost in the older men (0.0 ± 0.2 vs. 0.8 ± 0.1 mmol/l, $P < 0.007$).

CONCLUSIONS — Older men are prone to more severe cognitive impairment during hypoglycemia than younger men and are less likely to experience prior warning symptoms if blood glucose falls. This effect of normal aging may contribute to the risk of severe hypoglycemia in older diabetic patients treated with sulfonylureas and insulin.

Patients with diabetes are at risk of hypoglycemia as soon as they start treatment with exogenous hypoglycemic agents. Indeed, the fear of hypoglycemia is one of the most important limitations on optimal diabetes control (1), and much work has been done on the protective responses to hypoglycemia both in healthy adults and in patients with type I diabetes. In the latter, defects in the "normal" glucoregulatory pathways have been demonstrated (2) and are associated with increased risk of asymptomatic and severe hypoglycemia (3–5).

Increasing age has been quoted as a contributor to the loss of awareness of hypoglycemia in diabetes (6), and there is evidence of change in the physiological responses to hypoglycemia related to time of life in health. Healthy adults have less vigorous hormonal responses to hypoglycemia than do children and adolescents (7), and there are reports in the literature of diminishing growth hormone responsiveness to hypoglycemia with advancing age (8). Three studies have recently been published looking more extensively at counterregulation to controlled hypoglycemia in older healthy subjects, variably reporting diminished or similar hormonal and symptomatic responses in the older subjects (9–11). None of the studies were able reliably to identify the glucose thresholds for cognitive impairment and so could not examine the important question of whether the normal protective hierarchy of symptomatic responses to hypoglycemia preceding the onset of significant cognitive impairment is preserved in the elderly. This is an important issue because in patients with diabetes, changes in this hierarchy may contribute to the dangerous phenomenon of hypoglycemia without warning symptoms and hypoglycemia presenting as neuroglycopenia rather than as autonomic activation (12–14). Such neuroglycopenia is a common presentation of hypoglycemia in type II diabetic patients on sulfonylurea therapy (15–19), and these patients are often older. To clarify the effect of normal aging on responses to hypoglycemia and in particular to identify the relationship between the glucose thresholds for subjective awareness and evidence of intellectual impairment, we have therefore carried out controlled hypoglycemic clamp studies in two groups of healthy men, one group aged 60–70 years and the other aged 22–26 years, measuring aspects of cognitive function as well as symptomatic and hormonal responses.

RESEARCH DESIGN AND METHODS

— Seven healthy older men aged 65 ± 3 years comprised group 1. Group 2 was seven healthy younger men aged 23 ± 2 years. No subject had a personal or family history of diabetes, and each was screened by history, examination, and electrocardiography to exclude ischemic heart disease, convulsive disorder, and hypertension. No subject was taking medication. Two of the younger men were smokers. The subjects were not obese (BMI 23–26 in the older men and 21–24 in the younger men).

Each subject was admitted to the Metabolic Ward at Guy's Hospital, London, U.K., between 7:00 and 8:00 A.M., having not eaten or drunk after midnight and having abstained from alcohol or tobacco for 24 h. Two intravenous catheters were placed using 1% intradermal lidocaine as local anesthetic. The first catheter, for infusion of glucose and insulin, was inserted in

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a large vein of the nondominant hand, and the second, for sampling of arterialized venous blood, was placed retrogradely in a distal wrist or hand vein of the same arm and kept patent with a slow saline infusion. The hand was rested in a box of air heated to 55°C (20).

Subjects then trained on the apparatus for measuring four-choice reaction time (21,22). In this test, the subject is presented with a computer screen divided into four quadrants. A computer-generated signal appears in one quadrant at a time, and the subject has to clear the signal by pressing a corresponding button on an adapted keypad. Up to 500 signals are presented in 5 min. The mean time of the reactions and the accuracy (the percentage of correct responses) are recorded. Training occurs over a maximum of five assessments and is recognized as stability in the timing and accuracy of the reaction. Four-choice reaction time assesses a complex psychomotor function, involving perception, information processing, and a coordinated response. It is sensitive to acute hypoglycemia and reflects one (although by no means all) important function (reaction time) where impairment during acute clinical hypoglycemia in situations such as driving or operating machinery can have profound effect.

