Roles of Circadian Rhythmicity and Sleep in Human Glucose Regulation*

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I. Introduction

In normal man, plasma glucose homeostasis results from a tightly controlled balance between glucose delivery (from the liver in the postabsorptive state and from the gut in the postprandial state) and glucose utilization. Insulin plays a key role in this process by inhibiting hepatic glucose production and by stimulating glucose uptake by insulin-sensitive tissues (mainly skeletal muscle and adipose tissue).

Human insulin secretion is a complex oscillatory process, including rapid pulses recurring every 10 to 15 min superimposed on slower oscillations with periods in the range of 90–120 min (1, 2). The so-called counterregulatory hormones, mainly glucagon, catecholamines, cortisol, and GH, are able to increase blood glucose concentrations by stimulating hepatic glucose production and/or inhibiting tissue glucose uptake. The daily secretion of cortisol and GH follows a complex pattern of temporal organization that reflects the control of their pulsatile release by the interaction of circadian rhythmicity (i.e., an endogenous oscillatory signal with a near 24-h period generated in the suprachiasmatic nuclei of the hypothalamus) and the sleep or wake state. Cortisol secretion is markedly modulated by circadian rhythmicity, while the majority of the daily GH output occurs after the onset of sleep. In the present review, the term “diurnal” will be used to designate temporal variations recurring regularly at a time interval of 24 h, regardless of their underlying causal mechanisms.

Human sleep is generally consolidated in a single 7- to 9-h period, whereas fragmentation of the sleep period in several bouts is the rule in other mammals. An important metabolic consequence of this organization of sleep and wake states is that an extended period of total fast must be maintained on a daily basis, generally during the overnight period. The consolidation of the sleep period is probably responsible for the fact that the wake-sleep and sleep-wake transitions in man are associated with physiological changes that are usually more marked than those observed in animals. Man is also unique in his capacity to ignore circadian signals and to maintain wakefulness despite an increased pressure to go to sleep. Voluntary sleep curtailment, rapid travel across time zones (i.e., “jet lag”), and shift work rotations are highly prevalent conditions in modern society, and their hormonal and metabolic implications have only begun to be recognized (3).

While the roles of sleep and circadian rhythmicity in the modulation of endocrine function have been most investigated for hormonal secretions that are directly dependent on the hypothalamo-pituitary axes, it is also well established that the characteristics of normal glucose regulation vary across the 24-h cycle (4). Abnormalities in the diurnal variation of glucose tolerance have been recently demonstrated in aging, obesity, and diabetes. These findings, which form the topic of the present review, may have significant clinical implications regarding the importance of time of day for the diagnosis and management of conditions of impaired glu-
cose tolerance. Indeed, a detailed understanding of the chronobiology of glucose regulation may provide strategies to improve dietary schedules and optimize the effects of hypoglycemic agents and insulin.

II. Characteristics and Causal Mechanisms of 24-h Rhythms of Glucose Regulation in Normal Young Subjects

A. 24-h variations in glucose tolerance

1. Daytime variations in glucose tolerance
   
a. In response to oral glucose. It has been recognized for more than two decades that, in normal subjects, the response to an oral glucose tolerance test varies according to time of day (5–10). In the afternoon and evening, blood glucose levels 1–2 h after ingestion of a 75-g oral glucose load are generally 1.7–2.8 mmol/liter (30–50 mg/dl) higher than when the test is performed in the morning. The term “afternoon diabetes” was coined to describe this phenomenon because of the increased potential of a false-positive diagnosis of diabetes in the afternoon, as compared with the morning (11). Well-controlled studies have demonstrated that “afternoon diabetes” does not reflect a difference in duration of prior fast but represents a true effect of time of day (9, 10, 12, 13). The observation of increased glucose responses to a standard oral glucose load is not limited to the afternoon and evening but actually persists during most of the night. The upper panel of Fig. 1 illustrates the results of a study involving the administration of eight consecutive 50-g glucose loads presented at 3-h intervals during the same 24-h cycle to normal volunteers. To control for the sequence effect, each subject received the first load at a different time point. The subjects remained seated in a comfortable armchair throughout the study and were allowed to sleep during the period 2300 h to 0700 h. Glucose levels in response to these repeated stimuli were clearly higher in the evening and during the first half of the night than in the morning and early afternoon.

   The insulin response to oral glucose is also affected by time of day, the increase being generally higher and of shorter duration in the morning and lower, delayed, and more prolonged in the evening (10, 12, 14).

   b. In response to identical meals. A morning to evening variation in glucose responses to identical mixed meals, consistent with the diurnal variation in responses to oral glucose, has also been demonstrated in several studies (15–19). The presence and magnitude of a morning to evening difference seemed to be dependent on meal size and composition (16–18). Indeed, the magnitude of the morning to evening increase in postmeal glucose responses increases with the size and carbohydrate content of the meal (17). A number of studies have indicated that effects of time of day may be more prominent in women than in men (16, 18, 20). In all early studies (15–18), the “evening” meal was actually given in the late afternoon, between 1630 and 1800 h. Even larger and more consistent effects of time of day were subsequently observed when the evening meal was consumed later, around 2000 h (19, 21). An example is shown in Fig. 1, which shows the glucose responses in response to the same meal (which included 43% of carbohydrates) given at 0800, 1400, and 2000 h. The area under the curve is more than 2-fold larger in the evening than in the morning. Measurements of serum insulin and of insulin secretion rates (ISR; derived from plasma C-peptide levels using a mathematical model for C-peptide distribution and clearance) indicate that postmeal serum insulin levels and ISR responses also increase when the day progresses, but to a lesser degree than glucose
responses. Thus, in the study illustrated in Fig. 1, peak levels of ISR were similar in the morning and in the evening, but the area under the curve was approximately 50% larger in the evening. The temporal patterns of plasma glucose and ISR have also been examined in subjects who received continuous enteral nutrition (22, 23). As exemplified in the mean profile shown in Fig. 1, despite the fact that the caloric intake was maintained constant, plasma glucose levels increased slowly from early afternoon until bedtime.

c. In response to intravenous glucose. Variations in the glucose and insulin responses to glucose stimulation across the daytime are more pronounced when the stimulus is given intravenously, rather than orally (4, 10, 24). Gastrointestinal factors are thus not the primary cause of the morning to evening decrease in glucose tolerance. The progressive decrease in glucose tolerance in the evening and early part of the night has also been clearly documented in studies in which the subjects were given a low dose iv infusion of glucose at a constant rate (e.g., 5 g/kg/24 h) for prolonged periods of time (24–30 h) and maintained at bed rest (2, 25). Irrespective of the timing of the initiation of the infusion, glucose concentrations begin to increase in the late afternoon or early evening. A mean profile of plasma glucose levels in recumbent fasted subjects studied during constant glucose infusion is shown in Fig. 1. Because the increase in glucose levels begins well before sleep time, and is observed in the absence of changes in activity state, it is likely to reflect an effect of circadian rhythmicity.

2. Nighttime variations in glucose tolerance

a. During overnight fast: the controversial “dawn phenomenon.” The consolidation of human sleep in a single 7- to 9-h period implies that an extended period of fast must be maintained overnight. A large number of studies have sampled levels of glucose and insulin in subjects sleeping in the laboratory and have observed that, despite the prolonged fasting condition, glucose levels remain stable or fall only minimally during the night (26–32). In contrast, during the daytime period, if subjects are fasting in a recumbent position, in the absence of any physical activity, daytime periods (24–30 h) and maintained at bed rest (2, 25). Irrespective of the timing of the initiation of the infusion, glucose concentrations begin to increase in the late afternoon or early evening. A mean profile of plasma glucose levels in recumbent fasted subjects studied during constant glucose infusion is shown in Fig. 1. Because the increase in glucose levels begins well before sleep time, and is observed in the absence of changes in activity state, it is likely to reflect an effect of circadian rhythmicity.

b. During constant glucose infusion or enteral nutrition. Experimental protocols allowing for the study of nighttime glucose tolerance during sleep without awakening the subjects include constant intravenous glucose infusion and continuous enteral nutrition. Confounding effects of food ingestion and prolonged fasting are avoided by replacing the normal caloric intake by a constant input, thereby creating a steady-state condition with levels of glucose and insulin secretion within the physiological range. Sleep has been polygraphically recorded under both conditions, and normal sleep parameters are observed after a period of habituation to the laboratory procedures. Thus, both constant glucose

in blood glucose levels and/or insulin requirements in the prebreakfast hours, similar to that occurring in diabetic patients but of much lesser magnitude, may occur in healthy subjects. Remarkably, none of the studies of the dawn phenomenon, whether in normal subjects or diabetic patients, have included polygraphic sleep recordings or controlled the sleep/wake state.

Fig. 2. Twenty four-hour patterns of blood glucose (top panel), glucose production (middle panel), and glucose utilization (lower panel) in normal recumbent subjects studied overnight and allowed to sleep from 0030 h until 0700 h (open symbols and solid line; mean ± SEM) and in normal recumbent subjects kept awake during the daytime (shaded area). The abscissa shows both 24-h clock times for time of day (top) and night (bottom). Data sources: Ref. 29 and unpublished data from F. Féry (Université Libre de Bruxelles, Belgium). [Adapted with permission from F. Féry: Journées de Diabetologie de l’Hôtel-Dieu, Flammarion Medicine-Sciences, 1996, pp 211–224 (175).]
infusion and continuous enteral nutrition offer the possibility of examining glucose tolerance during the sleep state, although under conditions that are clearly artificial. In particular, prolonged glucose infusion results in a marked inhibition of endogenous glucose production (37–39). Both experimental conditions have been used in extended studies in normal subjects (22, 23, 25) and results have demonstrated a marked decrease in glucose tolerance during nocturnal sleep (illustrated in the lower panels of Fig. 1). Despite the differences in the mode and nature of caloric intake, the glucose profiles observed in both conditions are remarkably similar and showed that glucose tolerance is markedly decreased during nocturnal sleep. Indeed, when individual profiles were analyzed, the overall increase in plasma glucose ranged from 20 to 30%, despite the maintenance of rigorously constant rates of caloric intake. Maximum levels occur around the middle of the sleep period, well before dawn. During the later part of the night, i.e., at the time of the so-called “dawn phenomenon,” glucose tolerance begins to improve and glucose levels progressively decrease toward morning values.

3. Studies delineating the respective roles of sleep and time of day. Studies involving intravenous glucose infusion or continuous enteral nutrition at a constant rate for 24–30 h showed that glucose tolerance begins to decrease well before bedtime and continues to deteriorate until approximately the middle of the night (23, 25), suggesting that both sleep-independent effects and sleep-dependent effects could be involved in producing the overall 24-h pattern. To define the respective roles of circadian rhythmicity (intrinsic effects of time of day independent of the sleep or wake condition) and sleep (intrinsic effects of sleep per se irrespective of the time of day) in the 24-h variation of glucose tolerance, experimental protocols that take advantage of the fact that circadian rhythms require several days to adapt to a change of sleep-wake and dark-light cycles have been used (23, 40). These protocols involve an abrupt delay of the sleep period by 8–12 h, and therefore allow for the effects of time of day to be observed in the absence of sleep, and the effects of sleep to be observed at an abnormal circadian time, i.e., a time when sleep does not normally occur. During wakefulness, the level of physical activity is kept minimal and essentially constant. Sleep quality is polygraphically monitored. Figure 3 shows the mean profiles of plasma glucose and ISR observed in a study involving a 12-h shift of the sleep-wake cycle in normal young subjects receiving a constant glucose infusion (40). The findings are consistent with the concept that both circadian rhythmicity and sleep modulate glucose regulation. Indeed, during sleep deprivation, glucose concentrations and ISR increase to reach a nocturnal maximum at approximately the same time as during normal sleep and then return to daytime levels. After daytime sleep onset, a sharp rise in glucose levels and ISR was again observed. The quantitative analysis of the size of the elevations seen in the absence of sleep and during daytime sleep suggests that, in normal conditions of nocturnal sleep, the effects of circadian rhythmicity and sleep are superimposed. Similar findings regarding the role of sleep in modulating glucose regulation were obtained in a study involving an 8-h shift of the sleep-wake cycle in subjects receiving continuous enteral nutrition (23).

B. Causal mechanisms

1. Mechanisms underlying daytime variations in glucose tolerance. In a general sense, decreased glucose tolerance in the later part of the day could result from impaired glucose utilization and/or excessive glucose production. A role for time-dependent alterations in insulin secretion, action, and/or clearance could be implicated in variations of both glucose production and/or utilization across the daytime period. Morning to evening differences in a number of factors that may contribute to the deterioration of glucose tolerance have been clearly identified, and evidence for a role of certain counterregulatory hormones in causing these differences has been obtained.

   a. Factors intrinsic to glucose regulation. There is evidence to indicate that glucose utilization by insulin-dependent as well as non-insulin-dependent tissues decreases as the day progresses. A more than 2-fold reduction in glucose utilization in the later part of the day has indeed been directly demonstrated in a study combining [3H]glucose infusion with hepatic and femoral venous catheterization (39). In contrast, splanchnic glucose uptake was slightly higher in the afternoon than in the morning (39). Evidence consistent with a reduction in insulin-independent glucose utilization has been obtained in a study involving a frequently sampled intravenous glucose tolerance test (IVGTT) at 0800 h and
1800 h and its analysis using the minimal model approach (41). Indeed, a modest 15–20% decrease of the insulin-independent glucose utilization parameter $S_0$ (i.e., “glucose effectiveness”) of the minimal model analysis was observed (41). In a more recent study (42), a larger decrease in $S_0$ was reported, perhaps because the evening test was performed later, at 2000 h. Indirect evidence for a reduction in glucose utilization has also been obtained in studies demonstrating the existence of diurnal variations in glucose tolerance in subjects receiving intravenous glucose infusions at a constant rate for prolonged periods of time (2, 25, 40). Indeed, under these conditions of mild hyperglycemia and hyperinsulinemia, endogenous glucose production is markedly inhibited in normal subjects (37–39), and therefore temporal variations in plasma glucose levels mainly reflect changes in glucose utilization. Whether there is also a variation in basal hepatic glucose output across the daytime has not been determined. Indeed, experimental conditions under which glucose fluxes were directly or indirectly evaluated all involved a near total suppression of glucose production and therefore could not evaluate possible variations in basal glucose output.

Conflicting evidence for reduced insulin sensitivity in the afternoon and evening as compared with the morning was obtained in studies performed in the early 1970s. Indeed, Gibson and Jarrett (43) reported that the blood glucose fall after intravenous injection of 0.1 U/kg of insulin was 15% smaller at 1700 h than at 0900 h. This finding was confirmed in a later study (44), which included the performance of an insulin tolerance test at six different clock times spanning the 24-h cycle. Chronobiological analysis of the data indicated that the rate of glucose disappearance was largest at 0800 h and lowest during the evening and nighttime. In contrast, Carroll and Nestel (10), using the same dosage of intravenous insulin, did not observe a significant morning (0700 h) to evening (1900 h) difference in glucose response. The weight of the evidence tends, however, to be on the side of the reduced insulin sensitivity in the evening. Indeed, a study using a glucose-controlled insulin infusion system (Biostator; Ref. 45) has shown that the insulin-glucose ratio over a 24-h period of constant low dose glucose infusion undergoes a consistent diurnal variation, with relatively stable daytime levels followed by a pronounced nocturnal elevation, suggesting the existence of a marked decrease in insulin sensitivity during the nighttime. However, the studies were initiated in the morning, and thus the evening and nighttime periods corresponded to more than 12 h of insulin infusion using the Biostator device, a condition that has been shown in later studies to be associated with an aggregation and partial inactivation of the infused insulin (46). Therefore, the magnitude of the 24-h variation in insulin sensitivity was probably overestimated in this study. The finding in subjects receiving a constant glucose infusion of lower levels of leg glucose uptake at 1800 h, as compared with 0800 h in the face of similar levels of serum insulin, is also indicative of a degree of insulin resistance in the later part of the day (39). The most recent studies on variations of insulin sensitivity ($S_t$) across the daytime used the minimal model analysis of the frequently sampled IVGTT. In one study, a 30% reduction in $S_t$ at 1800 h, as compared with 0800 h, was observed (41), whereas in another study, no significant morning to evening change was detected (42).

There is also evidence to support a role for inappropriately low insulin secretion in causing decreased glucose tolerance in the later part of the day. After an intravenous injection of tolbutamide, two separate studies have found that the insulin response is larger in the morning than in the afternoon (10, 47). The role of insulin secretion in morning to evening variations of glucose tolerance was also investigated by examining responses to intravenous infusions of glucose and glucagon or glucagon only (48). Levels of insulin were lower in the afternoon than in the morning after both types of stimuli, thus suggesting decreased β-cell responsiveness in the later part of the day. Analysis of glucose and insulin responses to a frequently sampled IVGTT indicated the existence of a nearly 25% reduction in first phase insulin secretion in the evening as compared with the morning (41). In the same study, a nearly 50% decrease in the slope of glucose potentiation relating acute insulin rise to intravenous arginine was also observed at 1800 h when compared with 0800 h (41). In a recent study using graded glucose infusions (rates 2, 4, 6, and 8 mg/kg/min), ISRs were found to be higher in the morning than in the evening at all infusion rates, and the slope of the linear regression line relating glucose to ISR was 40% lower in the evening than in the morning, consistent again with a marked decrease in β-cell responsiveness in the evening (42). Comparison of the insulin-secretory responses to identical meals presented at 0800 h and 2000 h also provided evidence for variations of β-cell responsiveness across the daytime because the 25–50% increase in ISR from morning to evening was not commensurate with the approximate 100% increase in glucose response (19). Contrasting with the overall consensus regarding decreased insulin secretion during the later part of the day, a recent report (49), describing patterns of insulin secretion during euglycemic and hyperglycemic clamps, claimed that a circadian rhythm of insulin secretion with maximum levels in the afternoon and early evening and minimal levels during the nighttime and early morning (i.e., in the direction opposite to that found in all previous studies) could be evidenced at high glucose levels. Whether this discrepant finding reflects an alteration in regulation of insulin secretion at supraphysiological levels or other methodological differences remains to be determined.

In summary, there is good evidence to indicate that reduced glucose utilization, decreased insulin sensitivity, and inappropriately low insulin secretion are involved in causing decreased glucose tolerance in the later part of the day. There are no data to support a role for variations in glucose production. There appears to be no consistent variations in insulin clearance across the daytime portion of the 24-h cycle (10).

b. Factors related to neuroendocrine control of glucose regulation. The demonstration, under a variety of experimental conditions, of the existence of a consistent morning to evening variation of glucose tolerance in response to the same stimulus, and unrelated to changes of activity levels or environmental parameters, suggests that this temporal variation must be, at least partially, controlled by signals originating from a robust pacemaker generating a 24-h, i.e., circadian, signal. In mammals, the mechanism responsible for
cortisol concentrations is likely to be a causal mechanism for optimal glucose tolerance with minimal insulin-secretory responses in the morning and diminished insulin sensitivity without appropriate increases in insulin secretion 6–15 h later, i.e., in the afternoon and evening.