No less than 30 min after placement of the intravenous catheters, blood samples were taken for measurement of fasting glucose, insulin, C-peptide, and counterregulatory hormones. At time = 0 min, a primed continuous infusion of regular insulin (human Actrapid, Novo Nordisk, Pease Pottage, Surrey, U.K.; prepared in a 4% solution of autologous blood in 0.9% saline) was started at a maintenance rate of 1.5 mU $\cdot$ kg^{-1} $\cdot$ min^{-1} and run for 180 min. Plasma glucose, measured at the bedside at least once every 5 min, was maintained at 5 mmol/l for 40 min, then reduced in successive steps to 3.8, 3.4, 2.8, and 2.4 mmol/l before being restored at 140 min to 5 mmol/l for a final 40 min. Each glucose plateau was reached over 15 to 20 min and maintained for at least 20 min, so each step lasted 40 min in total, except the nadir, which was reached rapidly and held for a total of 20 min. Blood samples for later hormone measurement were taken at 20, 30, and 40 min, with symptom scores and four-choice reaction times recorded at 20 and 40 min, into each plateau. Samples for insulin, C-peptide, and pancreatic polypeptide were taken less frequently, at −40, 0, 80, 120, 140, 160, and 180 min only. At the end of any study, subjects received lunch. Glucose monitoring was continued until stable euglycemia was maintained spontaneously, after which all intravenous lines were withdrawn.

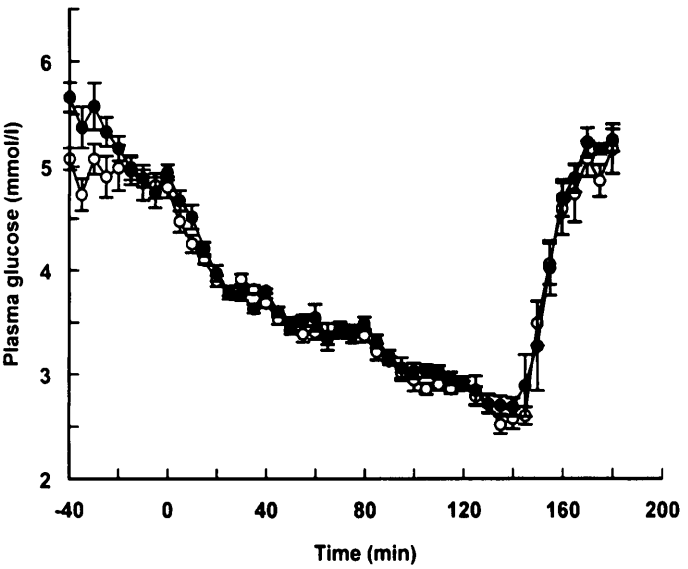

Figure 1—*Plasma glucose profiles during hyperinsulinemic clamps. The points represent means ± SE: younger men, ○; older men, ●. The hypoglycemic stimulus was the same in each group.*

Symptom scores were recorded by questionnaires in which each of 10 symptoms were ranked individually from 1 (absent) to 7 (very severe). Autonomic symptom scores were calculated from the scores for sweating, anxiety, trembling, heart pounding, feeling hot, and tingling. Neuroglycopenic symptom scores were calculated from the scores for difficulty speaking, confusion, dizziness, irritability, drowsiness, and blurred vision (23). Because the more recent classifications of hypoglycemic symptoms have cast doubt on attribution of "tingling" as autonomic and "blurred vision" as neuroglycopenic, a second analysis was also performed excluding these, and the results were compared (24). Tiredness and hunger were not included because they were reported by our subjects in the euglycemic studies.