2. Mechanisms underlying nighttime variations in glucose tolerance a. Factors intrinsic to glucose regulation. Two studies that have measured overnight glucose turnover in fasted subjects maintained at bed rest have shown that the stability of glucose levels during an overnight fast is achieved by precisely matched changes in glucose utilization and glucose production that fall in parallel during the first part of the night and then increase concomitantly in the predawn hours (29, 34). Examples of the overnight profiles of glucose production and glucose utilization are shown in Fig. 2. Unfortunately, neither study included polygraphic recordings of sleep, and therefore the effects of sleep quality on the overnight glucose profile could not be defined. The absence of a consistent pulse of GH secretion during the first half of the sleep period in the mean GH profiles illustrated in these reports (29, 34) suggests a significant impairment of sleep quality, as, under normal conditions, the first few hours of sleep are invariably associated with increased GH release (66). However, when the subjects were kept actively awake throughout the night, both the fall in glucose production and the fall in glucose utilization were dampened and of shorter duration than during sleep (29). The sleep-associated fall in hepatic glucose output is accompanied by a reduction in plasma glycerol and FFA, suggesting that, during sleep, hepatic glucose output may be partially regulated by peripheral signals derived from lipolysis. Support for this hypothesis has been obtained in a study examining overnight hepatic glucose output after a 72-h fast, when hepatic glucose output primarily represents gluconeogenesis (67). Under these conditions, the sleep-associated fall in hepatic glucose output was obliterated, and the declines in plasma FFA and glycerol were similarly absent, suggesting that these lipolytic products play a role in the regulation of hepatic glucose output during late nocturnal sleep (67).

Studies that have examined glucose regulation during polygraphically recorded sleep have further delineated the factors implicated in the decrease in glucose utilization during the early part of the night. Figure 4 illustrates mean profiles of plasma glucose, ISR, plasma GH, and sleep stages in a group of normal subjects who initiated nocturnal sleep (left panels) after 8–10 h of constant glucose infusion at a rate of 5 g/kg/24 h or who were kept awake throughout the night (right panels). The condition of intravenous low-dose constant glucose infusion for a prolonged period of time results in a marked inhibition of endogenous glucose production (38, 39), and thus temporal variations in plasma glucose levels mainly reflect changes in glucose utilization. Sleep onset and the first half of the sleep period are accompanied by a robust increase in plasma glucose, which is followed 10 min later by a more than 50% increase in ISR. The increase in plasma glucose appears to partially reflect the predominance of non-rapid eye movement (REM) stages in early sleep. A recent study has also reported an association between
pulsatile increases in insulin and glucagon secretion during sleep with non-REM stages (32). Positron emission tomography studies have indeed demonstrated that brain glucose metabolism is reduced by 30–40% during stages III and IV (68, 69). One study (70), comparing brain glucose utilization with systemic glucose turnover, estimated that brain glucose utilization falls during non-REM stages only and contributes to about two-thirds of the fall in systemic glucose utilization during sleep. The last third would then reflect decreased peripheral utilization. Diminished muscle tone during deep sleep probably contributes to decreased peripheral glucose uptake. Furthermore, in a study involving the estimation of the clearance of endogenously secreted insulin (as the ratio of the area under the ISR curve and the area under the simultaneously measured serum insulin concentrations) during various time
intervals across the 24-h cycle, an approximate 40% acceleration of the disposal of secreted insulin during the first half of nocturnal sleep was observed (40). Thus, an increase in insulin clearance could also contribute to the reduction in glucose utilization during the early part of the night. Finally, as will be discussed below, GH secretion during early sleep is also likely to play a role in decreasing peripheral glucose utilization.

During the later part of the sleep period, glucose levels and ISR decrease to return to presleep values despite the persistence of the constant glucose infusion (left panels of Fig. 4). The reduction of plasma glucose levels during the late part of the sleep is likely to partially result from the increase in wake and REM stages, as glucose utilization during these stages is higher than during non-REM stages (68–72). Other factors that may have also contributed to the decline of glucose levels during late sleep include the hypoglycemic activity of previously secreted insulin during early sleep, the increased insulin-independent glucose disposal due to transient mild hyperglycemia, and the increase in body movements associated with the higher frequency of awakenings. A role for temporal variations in cortisol concentrations is also likely, as will be indicated below.

Markedly different profiles of plasma glucose and ISR are observed during sleep deprivation (right panels of Fig. 4). During the first part of the night, the persistence of the waking condition prevents the decrease in brain glucose utilization, and GH secretion is absent. Thus, glucose levels increase only marginally. During the second half of the night, despite the persistence of bed rest and constant glucose infusion, glucose levels and ISR decrease significantly. The timing of this late night decrease in glucose levels and ISR coincides with the well documented abrupt decrements of alertness and performance that occur in sleep-deprived subjects 6–8 h after their usual bedtime (73, 74).

b. Role of hormonal rhythmicity. Major differences in the circulating levels of GH, cortisol, and epinephrine, important counterregulatory hormones, characterize the first and second half of a normal night of sleep in young adults (56). During the first half of the night, GH secretion is markedly stimulated, cortisol levels are suppressed, and epinephrine concentrations decrease. During the second half of the night, GH secretion is generally quiescent, cortisol concentrations are rapidly increasing, and epinephrine levels begin to return to daytime values. While there has been no study examining the impact of the nocturnal variations in plasma epinephrine on glucose regulation during sleep, temporal variations in both GH and cortisol appear to influence parameters of nighttime glucose tolerance.

There is evidence to suggest that the major pulse of GH secretion that occurs in association with sleep onset plays a role in modulating glucose regulation during the first half of the night. Indeed, the more recent studies that have used bolus administrations of low-dose exogenous GH, to mimic physiological pulsatile release, and examined their short-term metabolic consequences have shown that a primary effect is a rapid decrease in muscular glucose uptake (75, 76). Thus, during early sleep, increased GH secretion may facilitate the maintenance of stable glucose levels despite the fasting condition by inhibiting muscular glucose uptake. In subjects receiving constant glucose infusion, there is a positive correlation between the magnitude of the sleep-associated elevation in glucose levels and the amount of concomitant GH secretion (56). When nocturnal GH secretion is amplified by bedtime intravenous injection of a low dose of GH-releasing hormone (GHRH), a near 50% increase in the postsleep elevation of glucose levels is observed (77), suggesting that sleep-onset GH secretion indeed inhibits glucose utilization during early sleep.

The putative role of the large temporal variation of cortisol levels in modulating parameters of glucose tolerance during sleep remains to be elucidated. A recent study has suggested that the low cortisol concentrations that prevail in the late evening and early part of the night may have a delayed effect on insulin sensitivity in the later part of the night and in the early morning (58). Thus, increased glucose utilization during the second half of the night could reflect a transient enhancement of insulin sensitivity related to the circadian trough of cortisol concentrations occurring 4–6 h earlier. Further studies are necessary to discriminate between the rapid inhibitory effects of cortisol on insulin secretion (57, 59–65) and its delayed effects on insulin action (78, 79) in the control of physiological variations in glucose tolerance during wake and during sleep.

III. Alterations of 24-h Rhythms of Glucose Regulation in Normal Aging

Aging is associated with a deterioration of glucose tolerance and the appearance of peripheral insulin resistance (80, 81). A few studies have also indicated the existence of an age-related defect in insulin secretion (82–84). Increased adiposity appears to be an almost universal correlate of old age, even in normal weight subjects, and is thought to be partially caused by diminished GH secretion (85). The sleep-associated release of GH is still apparent in most older adults, but is markedly diminished (86). Mean cortisol levels increase by 20–50% between 20 and 80 yr of age, primarily because of a progressive elevation of the level of the nocturnal nadir (87). The diurnal rhythmicity of cortisol secretion is preserved in old age, but its amplitude is dampened, and the timing of the early morning elevation is advanced (87). Comparisons of groups of young and older adults have shown that, in addition to the 24-h profiles of GH and cortisol, a number of other 24-h rhythms, such as those of body temperature (88, 89) and plasma melatonin (86, 90), are dampened and/or advanced in old age. Studies performed under constant behavioral and environmental conditions have suggested that these alterations result from age-related changes in the output of the circadian pacemaker and are not an immediate response to modifications in sleep-wake habits (89). Sleep disturbances are common in the elderly and consist primarily of increased wakefulness and decreased slow-wave sleep (91, 92). The timing of sleep tends to be modified as well, with earlier bedtimes and earlier morning awakenings (89, 92). Very few studies have examined whether these perturbations of circadian rhythmicity and sleep result in disturbances in the diurnal variation of glucose tolerance in the elderly and whether they may play a role in the development of impaired glucose tolerance during senescence.
A. Daytime variations in glucose tolerance

Early studies examining the effect of time of day on oral glucose tolerance indicated that the morning to afternoon increase in glucose responses was also present in older adults (age > 45 yr; Refs. 8, 9, and 14) and that the magnitude of this effect may be larger in older adults than in younger subjects (14). This apparent increased amplitude of the morning to afternoon variation could reflect an advance of the overall rhythm of glucose tolerance, consistent with the advance of circadian rhythmicity and sleep-wake habits that accompany old age. Indeed, in young subjects, glucose tolerance worsens further from afternoon to evening. In older adults, it is conceivable that “evening” levels of glucose tolerance are already attained in the afternoon. In one study in older subjects receiving a constant glucose infusion (93), the progressive morning to evening increase in glucose levels usually seen in normal nonobese young adults was still present, and only minimally dampened, in the older volunteers. Peak glucose and ISR levels were achieved earlier in the older than in the young volunteers, consistent with an advance of circadian timing. Relative increases in ISR over the same time period were, however, smaller than in young lean men, suggesting an age-related failure of the β-cell to respond appropriately to glucose elevations. The effects of aging on variations in glucose responses to meals across the daytime remain to be determined. It is also not known whether the insulin resistance of the elderly is stable or undergoes a consistent morning to evening variation.

B. Nighttime variations in glucose tolerance

Studies that have examined glucose and insulin levels during an overnight fast in older adults have generally observed stable or slightly declining levels from late evening to morning (83, 94). The rates of glucose production (Ra) and glucose utilization (Ra) fell in parallel during the early part of the night and then remained stable (94). This is in contrast to the profiles of Rg and Rs seen in young adults, where both parameters increase concomitantly during the second part of the night (29, 34). Sleep has not been controlled in any of these overnight studies.

Two studies (95, 96) have been specifically designed to determine whether the dawn phenomenon occurs in normal elderly subjects and could thus explain the frequent finding of mildly elevated fasting glucose levels in this population. Meneilly et al. (95) performed a euglycemic insulin clamp involving physiological hyperinsulinemia in the morning (0930–1200 h) as compared with the dawn period (0530–0800 h) in five healthy older adults and measured insulin levels, insulin clearance, insulin-mediated glucose disposal, and hepatic glucose production. Sleep-wake conditions were not controlled. There were no differences in any of the parameters measured between the two time periods, except for a nearly 20% increase in insulin clearance in the dawn period, as compared with the morning. The authors conclude that the dawn phenomenon does not occur in normal older adults (95). A similar conclusion was reached by Rosenthal and Argoud (96), who measured glucose production and plasma glucose and insulin levels in healthy young and elderly sub-

IV. Diurnal Variations of Glucose Regulation in Obesity

A. Daytime variations in glucose tolerance

Several studies in obese subjects have examined the profiles of glucose and insulin after meals at different times of the day (27, 99). It was concluded that, although hyperse-
cretion of insulin can be documented in obesity, the temporal pattern of secretion is largely unaltered, which suggests that the functioning \( \beta \)-cell mass is enhanced, but normal regulatory mechanisms influencing secretion are still operative (27). However, as meals were of variable size and composition, possible circadian variations in metabolic and hormonal responses to a constant stimulus could not be delineated from such studies.

Interestingly, early studies examining the response to a standardized oral glucose load administered once in the morning and once in the afternoon have shown an inverse relationship between the decrease in glucose tolerance from morning to afternoon and the degree of obesity (8, 14). Similar observations have been obtained in obese children who underwent an oral glucose tolerance test at 0900 and 1500 h (100). In the control children, there was a significant drop in the insulin-glucose ratio in the afternoon, whereas in the obese group this ratio remained high, with no significant change across the day. The existence of an abnormality in the daytime variation of components of glucose tolerance in obesity has been recently confirmed and extended in a study using the frequently-sampled IVGTT performed either at 0800 or 1800 h (41). In contrast to lean controls, obese adult subjects showed no morning to evening variation in glucose tolerance, no decline in insulin sensitivity in the afternoon, and only a marginally significant decline in \( \beta \)-cell responsiveness to glucose in the later part of the day.

Abnormalities in the daytime profile of glucose tolerance and insulin secretion in obesity were further demonstrated in subjects receiving a continuous intravenous glucose infusion (101). In contrast to lean subjects who showed a marked decline in glucose tolerance toward the end of the day, plasma glucose levels in the obese subjects remained stable from morning to evening despite a steady decrease in ISR, indicating an improvement (rather than a deterioration) of glucose tolerance as the day progresses.

B. Nighttime variations in glucose tolerance

A few reports have indicated that, similar to what is observed in normal lean subjects, plasma glucose levels, insulin concentrations, and ISR decline progressively across the night in obese subjects who have had a normal meal schedule during the previous day (27, 31, 99). In contrast, one study showed that, when the overnight fast follows an entire day of fasting, a progressive rise in plasma glucose, serum insulin, and ISR occurs across the nighttime period, with the evening to morning increase in plasma glucose during the overnight fast averaging approximately 0.5 mmol/liter (102). Serum insulin and ISR increased, respectively, by 10–15 pmol/liter and 20–30 pmol/min. It was hypothesized that the prolonged fasting condition, which, consistent with previous observations (103, 104), resulted in a stimulation of evening cortisol secretion and nocturnal GH release, was
responsible for the abnormal overnight profile of glucose tolerance. A nocturnal rise in circulating leptin levels, similar in timing and relative magnitude to that occurring in lean adults but set around much higher levels, has been found in markedly obese subjects (33). Sleep was not recorded in any of these previous overnight studies in obese subjects.

Continuous intravenous glucose infusion throughout the night with simultaneous polygraphic sleep recordings allowed for an evaluation of the role of sleep in the nocturnal changes in glucose tolerance in obese subjects (101). Despite the fact that sleep parameters were normal, obesity appeared associated with well defined alterations in nocturnal metabolic profiles, with specific defects characterizing the early and later portions of the sleep period. After sleep onset, the normal elevations in glucose and ISR were markedly reduced in the obese subjects, when compared with lean controls, probably because of the concomitant dampening of GH release. During the later part of the sleep period, obese subjects failed to significantly suppress ISR in contrast to control subjects in whom the second part of the sleep was accompanied by markedly declining glucose and insulin concentrations, which returned to presleep levels before awakening. The absence of a significant decline in ISR before awakening in obese subjects may reflect a prolongation of the secretory response to sleep onset due to insulin resistance. In addition, in overweight subjects, changes in ISR during the second half of sleep appeared to be less markedly and less consistently influenced by changes in cortisol levels, suggesting that in obesity there may be a relative insensitivity of the \( \beta \)-cell to circadian cortisol changes (58, 101). It is likely that these dual defects in the nighttime control of the glucose-insulin regulation are involved in the reversal of the daytime variation of glucose tolerance in obesity.

C. Significance and clinical implications

The roles of sleep and circadian rhythmicity in glucose regulation may be particularly important in obese individuals. On the one hand, and interestingly, the behavioral rhythms of carbohydrate preference in obese subjects parallel the diurnal variation of glucose tolerance, as carbohydrate intake is generally lower in the morning and higher in the evening (105). Further studies are needed to elucidate the physiological significance and clinical implications of the chronobiological abnormalities in glucose tolerance and eating patterns in the initiation and maintenance of obesity. On the other hand, in view of the relationships between sleep quality and glucose regulation in normal man (106), the role of sleep disturbances on glucose tolerance should be better evaluated in the obese subject. Indeed, alterations in carbohydrate metabolism and insulin sensitivity may be aggravated in the presence of sleep apnea syndrome, a prevalent condition in the obese population. A positive relationship between the degree of insulin resistance and the severity of sleep apnea syndrome has been reported (107). Furthermore, an independent association between the incidence of sleep apnea and the levels of fasting insulin has been recently demonstrated (108). A few studies have examined nocturnal hormonal release in patients with obstructive apnea (109, 110) and showed a marked decrease in nocturnal GH release, which may be partially reversed by treatment with continuous positive airway pressure. While the restoration of GH secretion in early sleep was not associated with significant changes in overnight glucose and insulin levels, the possibility of an improvement in daytime insulin sensitivity remains to be investigated. These findings certainly deserve further investigations as insulin resistance and hyperinsulinemia are now considered as major risk factors for atherosclerotic cardiovascular disease.

d. Alterations of 24-h Rhythmicity of Glucose Regulation in Non Insulin-Dependent Diabetes Mellitus (NIDDM)

A. Alterations in daytime variations in glucose tolerance

In contrast with the numerous studies that have investigated the circadian changes in glucose tolerance in nondiabetic subjects, very few studies have addressed this specific topic in patients with NIDDM. Early observations on daytime variations in oral glucose tolerance in a large population showed that the degree of deterioration of glucose tolerance in the afternoon, when compared with that in the morning, was least in those subjects with the highest morning glucose levels (4, 8). In ongoing studies in obese patients with NIDDM in our laboratory, changes in plasma glucose levels during a continuous intravenous low-dose glucose infusion show a progressive decrease from morning to evening. This pattern is clearly opposite to that observed in lean nondiabetic subjects and is similar to that seen in obese nondiabetic individuals (101). A recent study in patients with NIDDM studied during a hyperglycemic clamp for 72 h (111) demonstrated a large and robust 24-h variation in the amount of glucose that needed to be infused to maintain plasma levels around 12 mmol/liter. The rate of infusion had to be increased more than 3-fold from morning to evening, indicating that, in NIDDM, glucose tolerance increases markedly as the day progresses. Levels of insulin secretion appeared relatively constant. This pronounced diurnal variation in rate of glucose infusion indicates the existence of a robust 24-h rhythm in insulin sensitivity opposite to that occurring in normal subjects, i.e., with minimal sensitivity in the morning and maximal sensitivity in the late evening.

B. Alterations in nighttime variations in glucose levels during fasting

The existence of a paradoxical elevation in blood glucose at the end of the sleep period in fasted diabetic subjects was first reported by Hatlehol (112) in 1924, and similar findings were described in a series of studies conducted over the next three decades (113–116). In 1967, Faiman and Moorhouse (117) sampled blood at 4-h intervals across a 72-h fast in diabetic subjects and observed, superimposed on the expected decline associated with the starvation condition, a reproducible 24-h variation of glucose concentrations, with more rapidly declining levels across the daytime period and increasing levels during the nighttime. Peak levels occurred near 0800 h and the amplitude of the cycle was proportional to the overall blood glucose level, i.e., the more hyperglycemic
patients had the largest glucose excursion over the 24-h cycle. In their discussion of their findings, the authors reviewed previous studies (112–116) and remarked that “the diurnal cycle does not appear to be related to food or activity” (117). These pioneering studies, which were limited by the techniques available at the time (i.e., infrequent blood sampling and lack of estimation of the components of glucose tolerance), were generally supportive of the existence of an elevation of blood glucose levels around dawn.