The study was approved by the Lewisham and North Southwark Committee on Ethical Practice. Written informed consent was obtained from each subject before enrollment.

Laboratory assays

Blood glucose was measured using a glucose oxidase method (Yellow Springs glucose analyzer, YSI, Yellow Springs, OH). Catecholamines were measured by high-performance liquid chromatography (25); cortisol (26), growth hormone (27), pancreatic polypeptide, and free insulin (28) concentrations were measured by radioimmunoassay. Intra-assay variation for any assay was <10%. Thresholds for hormone responses were calculated arbitrarily in two ways: *1*) in statistical terms as the blood glucose level at which a given hormone concentration exceeded the mean of the five baseline (euglycemic) levels by >2 SD on two or more consecutive samples and 2) as a change in hormone level of probable clinical significance, namely, a rise over baseline in at least two consecutive samples that exceeded 0.44 pmol/l for epinephrine, 0.3 pmol/l for norepinephrine, 192 nmol/l for cortisol, and 18 mU/l for growth hormone. To define thresholds for changes in symptom scores, the observation that the selected symptoms do not change during euglycemic clamping in healthy subjects led us to define the glucose threshold for symptoms as the plasma glucose level at which symptom scores increased by two points or more on at least two consecutive ratings. Similarly, a significant deterioration in reaction time was considered to have occurred when there were two or more consecutive increments of 10% or more over the last of five measurements recorded at baseline. Because some subjects show impaired function as a slowing of reaction time, while others may maintain speed but become more inaccurate, we also sought loss of accuracy, defined as an increase of 2% or more over baseline in error rate. These definitions were based on

Table 1—*Hormonal responses to stepped hypoglycemia in younger and older men*

	Hormone peak response			Area under curve (per 140 min)		
	Older	Younger	*P* value	Older	Younger	*P* value
Epinephrine (nmol/l)	7.7 ±1.4	6.4 ± 1.4	0.5	348 ± 63	280 ± 45	0.4
Norepinephrine (nmol/l)	2.8 ± 0.7	1.5 ± 0.4	0.2	391 ± 60	260 ± 17	0.08
Glucagon (nmol/l)	32 ± 11	48 ± 16	0.4	15,605 ± 931	17,828 ± 1,396	0.2
Growth hormone (mU/l)	23 ± 3	48 ± 9	0.02	4,442 ± 3,089	1,397 ± 226	0.4
Cortisol (nmol/l)	445 ± 31	344 ± 45	0.09	59,304 ± 2,314	50,670 ± 5,180	0.15
Pancreatic polypeptide (pmol/l)	77 ± 16	62 ± 8	0.4	6,284 ± 2,415	5,111 ± 461	0.3

Data are means ± SE.

repeated measures made over 4 h in healthy volunteers using the same apparatus, in which we find a coefficient of variation of 5% in reaction time and 2% in accuracy (J.L., S.A.A., unpublished observations). If a significant change did not occur during hypoglycemia, the glucose nadir was entered as the threshold for the statistical analyses only.

Presentation of results

Demographic data are quoted as means ± SD, all other data are quoted as means ± SE. Hormone responses (area under curve) and comparison of thresholds were made by unpaired *t* testing. *P* values <0.05 were considered significant.

RESULTS

Plasma glucose, insulin, and C-peptide

Insulin infusion raised plasma insulin levels to peak levels of 534 ± 60 pmol/l in the older men and to 576 ± 54 pmol/l in the younger men ($P = 0.6$) and suppressed C-peptide levels to 11.49 ± 1.77 and 8.84 ± 0.88 µmol/l ($P = 0.15$), respectively. Fasting plasma glucose levels were slightly higher in the older men (5.9 ± 0.1 vs. 5.2 ± 0.1 mmol/l, $P = 0.0005$), but no subject had a value of >6.3 mmol/l and all had normal HbA_{1c}, making undiagnosed diabetes unlikely in any subject. There were no significant differences between the plasma glucose levels at 0 min, at any plateau, or at the glucose nadir between the groups (Fig. 1).