1. The dawn phenomenon. Using a closed-loop (feedback-controlled) intravenous insulin infusion (i.e., the Biostator), one study has described the existence of a clear-cut dawn phenomenon in both non-insulin-treated and insulin-treated NIDDM patients (118). The magnitude of the early morning increase in insulin requirements was similar to that observed in patients with insulin-dependent diabetes (Table 1). For instance, intravenous insulin requirements were shown to increase at least 100% between 0600 and 0900 h in about 75% of patients with NIDDM (118). However, the prevalence and the magnitude of the dawn phenomenon may have been overestimated because of a technical limitation of the Biostator, which, after extended utilization (e.g., 10–12 h), causes insulin aggregation and degradation (46). In a study (119) where albumin was added into the insulin solution to prevent the waning of the biological activity of infused insulin over time (120), insulin requirements were found to increase by approximately 40% after 0600 h in NIDDM patients usually treated by diet or oral drugs, and the magnitude of this increase was found to be quite reproducible (119). Thus, it appears that the initial description of the dawn phenomenon in NIDDM exaggerated the magnitude of the morning elevation in insulin requirements.

In more recent years, at least nine independent studies (Table 1), including a total of more than 100 patients, have examined overnight changes in glucose levels in NIDDM (31, 94, 102, 121–126). These studies have differed in terms of subject population (degree of obesity, age, severity and duration of diabetes, type of treatment) as well as in terms of duration of the fast preceding the overnight period of study. Indeed, in some studies, the last meal was a dinner on the day preceding the study (i.e., 30 h of fast before midnight; Ref. 102), whereas in others an evening snack was given on the day of the study (i.e., 3–4 h before midnight; Refs. 31 and 126). None of the studies included polygraphic sleep recordings so that the role of sleep quality in modulating overnight glucose regulation could not be evaluated.

A significant elevation in plasma glucose levels between the middle of the night (i.e., 0300–0400 h) and the morning (i.e., 0800 h) was observed in four of the nine studies (102, 121, 122, 126). Some of the largest elevations (illustrated in Fig. 6) were observed in the study in which the patients underwent a 30-h period of total fast and the overnight study period corresponded to the last 12 h of the fast (102). Despite continued fasting, plasma glucose levels stopped declining in the evening and subsequently rose throughout the night to reach a morning maximum (+ 24% above the evening nadir). Elevated plasma glucose levels persisted until approximately noon. In another study in which the subjects were fasted for 6 h before midnight (121), a significant, although modest, overnight plasma glucose rise (+ 1.4 mmol/liter from 0300 to 0800 h) was observed, and the magnitude of this dawn phenomenon was greater in diabetic patients treated by diet and oral hypoglycemic agents, who had also the worst metabolic control as assessed by their HbA1c level, than in patients treated by diet alone who showed the best overall glycemic control (121). In another study, where blood samples were drawn at 30-min intervals between 2100 and 0800 h, a marked dawn

Table 1. Studies of overnight glucose regulation in NIDDM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Type of subjects</th>
<th>Type of treatment</th>
<th>Duration of fast</th>
<th>Time interval for comparison</th>
<th>% Increase in rate of insulin delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolli and Gerich, 1984 (118)</td>
<td>8</td>
<td>Nonobese</td>
<td>Insulin</td>
<td>5–7 h</td>
<td>24–06 vs. 06–09</td>
<td>+66%</td>
</tr>
<tr>
<td>Dimitriadis et al., 1988 (119)</td>
<td>5</td>
<td>Nonobese</td>
<td>Diet or diet + oral agents</td>
<td>5–7 h</td>
<td>24–06 vs. 06–09</td>
<td>+47%</td>
</tr>
<tr>
<td>Dimitriadis et al., 1988 (119)</td>
<td>11</td>
<td>Nonobese</td>
<td>Diet or diet + oral agents</td>
<td>&gt;5 h</td>
<td>24–06 vs. 06–08</td>
<td>+42%</td>
</tr>
</tbody>
</table>

Table 1. Studies of overnight glucose regulation in NIDDM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Type of subjects</th>
<th>Type of treatment</th>
<th>Duration of fast</th>
<th>Time interval for comparison</th>
<th>% Increase in rate of insulin delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holman and Turner, 1979 (123)</td>
<td>9</td>
<td>Nonobese</td>
<td>Diet only</td>
<td>6 h</td>
<td>0100 vs. 0800 h</td>
<td>+8% (NS)</td>
</tr>
<tr>
<td>Atiea et al., 1987 (121)</td>
<td>9</td>
<td>Nonobese</td>
<td>Diet only</td>
<td>6 h</td>
<td>0300 vs. 0800 h</td>
<td>+11%</td>
</tr>
<tr>
<td>Polonsky et al., 1988 (124)</td>
<td>10</td>
<td>Nonobese</td>
<td>Diet + oral agents</td>
<td>6 h</td>
<td>0300 vs. 0800 h</td>
<td>+24%</td>
</tr>
<tr>
<td>Chen et al., 1988 (94)</td>
<td>8</td>
<td>Obese</td>
<td>Diet or diet + oral agents</td>
<td>6 h</td>
<td>0200 vs. 0800 h</td>
<td>No increase</td>
</tr>
<tr>
<td>Yki-Jarvinen et al., 1989 (126)</td>
<td>7</td>
<td>Obese</td>
<td>Diet + oral agents</td>
<td>7.5 h</td>
<td>0345 vs. 0800 h</td>
<td>+27%</td>
</tr>
<tr>
<td>Reaven et al., 1988 (125)</td>
<td>18</td>
<td>Nonobese</td>
<td>Diet only</td>
<td>7 h</td>
<td>0445 vs. 0800 h</td>
<td>+5% (NS)</td>
</tr>
<tr>
<td>Garvey et al., 1988 (31)</td>
<td>8</td>
<td>Nonobese</td>
<td>Diet only</td>
<td>6 h</td>
<td>Not applicable</td>
<td>No increase</td>
</tr>
<tr>
<td>Beebe et al., 1990 (122)</td>
<td>7</td>
<td>Obese</td>
<td>Diet or diet + oral agents</td>
<td>6 h</td>
<td>03–06 vs. 06–09</td>
<td>+8%</td>
</tr>
<tr>
<td>Shapiro et al., 1991 (102)</td>
<td>7</td>
<td>Obese</td>
<td>Diet or diet + oral agents</td>
<td>30 h</td>
<td>2000 vs. 0800</td>
<td>+24%</td>
</tr>
</tbody>
</table>

*Albumin added to insulin solution to prevent waning of biological action over time.

Not taking into account a late evening snack
increase in plasma glucose levels (+ 2.2 mmol/liter between 0400 and 0800 h, \( P < 0.05 \)) was observed in poorly controlled NIDDM patients (126). The last meal was given at 1600 h, i.e., 8 h before midnight, but a snack was ingested at 2000 h. Interestingly, in this study, the dawn phenomenon disappeared completely after 3 weeks of insulin therapy, which improved the overall glycemic control and decreased fasting plasma glucose levels by half. Finally, our group has obtained some evidence suggesting that the occurrence of an early morning increase in plasma glucose levels in patients with NIDDM may be partially dependent on the size and timing of the last meal on the previous day (122). The profiles of plasma glucose resulting from different types of temporal distribution of daily caloric intake were compared in the same group of patients, and a dawn phenomenon was only consistently observed when the last meal was ingested early in the evening and included no more than 30% of the total daily caloric requirements. As further discussed below, this observation is consistent with the concept that the dawn phenomenon in NIDDM patients during a normal overnight fast partially reflects counterregulatory mechanisms activated by the fasting condition. In several other studies in which 30-min interval sampling was performed over a 24-h period, no significant overnight rises in plasma glucose and insulin concentrations were observed in various populations of NIDDM patients: modestly overweight patients with mild or severe NIDDM (94, 125), both lean and obese patients.
with severe hyperglycemia (31), and obese, poorly controlled, patients (124).