Counterregulatory hormone responses

Baseline counterregulatory hormone levels did not differ significantly between the groups (epinephrine, 0.18 ± 0.03 vs. 0.26 ± 0.05 nmol/l; older vs. younger, $P = 0.19$; growth hormone, 2.9 ± 1.0 vs. 2.1 ± 0.8 U/l, $P = 0.5$; and cortisol 261 ± 14 vs. 304 ± 34 mmol/l, $P = 0.27$), with the exception of norepinephrine, which was slightly higher in the older men (2.03 ± 0.2 vs. 1.3 ± 0.1 nmol/l, $P = 0.01$). There were no significant differences in the responses of epinephrine (Fig. 2), norepinephrine, glucagon, cortisol, and pancreatic polypeptide, whether analyzed as the peak response or the area under the curve (Table 1). Growth hormone peaks were higher in the younger men, but the total response as reported in the area under the curve was not greater. There were also no significant differences in the glucose levels associated with the onset of any of the responses of these hormones between the two groups, whether the statistical method (more than the baseline mean ± 2 SD) or the previously decided "clinically relevant" values were used to define a response (Table 2).

Symptom responses

Despite the similarity of hormonal responses, there were significant differences in the symptom responses between the two groups (Fig. 3). The older subjects were not aware of the "typical" symptoms of hypoglycemia until plasma glucose had reached a lower glucose level (3.0 ± 0.2 mmol/l) than that required to initiate symptoms in the younger men (3.6 ± 0.1 mmol/l, $P = 0.02$). This was entirely due to a lowering of the glucose level stimulating autonomic symptoms (Table 3). The data were not affected by the inclusion or exclusion of the symptom of "tingling," originally classified as autonomic but more recently dropped. The older men also reported significantly lower intensity of symptoms (peak scores 21 ± 2 vs. 27 ± 2, $P = 0.03$); again, this was due to changes in the reporting of autonomic symptoms. This difference was weakened (20 vs. 25, $P = 0.06$) by the exclusion of tingling, which was a prominent symptom in the younger men only, reported by five out of seven. Neither the

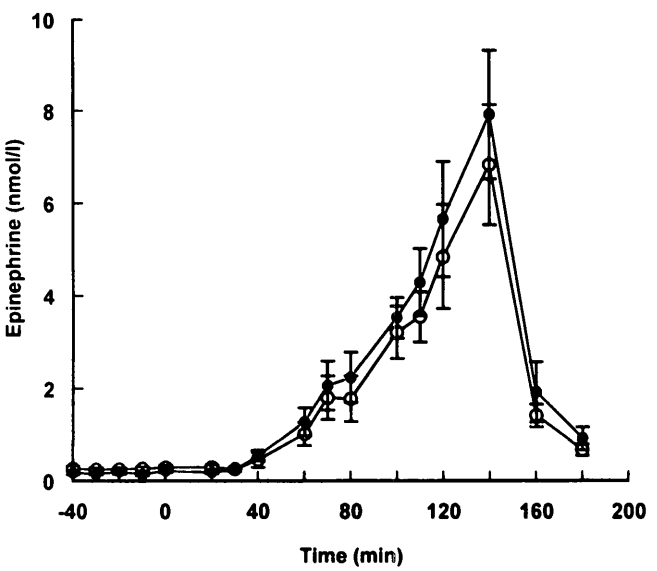

Figure 2—*Epinephrine responses to the hypoglycemic challenge. The curves are not different. Symbols as in Fig. 1.*

Table 2—*Glucose thresholds for release of counterregulatory hormones in younger and older men*

	Basal mean ± 2 SD			Clinical response		
	Older	Younger	*P* value	Older	Younger	*P* value
Epinephrine	3.7 ± 0.1	3.5 ± 0.1	0.06	3.4 ± 0.2	3.2 ± 0.2	0.30
Norepinephrine	3.3 ± 0.2	3.5 ± 0.2	0.7	3.4 ± 0.2	3.5 ± 0.2	0.82
Glucagon	2.9 ± 0.1	2.7 ± 0.2	0.44	—	—	—
Growth hormone	3.5 ± 0.1	3.3 ± 0.1	0.09	3.2 ± 0.2	2.8 ± 0.1	0.09
Cortisol	3.5 ± 0.1	3.3 ± 0.1	0.18	2.9 ± 0.2	2.8 ± 0.1	0.41

Data are means ± SE.

glucose threshold nor the intensity of neuroglycopenic symptoms were affected by aging, although blurred vision (again originally classified as neuroglycopenic) was reported by three of the older and by only one of the younger men.

Cardiovascular responses

There were only small changes in heart rate and blood pressure in each group. Heart rate did not change significantly in either (−2 ± 4 vs. +3 ± 5 beats per minute, $P = 0.4$). Blood pressure tended to fall in the older men, but the differences were not significant (change in systolic blood pressure −10 ± 9 vs. +5 ± 5 mmHg, $P = 0.2$, and in diastolic blood pressure −11 ± 4 vs. −9 ± 2 mmHg, $P = 0.4$).

Choice reaction time

The older men showed a much more marked deterioration in four-choice reaction time than the younger men (Fig. 4, comparing areas under the curves, $P = 0.016$). The reaction time also deteriorated earlier in the older men, at 3.0 ± 0.1 mmol/l vs. 2.6 ± 0.1 mmol/l in the younger men ($P = 0.07$). Although the *P* value does not indicate statistical significance, the estimate of threshold in the younger men is an overestimate because two subjects did not demonstrate any significant change during hypoglycemia and their glucose nadirs were used in the statistical calculations. Each of these men showed a significant loss of accuracy, however, as evidence of impaired performance on the four-choice reaction time, and no subject completed the study without a change in either speed or accuracy.

Comparing the difference in mean reaction time at each time point with an unpaired *t* test, there were significant differences at 80 min ($P = 0.02$, after 20 min of a plasma glucose of 3.4 mmol/l), at 100 min ($P = 0.04$, beginning of reduction to 2.8 mmol/l), and also at 160 min ($P = 0.002$), this last suggesting that the older men took longer to recover cognitive function.

Accuracy in reaction deteriorated at 2.8 ± 0.1 and 2.8 ± 0.1 mmol/l for the older and younger men, respectively. The glucose thresholds for any change in performance (speed or accuracy, taking the glucose value for whichever parameter changed first) was 3.0 ± 0.2 mmol/l in the older men and at 2.8 ± 0.1 mmol/l, $P = 0.27$.

There was thus a clear difference in the hierarchy of responses during hypoglycemia associated with aging. In the younger men, symptom scores rose before (i.e., at a higher plasma glucose level) any evidence of deterioration in performance of the four-choice reaction time. In the older men, this trend was either lost or actually reversed. The difference between the glucose level for symptom generation and that for cognitive dysfunction was 0.0 ± 0.2 mmol/l in the older men and 0.8 ± 0.1 mmol/l in the younger men, $P < 0.0068$.

Reaction times at baseline were slightly but significantly lower in the older men (789 ± 121 vs. 503 ± 23 ms, $P = 0.04$). To ensure that the difference in deterioration in the older men was not due to a higher baseline, we analyzed the percentage change from baseline to glucose nadir. This percentage change was greater in the older men (35 ± 6 vs. 21 ± 6%), but did not achieve significance ($P = 0.1$) because of an outlier in the younger men. This individual showed a deterioration of 56%, which is outside the range of the others in his group (7–23%). When his data were excluded, the percentage change achieved the same significance as the absolute (mean percentage change 15 ± 3, $P = 0.019$ vs. older men).