2. Causal mechanisms underlying the dawn phenomenon
   a. Insulin secretion and clearance. The dawn phenomenon observed in NIDDM patients may result from changes in insulin and/or counterregulatory hormones. In studies that were unable to demonstrate a dawn phenomenon in NIDDM patients (31, 94, 123–125), plasma glucose and serum insulin levels (or ISR) changed in parallel, showing a decrease or stable levels during the later part of the night. In studies showing a clear-cut dawn phenomenon in NIDDM patients (102, 126), serum insulin levels and/or ISR failed to parallel the nocturnal glucose increase (Fig. 6). Such abnormal patterns reflect the well known decreased B cell responsiveness to glucose of NIDDM patients. This reduced responsiveness could contribute to the greater nocturnal glucose rise seen in diabetic patients as compared to nondiabetic control subjects (102). In NIDDM patients showing a nocturnal glucose elevation after a prolonged fast (102), no increase in insulin clearance across the night could be detected, ruling out a contribution of increased clearance of the hormone in causing the nocturnal elevation observed in these patients. In two other studies (31, 124), changes in plasma insulin levels were confirmed by parallel changes in plasma C peptide levels, consistent with a lack of overnight changes in insulin clearance.

   b. Counterregulatory hormones. Unfortunately, in the studies performed on patients with NIDDM under the usual conditions of overnight fast after a normal daytime meal schedule (31, 94, 123–125), the circulating levels of counterregulatory hormones were not measured. The only exception is a study where plasma GH levels were measured at hourly intervals in subjects studied before and after insulin therapy (126). A dawn phenomenon was observed before, but not after, treatment, but there were no detectable changes in the overnight GH profiles between the two conditions. When GH and cortisol profiles were measured in NIDDM patients and nondiabetic control subjects studied after a prolonged fast (Fig. 6), cortisol concentrations were found to be higher in diabetic subjects throughout the study period, but particularly so during the evening and nighttime periods (102). In both groups of subjects, the nocturnal glucose elevation was temporally and quantitatively correlated with the magnitude of the early morning cortisol rise. The secretion of GH was increased in the evening and nighttime periods compared with the daytime values, and in NIDDM patients, but not in control subjects, the size of the nocturnal glucose elevation was directly related to the magnitude of the increase in GH secretion ($r = 0.88, P < 0.01$). Glucagon concentrations were similar in both groups of subjects and remained essentially constant throughout the study period. Thus, the higher nocturnal glucose elevation in fasting NIDDM patients as compared with control subjects appears to be caused by increased evening and nighttime cortisol secretion associated with a simultaneous increase in GH release and a defective response of insulin secretion (102). Overall, in both nondiabetic and diabetic subjects, the overnight pattern of glucose changes after a day of total fast appears to partially reflect counterregulatory activation of cortisol and GH by the prolonged fasting condition.

   c. Glucose production vs. glucose utilization. Few studies have measured glucose fluxes during an overnight fast in NIDDM patients. In one study performed in severely hyperglycemic diabetic patients who took their last evening meal at 1800 h, both $R_{g}$ and $R_{d}$ decreased progressively from 2200–0900 h, and no dawn phenomenon was detected (94). In another study where a clear-cut dawn phenomenon was evidenced in moderately hyperglycemic NIDDM patients, the late night increase in plasma glucose levels appeared due to accelerated hepatic glucose production, primarily via enhanced gluconeogenesis from lactate (126). Furthermore, in these subjects, suppression of the dawn phenomenon after 3 weeks of insulin therapy resulted from inhibition of $R_{g}$, achieved by a decrease in the proportion of lactate diverted toward gluconeogenesis. In addition, plasma FFA concentrations showed a robust increase at dawn, and both overall nocturnal FFA concentrations and dawn FFA rise were markedly decreased after 3-week insulin therapy (126).

   In a recent study involving the maintenance of a hyperglycemic clamp for 72 h in NIDDM patients, a marked and reproducible diurnal variation in the rate of infusion of exogenous glucose needed to maintain stable glucose levels was demonstrated (111). The rate of glucose infusion dropped by more than half from late afternoon to approximately the middle of the night (i.e., 0300–0400 h), and isotopic measurements indicated that this variation reflected a pronounced increase in glucose production across the evening and first half of the usual sleep period. During the second half of the night and throughout the morning, glucose production appeared to decrease, as the rate of glucose infusion needed to maintain stable blood glucose levels more than doubled. This diurnal pattern was interpreted as reflecting changes in insulin sensitivity (111). In addition, during nighttime sleep, it is possible that the reduction in cerebral glucose utilization that normally occurs during sleep in nondiabetic subjects (68–72), may have contributed to the observed decrease in glucose infusion rate.

C. Significance and clinical implications

From the numerous and often contradictory studies on daytime and nighttime variations in glucose regulation in NIDDM, it is possible to conclude that at least two types of alterations characterize the diabetic, as compared with the nondiabetic, state. First, glucose tolerance increases from morning to evening, partially because of improved insulin sensitivity. This is in sharp contrast to the normal situation, where glucose tolerance and insulin sensitivity are maximal in the morning, rather than the evening. Studies examining the effect of time of day on meal tolerance in diabetic subjects are thus needed to derive guidelines regarding optimal composition of breakfast, lunch, and dinner in NIDDM patients. Second, an elevation of glucose levels at the end of an overnight fast, i.e., a so-called dawn phenomenon, may be observed in some NIDDM patients. The existence of a dawn phenomenon seems to be more frequent in patients who are severely hyperglycemic and to be facilitated by an extended duration of fast before bedtime. Causal mechanisms under-
lying these alterations in the chronobiology of glucose regulation in NIDDM remain to be identified. Limited evidence (58, 102, 111) suggests that abnormalities in the interactions between the rhythmicity of cortisol levels, insulin secretion, and insulin sensitivity could be involved.

VI. Alterations of 24-h Rhythmicity of Glucose Regulation in Insulin-Dependent Diabetes Mellitus (IDDM)

A. Alterations in daytime variations in glucose tolerance

In IDDM, insulin requirements to control glycemia vary across the daytime. It is a well-established rule in insulin therapy that a higher insulin dose per gram of carbohydrate should be delivered for breakfast than for a later meal (127–132). This diurnal variation in insulin requirements is consistent with the morning to evening improvement in glucose tolerance seen in NIDDM patients and differs from the pattern observed in nondiabetic individuals whose glucose tolerance is optimal in the morning and declines as the day progresses. One possible explanation for the increased need for insulin at breakfast in insulin-treated diabetic patients may be the relative underinsulinization at the end of the night under the condition of classic subcutaneous insulin therapy. However, in one well-documented study, breakfast insulin requirements were not different after an overnight fast and after a midnocturnal (0200–0500 h) insulin infusion (130). Interestingly, in this study, nonobese diabetic patients required approximately 60% more insulin for breakfast than for other meals, but obese IDDM patients did not demonstrate increased insulin resistance at breakfast (130). This difference in morning insulin resistance between obese and nonobese IDDM subjects is suggestive of a role of nocturnal GH secretion (which is largely suppressed in obesity) in causing morning insulin resistance. One study, which used the Biostator to provide adequate insulinemia to ensure fasting euglycemia and examined systematically the effects of meal size, time of day, and sequence of meal ingestion on insulin requirements in normal-weight IDDM subjects, failed to demonstrate an increased need for insulin at breakfast (133). Although insulin requirements showed a highly significant association with meal size and, to a lesser extent, were also influenced by the size of the preceding meal (more insulin was required for a given meal if the preceding meal was smaller), no significant effect due to time of day of meal ingestion was observed (133). However, this negative result could be related to the progressive degradation of insulin associated with prolonged use of the Biostator (46), since all studies were initiated in the morning and ended in the evening.

B. Alterations in nighttime variations in glucose tolerance

Several studies have shown that the rate of subcutaneous (134, 135) or intravenous (136, 137) insulin infusion necessary to maintain overnight plasma glucose concentration in the normal range in IDDM patients increases during the second part of the night. If the greater insulin requirements in the early morning hours are not met, hyperglycemia develops. Such phenomenon may correspond to the so-called “dawn phenomenon.” However, in IDDM patients, and in contrast to other populations examined in the preceding sections of this review, morning hyperglycemia may have several other causes (138). Strictly speaking, the term “dawn phenomenon” in IDDM should be limited to indicate specifically the increase in insulin requirements (or development of hyperglycemia if the greater need for insulin is not met) in the later part of the night in the absence of declining insulin delivery (due to waning of evening injected insulin), as well as in the absence of early nocturnal hypoglycemia (leading to reactive posthypoglycemic late hyperglycemia known as the Somogyi effect) (139, 140). Because in most insulin-treated diabetic patients, plasma insulin concentrations usually fall overnight (135), the contribution of relative insulin deficiency and that of the dawn phenomenon cannot be separated. Consequently, the contribution of the dawn phenomenon to fasting hyperglycemia cannot be quantified merely on clinical grounds, but requires an experimental assessment.

1. The dawn phenomenon

a. During intravenous insulin infusion. There are two general methods of documenting the dawn phenomenon in insulin-requiring diabetic patients: to infuse insulin at a constant rate and measure the rise of glucose concentrations or to clamp blood glucose at a constant level and measure the infusion rate of insulin necessary to maintain it. Table 2 summarizes the studies of the dawn phenomenon that have used these methods. Unfortunately, most of these studies were performed using the so-called artificial pancreas (Biostator) (118, 136, 141–145), and it was subsequently shown that the delivery of biologically active insulin by this device may wane over a period of time because of aggregation of insulin in the plastic tube and/or heat inactivation of insulin by the peristaltic pump (46). This artifact may have contributed to overestimate the magnitude of the dawn phenomenon in IDDM patients. When insulin was infused overnight using a Harvard syringe pump (137, 146–149), which does not inactivate the insulin contained in the solution, or albumin was added to the solution to prevent the reduction in biologically active insulin, the magnitude of the late nocturnal increase in insulin requirements was generally 20–40%, which is considerably lower than that reported by earlier studies using the Biostator (50–100%). These estimates are necessarily approximate because, as indicated in the summary given in Table 2, markedly different periods were used for comparison of early night (ranging from 2300–0600 h) and early morning (ranging from 0500–0900 h) in various studies, and different procedures were used to express the results (either at a given time-point or as an average over several hours). None of the studies of the dawn phenomenon in IDDM included sleep recordings, so that the impact of sleep duration and quality could not be estimated.

b. In clinical practice. Even if the magnitude of the dawn phenomenon is smaller than originally reported in experimental studies using the Biostator, nocturnal variation in insulin requirements may play an important role in clinical practice in IDDM patients (140). The combination of the pattern of nocturnal insulin requirements, i.e., lowest levels in early night and highest levels in late night, and the phar-
macokinetics of the depot-insulin preparations given in the evening, i.e., peak plasma insulin bioavailability early in the night and lower circulating levels at dawn, is responsible for a high risk of nocturnal hypoglycemia as well as a fairly high frequency of morning hyperglycemia (138). In children receiving split-mixed insulin regimens, a rise in capillary blood glucose from midsleep to prebreakfast, often > 2 mmol/liter, is a common occurrence (150). In IDDM adult patients, a dawn rise in blood glucose is also frequently observed and, if > 3 mmol/liter, may lead to significant exacerbation of daytime hyperglycemia (151). Interestingly, conversion from conventional to basal-bolus insulin therapies can achieve a significant reduction in both frequency and magnitude of an early-morning rise in blood glucose (151). A dawn phenomenon may also occur in IDDM patients receiving continuous subcutaneous insulin infusion (pertinent studies are summarized in Table 2), although a marked dawn rise in blood glucose is rare when a single but adequate basal infusion rate is used (152, 153). Figure 7 shows hourly measurements of blood glucose, plasma-free insulin, glucagon, GH, and cortisol from 2200–0700 h in 10 IDDM patients treated by continuous subcutaneous insulin infusion and demonstrates a lack of dawn phenomenon under these conditions. Furthermore, when an early morning glucose elevation is present, it may be obviated by a carefully determined step-up in nocturnal basal insulin infusion rate (134, 135). Nevertheless, under usual clinical conditions, unless insulin is given at variable rates overnight, some degree of modest presleep and preawakening hyperglycemia must usually be tolerated to avoid nocturnal hypoglycemia (140).

Finally, it is worth noting that the occurrence of a dawn phenomenon has been very consistent in type 1 diabetic patients and that its magnitude appears to be highly reproducible within the same subject (149). However, it may be influenced by several factors, such as the duration of diabetes and the status of the counterregulatory system (149). Most important appears to be the quality of the metabolic control: the magnitude of the dawn phenomenon has been shown to be directly related to the level of HbA1c, to be reduced after several months of intensive therapy and, conversely, to be increased within the same subject (149). However, it may be obviated by a carefully determined step-up in nocturnal basal insulin infusion rate (134, 135). Nevertheless, under usual clinical conditions, unless insulin is given at variable rates overnight, some degree of modest presleep and preawakening hyperglycemia must usually be tolerated to avoid nocturnal hypoglycemia (140).

### Table 2. Studies of overnight glucose regulation in IDDM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Experimental condition</th>
<th>Time interval for comparison</th>
<th>Insulin delivery rate (mU/kg/min)</th>
<th>% Increase in plasma glucose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kern et al., 1984 (132)</td>
<td>8</td>
<td>Biostator</td>
<td>23–03 vs. 05–09</td>
<td>0.17</td>
<td>+62%</td>
</tr>
<tr>
<td>Campbell et al., 1985 (160)</td>
<td>7</td>
<td>Biostator</td>
<td>0230 to 0800 h</td>
<td>0.15</td>
<td>+121%</td>
</tr>
<tr>
<td>Campbell et al., 1985 (143)</td>
<td>10</td>
<td>Biostator</td>
<td>0330 to 0800 h</td>
<td>0.15</td>
<td>+95%</td>
</tr>
<tr>
<td>Campbell et al., 1986 (147)</td>
<td>8</td>
<td>Biostator</td>
<td>0300 to 0800 h</td>
<td>0.15</td>
<td>+89%</td>
</tr>
<tr>
<td>Campbell et al., 1988 (168)</td>
<td>6</td>
<td>Biostator</td>
<td>0200 to 0700 h</td>
<td>0.15</td>
<td>+65%</td>
</tr>
<tr>
<td>Davidson et al., 1988 (166)</td>
<td>8</td>
<td>Infusion pump</td>
<td>0400 to 0800 h</td>
<td>0.12</td>
<td>+33%</td>
</tr>
<tr>
<td>Beafrere et al., 1988 (161)</td>
<td>8</td>
<td>Infusion pump</td>
<td>0540 to 0800 h</td>
<td>0.28</td>
<td>+36%</td>
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<table>
<thead>
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<th>Reference</th>
<th>n</th>
<th>Experimental condition</th>
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<th>Insulin delivery rate (mU/kg/min)</th>
<th>% Increase in plasma glucose level</th>
</tr>
</thead>
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<tr>
<td>Clarke et al., 1980 (136)</td>
<td>6</td>
<td>Biostator</td>
<td>0600 to 0900 h</td>
<td>0.20 to 0.38</td>
<td>+90%</td>
</tr>
<tr>
<td>Bright et al., 1980 (164)</td>
<td>5</td>
<td>Biostator</td>
<td>0600 to 0900 h</td>
<td>0.22 to 0.29</td>
<td>+32%</td>
</tr>
<tr>
<td>Mathiesen et al., 1982 (131)</td>
<td>14</td>
<td>Biostator</td>
<td>01–04 to 04–07</td>
<td>0.18 to 0.23</td>
<td>+28%</td>
</tr>
<tr>
<td>Skor et al., 1983 (141)</td>
<td>5</td>
<td>Biostator</td>
<td>24–03 to 06–09</td>
<td>0.38 to 0.54</td>
<td>+42%</td>
</tr>
<tr>
<td>Vague et al., 1983 (142)</td>
<td>12</td>
<td>Biostator</td>
<td>24–04 to 04–07</td>
<td>0.35 to 0.37</td>
<td>+5%</td>
</tr>
<tr>
<td>Nestler et al., 1984 (130)</td>
<td>8</td>
<td>Biostator</td>
<td>01–06 to 06–09</td>
<td>0.33 to 0.50</td>
<td>+52%</td>
</tr>
<tr>
<td>Bolli and Gerich, 1984 (118)</td>
<td>20</td>
<td>Biostator</td>
<td>24–06 to 06–09</td>
<td>0.15 to 0.28</td>
<td>+87%</td>
</tr>
<tr>
<td>Kern et al., 1984 (132)</td>
<td>8</td>
<td>Biostator</td>
<td>23–03 to 05–09</td>
<td>0.14 to 0.21</td>
<td>+50%</td>
</tr>
<tr>
<td>Skor et al., 1985 (167)</td>
<td>5</td>
<td>Biostator</td>
<td>01–03 to 06–08</td>
<td>0.25 to 0.37</td>
<td>+48%</td>
</tr>
<tr>
<td>Dux et al., 1985 (155)</td>
<td>8</td>
<td>Biostator</td>
<td>01–03 to 06–08</td>
<td>0.12 to 0.29</td>
<td>+83%</td>
</tr>
<tr>
<td>Luyekx et al., 1985 (144)</td>
<td>10</td>
<td>Biostator</td>
<td>01–03 to 06–08</td>
<td>0.23 to 0.32</td>
<td>+39%</td>
</tr>
<tr>
<td>Borissova et al., 1992 (145)</td>
<td>8</td>
<td>Biostator</td>
<td>02–03 to 07–08</td>
<td>0.14 to 0.25</td>
<td>+79%</td>
</tr>
<tr>
<td>DeFeo et al., 1986 (146)</td>
<td>11</td>
<td>Harvard pump</td>
<td>0430 to 0700 h</td>
<td>0.12 to 0.16</td>
<td>+39%</td>
</tr>
<tr>
<td>Edge et al., 1990 (148)</td>
<td>26</td>
<td>Infusion pump</td>
<td>01–04 to 05–08</td>
<td>0.21 to 0.25</td>
<td>+19%</td>
</tr>
<tr>
<td>Perriello et al., 1991 (149)</td>
<td>114</td>
<td>Harvard pump</td>
<td>0240 to 0640 h</td>
<td>0.10 to 0.14</td>
<td>+40%</td>
</tr>
<tr>
<td>Boyle et al., 1992 (158)</td>
<td>6</td>
<td>Harvard pump</td>
<td>0200 to 0600 h</td>
<td>0.13 to 0.24</td>
<td>+85%</td>
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<tr>
<td>Aisen et al., 1992 (159)</td>
<td>10</td>
<td>Harvard pump</td>
<td>01–0430 to 0430–08</td>
<td>0.17 to 0.33</td>
<td>+94%</td>
</tr>
<tr>
<td>Trumper et al., 1995 (137)</td>
<td>13</td>
<td>Infusion pump</td>
<td>02–04 to 06–08</td>
<td>0.31 to 0.42</td>
<td>+35%</td>
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</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Experimental condition</th>
<th>Time interval for comparison</th>
<th>Insulin delivery rate (mU/kg/min)</th>
<th>% Increase in plasma glucose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geffner et al., 1983 (134)</td>
<td>6</td>
<td>Constant rate</td>
<td>0330 to 0630–0830 h</td>
<td>0.26</td>
<td>+88%</td>
</tr>
<tr>
<td>Koivisto et al., 1986 (135)</td>
<td>10</td>
<td>Step-up rate</td>
<td>0400 to 0800 h</td>
<td>0.17</td>
<td>+32%</td>
</tr>
<tr>
<td>Bending et al., 1985 (152)</td>
<td>12</td>
<td>Step-up rate</td>
<td>24–06 to 0800 h</td>
<td>0.26 (max)</td>
<td>No increase</td>
</tr>
<tr>
<td>Castillo et al., 1995 (153)</td>
<td>24</td>
<td>Constant</td>
<td>0300 to 0700 h</td>
<td>0.27</td>
<td>+2%</td>
</tr>
</tbody>
</table>
increased after only 2 weeks of deterioration of glycemic control (149).