CONCLUSIONS — The neurohumoral responses to hypoglycemia are associated with the generation of symptoms. In a progressive decline in plasma glucose concentration, these symptomatic responses

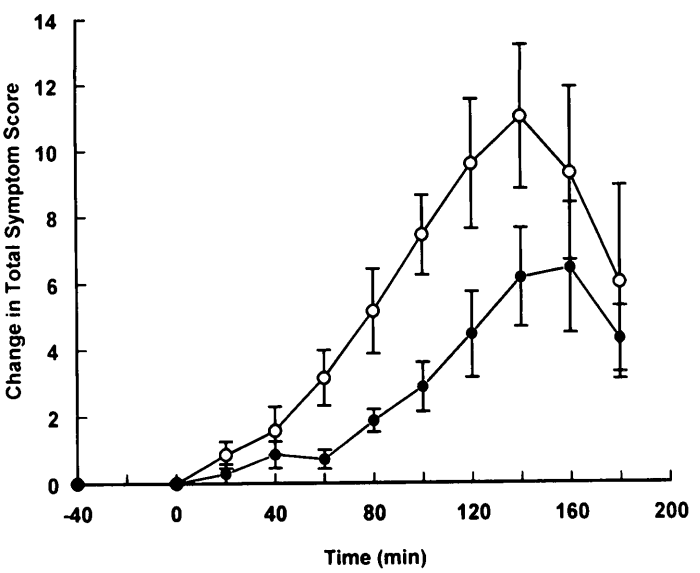

Figure 3—*Total symptom scores (increment over basal) from formal questionnaires using linear analogue scales during hypoglycemia. Symbols as in Fig. 1.*

Table 3—*Glucose thresholds for change in four-choice reaction time during stepped hypoglycemia in younger and older men*

	Older	Younger	*P* values
Symptoms			
Total	3.0 ± 0.2	3.6 ± 0.1	0.02
Autonomic	2.8 ± 0.2	3.4 ± 0.1	0.02
Neuroglycopenic	2.8 ± 0.2	2.8 ± 0.2	0.83
Cognitive function			
Reaction time	3.0 ± 0.2	2.6 ± 0.1	0.07*
Accuracy	2.8 ± 0.1	2.8 ± 0.1	1.0
Any change	3.0 ± 0.2	2.8 ± 0.1	0.27

Data are means ± SE. *Underestimate (see text).

usually precede the onset of the cognitive dysfunction that accompanies a failure of the glucose supply to the cerebral cortex (29). People at risk for hypoglycemia, most often people on drug therapy for diabetes, are therefore protected from severe neuroglycopenic episodes because the earlier responses tend to arrest the fall in plasma glucose. More importantly, patients learn to recognize the associated symptoms and take prompt corrective action, provided intellectual function is still adequate at the time. In patients with type I diabetes, the group most at risk for hypoglycemia, we and others have demonstrated a clear relationship between a lowering of the glucose level associated with the onset of the neurohumoral responses to hypoglycemia and increased risk of severe episodes (3,30,31). We have also shown a dissociation between the onset of the neurohumoral responses and the onset of cognitive dysfunction in people with a history of recurrent severe hypoglycemic episodes (13,32,33), which was also shown by Widom and Simonson (14).

While most work on this topic has been done in young people with and without type I diabetes, profound neuroglycopenia is a significant problem for patients with type II diabetes treated with sulfonylureas (15–19). These patients are typically older, and investigation of the pathophysiology of counterregulation in type II diabetes must logically start with details of the effect of aging on the physiological responses to hypoglycemia. Children and adolescents have more vigorous and earlier responses to hypoglycemia than young adults (7), but the data on the effects of aging after that are controversial. Older studies did suggest a loss of growth hormone and cortisol responses associated with older age (8); more recently, Meneilly et al. (9) described defective epinephrine and glucagon responses in older subjects, and Ortiz-Alonso et al. (11) found age to be associated with subtly reduced epinephrine, pancreatic polypeptide, and cortisol responses to a plasma glucose of 60 mg/dl (3.3 mmol/l). However, Brierley et al. (10) found no such effect of aging. Our study confirms this last, finding no effect of aging on the hormonal responses to hypoglycemia. The defect found in the two earlier studies may be due to the use of both men and women as subjects, since women have lower counterregulatory hormone responses to hypoglycemia (34), although the other study also used mixed-sex groups.