2. Causal mechanisms underlying the dawn phenomenon
   a. Insulin availability, clearance, and action. The progressive rise of plasma glucose levels from the early to the later part of the night may result from defective insulinization or increased insulin resistance. In patients with type 1 diabetes mellitus, the role of endogenous insulin may be considered as negligible, and insulin availability depends only on exogenous insulin administration. As already discussed, insulin availability may decrease during the second part of the night because of waning of insulin injected subcutaneously the evening before or, when a peristaltic pump is used, because of the degradation of the infused insulin. In several studies, the insulin clearance has been reported to increase in the early morning hours, and it has been suggested that this may be the primary mechanism of the dawn phenomenon in type 1 diabetes (154, 155). However, as discussed by several authors (139, 140), the finding was probably more apparent than real as it probably reflected insulin degradation by the Biostator and may also have been confounded by difficulties in measuring plasma-free insulin concentrations in diabetic patients with insulin antibodies (154, 155). At least four studies carried out under appropriate experimental conditions have concluded that the clearance of plasma insulin does not change appreciably overnight in patients with type 1 diabetes (146, 147, 156, 157). However, a few more recent studies, which also avoided artifacts in insulin delivery and plasma-free insulin measurements, did demonstrate an increased MCR of insulin during the dawn period (158, 159) and, in addition, suggested that this effect may be at least partially related to pulsatile GH secretion during the early part of the night. Thus, the presence or absence of altered insulin clearance and its possible relationship to GH secretion remains controversial. In any case, most authors now agree that the predominant cause of the dawn phenomenon is reduced insulin sensitivity, which may result in increased glucose production and/or impaired glucose utilization during the later part of the night (149, 157).
   b. Glucose production vs. glucose utilization. In IDDM patients, well documented studies have shown that insulin resistance in the early morning period results in fasting hyperglycemia primarily because of a failure to adequately inhibit glucose production from the liver (160, 161). Increased hepatic glucose production starts around the middle of the night (0300 h) and can be prevented by increasing the insulin delivery rate, as has been shown, for example, in diabetic patients treated with continuous subcutaneous insulin infusion (135). Despite the presence of hyperglycemia, glucose utilization does not begin to increase until the early morning (0600–0700 h), and the increase is not commensurate with the accelerated rate of production (which averages 65%), suggesting the presence of insulin resistance in peripheral (mainly muscular) tissues in addition to that observed in the liver (160). It is thus the mismatch (both in timing and in size) between the increase in glucose production and the increase in glucose utilization that is responsible for the morning hyperglycemia. Blackard et al. (162) have noted that the increase of glucose production may reflect the normal effect of arousal from sleep, a state associated with a marked decrease in glucose production (29), and suggested that the dawn phenomenon be renamed “sleep phenomenon.” Since none of these studies has included sleep recordings, the role for sleep-wake transitions in the pathogenesis of the dawn phenomenon remains to be elucidated.

In three studies in which insulin sensitivity has been examined in subjects with type 1 diabetes mellitus by means of
the classic euglycemic hyperinsulinemic clamp technique, no difference in insulin action between the early part of the night and the early morning hours has been found (154–156). However, in another study (157), insulin-mediated glucose disposal during a glucose clamp was found to be impaired at dawn as compared with the beginning of the night, both at low and high levels of plasma-free insulin, suggesting that decreased insulin sensitivity at that time of the day affects all insulin-dependent tissues, rather than only the liver. However, because of the dose-response curve of the effects of insulin on production and utilization of glucose (163), glucose overproduction may play the predominant role during the later part of the night when insulin levels are relatively low, whereas impaired glucose uptake may play a more important role soon after breakfast when plasma insulin levels become higher (140).

c. Roles of hormonal rhythmicity. The obvious parallelism between the elevation of plasma cortisol during the second part of the night and the dawn phenomenon originally suggested that cortisol may play a major role in the early morning hyperglycemia (136). However, the fact that the two phenomena occur essentially simultaneously does not support the hypothesis that the early morning cortisol elevation is responsible for the increase in insulin resistance (58, 78). Furthermore, suppression of cortisol secretion using metyrapone (164) or dexamethasone (141) does not significantly reduce dawn insulin requirements of type 1 diabetic patients. Plasma glucagon levels do not change overnight in IDDM individuals (137, 143, 153, 160), and plasma catecholamines show only a very modest rise at dawn (51, 132, 141, 143, 160).

Pharmacological blockade of both α- and β-adrenergic receptors does not prevent the late night increase in insulin requirement (160). Thus, the counterregulatory effects of cortisol, glucagon, and epinephrine do not seem to play a significant role in the dawn phenomenon of IDDM patients.

In contrast, consistent evidence indicates that early nocturnal GH surges are implicated in the development of the dawn phenomenon in type 1 diabetes mellitus. First, the integrated responses to nocturnal GH secretion correlate with insulin requirements and/or hyperglycemia at dawn in most (137, 148, 157, 160) but not all, studies (161). Second, suppression of nocturnal GH secretion by anticholinergic agents (121, 148, 165, 166) or somatostatin (157, 160, 167, 168) results in a virtual disappearance of the dawn phenomenon. Third, GH-deficient patients with type 1 diabetes do not exhibit a dawn phenomenon (169). Finally, when nocturnal surges in GH secretion are simulated by intravenous injection of GH in IDDM subjects in whom endogenous GH secretion has been suppressed by somatostatin, plasma glucose levels and glucose production increase and glucose clearance decreases to values observed in control experiments (160).

The precise mechanism by which GH contributes to the dawn phenomenon remains unclear. In addition to possible direct effects of GH on glucose metabolism (170) or on insulin clearance (169), one other explanation might be that GH appears to be a key factor regulating lipolysis during the night in patients with IDDM (170) and that elevating FFA levels may compete for glucose utilization and stimulate gluconeogenesis. However, even if such process has been documented, its precise contribution to the dawn phenomenon remains controversial (169). The role of GH in the pathogenesis of the dawn phenomenon in IDDM provides an explanation for several clinical features of this condition. Nocturnal surges in plasma GH levels are higher in such patients with suboptimal control (171, 172) and correlate with the overnight glucose increase (143). On the other hand, normalizing plasma GH levels by optimization of glycemic control may explain the attenuation of early morning hyperglycemia in diabetic patient receiving intensive insulin therapy (149).

C. Significance and clinical implications

Intrinsic daytime variations in glucose tolerance are probably of minor importance in IDDM patients when compared with the role played by other factors: regimen of insulin therapy (type of insulin, dosage, timing of injection, variability of subcutaneous absorption, etc.), diet habits (meal sizes, composition, and timing), and physical activity (intensity, duration, and timing). In contrast, although the magnitude of the dawn phenomenon and its underlying mechanisms are still controversial, nighttime variations in glucose tolerance have been well demonstrated in IDDM subjects and may be of clinical importance.

The discrete nature of insulin administration exposes the IDDM patient to an increased risk of hypoglycemia in the early to middle part of the night. In the later part of the night and in the morning, hyperglycemia frequently occurs. These problems may be avoided by the use of a basal-bolus insulin regimen (delaying the injection of evening intermediate insulin from supper to bedtime) instead of the classic twice-daily injection schedule. However, the time course of action of the most frequently used intermediate insulin preparations may be unsatisfactory to ensure the adequacy of basal insulin delivery, as such preparations are usually too potent during the first 4–8 h but not sufficiently active 10–14 h after subcutaneous injection. Pharmaceutical companies manufacturing insulin are currently investigating new preparations of long acting insulin with a flatter and more reproducible time course of activity. In some cases, nocturnal insulinization may be optimized by the use of a continuous subcutaneous insulin infusion via a portable pump where the delivery rate can be precisely adjusted to the nighttime variations of glucose tolerance of the individual patient.

Finally, glycemic control may be disturbed in diabetic patients who undergo jet lag or shift work rotations. In daily practice, such conditions require a careful adjustment of insulin therapy with the type, dose/ and/or timing of insulin administration being modified according to the new sleep-wake and meal schedules. This adjustment usually necessitates an increased frequency of ambulatory blood glucose monitoring to minimize the risks of hypo- and hyperglycemic episodes.

VII. Conclusions

Robust variations in glucose regulation across the 24-h cycle are now well demonstrated in both normal conditions and in states of impaired glucose tolerance. A large number

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of studies have documented reproducible changes in daytime and/or nighttime glucose utilization (both peripheral and central), insulin secretion, and insulin sensitivity in healthy subjects. Alterations of the normal daily profiles of these parameters of glucose tolerance have been identified in normal aging, obesity, NIDDM, and IDDM. While the ultimate cause of these diurnal variations obviously resides in the alternation of wake and sleep states and in the intrinsic effects of circadian rhythmicity, the primary factors responsible for transmitting these modulatory effects of central nervous system status to the peripheral control of glucose homeostasis are still poorly understood. The important roles of physiological variations in levels of counterregulatory hormones that are markedly dependent on sleep (i.e., GH) or circadian rhythmicity (i.e., cortisol) have only begun to be appreciated. The clinical implications of the 24-h variations in glucose regulation for the design of meal schedules and therapeutic regimens that may optimize glycemic control in conditions of impaired glucose tolerance, jet lag, and shift work still need to be delineated.

Major alterations of glucose tolerance occur during sleep, and sleep quality markedly influences nocturnal brain and tissue glucose utilization. The sleep state occupies approximately one third of the day throughout the adult lifetime. Therefore, chronic sleep disturbances, such as those occurring in elderly adults, in night workers, and in subjects with sleep apnea, may be associated with disturbances of glucose regulation. The demonstration of a robust sleep-induced decrease in glucose tolerance also strongly argues for the need to carefully monitor the maintenance of wakefulness in subjects undergoing metabolic testing, whether for research or therapeutic regimens that may optimize glycemic control in conditions of impaired glucose tolerance, jet lag, and shift work still need to be delineated.

Thus, the modulatory effects of sleep and circadian rhythmicity on glucose regulation appear to have important clinical implications for the diagnosis and treatment of abnormalities in carbohydrate metabolism.

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