In diabetes, the magnitude of the neurohumoral response to hypoglycemia is less important in the protection against severe hypoglycemia than the subjective awareness associated with it and the order in which the protective symptomatic responses occur relative to the onset of hypoglycemia-associated cognitive impairment. Our study finds, as did two of the previous studies (9,10), a loss of intensity of the symptoms associated with hypoglycemia with age, despite the normal hormonal levels. This implies a loss of sensitivity to the neurohumoral responses, which is to some extent supported by the failure of pulse pressure to widen in the older men. An effect of age on the functioning of the autonomic nervous system may have contributed to the lack of perceived symptoms, as performance on the traditional (largely cardiovascular) autonomic function diminishes with age (35). However, the similarity of norepinephrine and pancreatic polypeptide responses between the age-groups in our study suggests that this is not a major feature. In contrast, the elderly mixed-sex group in the study by Ortiz-Alonso et al. did not overall show fewer hypoglycemic symptoms during clamping. There was a tendency to a smaller increase in symptom score at a plasma glucose of 60 mg/dl (3.3 mmol/l), which did not achieve significance and, in contrast to our study, was lost at lower glucose levels. Symptom scores were slightly higher at the end of the baseline (euglycemic) phase of this study in the older age-group, and it may be that the data from this study are not so discrepant from the others.

The differences between the symptoms reported by our younger and older men were most marked when we included all the symptoms in our original question-

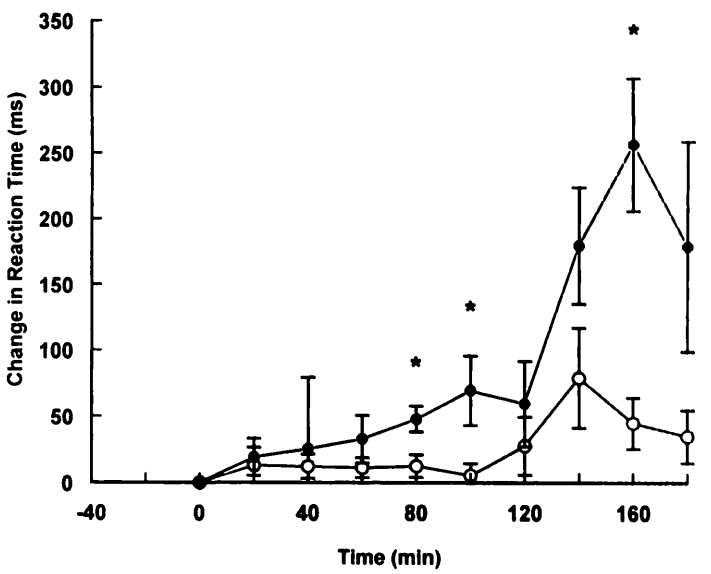

Figure 4—*Absolute increment in reaction times. Symbols as in Fig. 1.* *$P < 0.05$.

naires, which included some symptoms (notably tingling in the autonomic group and blurred vision in the neuroglycopenic group [23]) that were dropped in the most recent studies that grouped symptoms by statistical methods (24). For comparative purposes, we have also presented the analysis excluding these symptoms. However, the findings that tingling was more marked in younger men and that blurred vision was marked in older men not only establish their potential importance as age-related differences in hypoglycemia experience but may also explain why they were not so powerfully allocated into one or the other group by factor analysis in a study that included patients aged 13–79 years in single groups (24).

The new finding in our study lies in the demonstration of an important change in the hierarchy of the responses to hypoglycemia and in the delayed recovery of cognitive function in the older men. In the younger men, symptomatic and protective responses occurred at higher glucose levels than any evidence of cognitive impairment, but in the older men, cognitive impairment occurred first. This mirrors the situation in hypoglycemia-prone insulin-treated diabetic subjects (13,33) and indicates that the elderly are intrinsically at greater risk for asymptomatic serious hypoglycemia, from the beginning of any treatment with sulfonylureas and insulin. Our data also show a substantially increased susceptibility to cognitive impairment during hypoglycemia in our older men, with a greater deterioration in performance and also a slower rate of recovery. While there is no doubt that the result of a single cognitive function test cannot be extrapolated to all aspects of cognition, choice reaction time does reflect an important psychomotor function. Sudden unsuspected deterioration in reaction time in life situations (such as while driving or operating heavy machinery) might be disastrous, and the fact that this particular function was so adversely affected in the older men is evidence for a clinically relevant problem. Whether other cognitive functions will be differently affected in subjects of different ages is not known, but the demonstration that one important aspect of higher brain function is more susceptible to hypoglycemia in the elderly stands alone. It should be noted that these were healthy subjects with no previous experience of hypoglycemia, and the data have important implications for the risk and duration of confusion as a result of hypoglycemia in older people on treatment for diabetes.

Tiredness or boredom may contribute to impaired performance in cognitive function testing. Is it possible that the greater deterioration and delayed recovery seen in the older men during our study resulted from such factors rather than representing increased susceptibility to hypoglycemia alone? We do not have data on repeated measurements of four-choice reaction time during prolonged euglycemia specifically in this age-group, but the partial recovery in reaction time after restoration of euglycemia at the end of the study in the older men confirms the greater susceptibility of this test to hypoglycemia itself in this age-group, although an interaction with other factors cannot be ruled out. Clinically of course, an associated greater tendency to drowsiness during hypoglycemia in elderly men will further exacerbate the cognitive dysfunction.

The failure to demonstrate the loss of the protective hierarchy in hypoglycemic responses in earlier studies may be due in part to the use of mixed-sex study groups and the lower glucose concentrations needed to generate symptomatic and protective responses to hypoglycemia in women (34). Another confounding variable is the nature of the tests used to examine cognitive function repeatedly during experimental hypoglycemia. The four-choice reaction time changes earlier (i.e., is more sensitive) than the battery of cognitive function tests used elsewhere (2.4 mmol/l [29] vs. ~3 mmol/l), probably because such a battery takes time to administer (time during which either plasma glucose or cerebral function may be altering) and tests a wide variety of cognitive functions, some of which may be insensitive (or irrelevant) to acute hypoglycemia but will dilute a positive result. It is noteworthy that in the Meneilly study (9), the only changes in any cognitive function test that achieved statistical significance were seen in the older patients, supporting an increased susceptibility to hypoglycemia-induced cognitive impairment. This effect was lost when the scores were summated into a single *Z* score. Cognitive function was not measured in other studies of counterregulation in the elderly (10,11).

In conclusion, we find no evidence to support the hypothesis that aging in healthy men is associated with diminished or delayed counterregulatory hormone responses to hypoglycemia. We do however find that, despite an apparently similar hormonal response, older men lose awareness of hypoglycemia and are at risk for greater and more prolonged cognitive impairment. Most importantly, normal aging in men is associated with a change in the usual "protective" hierarchy of counterregulation, with cognitive dysfunction detectable at a higher plasma glucose than symptom generation and also with delayed recovery of intellectual function after hypoglycemia. This means that elderly men who require treatment for diabetes are likely to be at special risk for hypoglycemia without warning symptoms and at increased risk of severe hypoglycemia, once treatment with exogenous hypoglycemic agents is initiated. This possibility needs urgent further investigation in people with diabetes.

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