Stress and Diabetes Mellitus

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Stress is a potential contributor to chronic hyperglycemia in diabetes. Stress has long been shown to have major effects on metabolic activity. Energy mobilization is a primary result of the fight or flight response. Stress stimulates the release of various hormones, which can result in elevated blood glucose levels. Although this is of adaptive importance in a healthy organism, in diabetes, as a result of the relative or absolute lack of insulin, stress-induced increases in glucose cannot be metabolized properly. Furthermore, regulation of these stress hormones may be abnormal in diabetes. However, evidence characterizing the effects of stress in type I diabetes is contradictory. Although some retrospective human studies have suggested that stress can precipitate type I diabetes, animal studies have shown that stressors of various kinds can precipitate—or prevent—various experimental models of the disease. Human studies have shown that stress can stimulate hyperglycemia, hypoglycemia, or have no affect at all on glycemic status in established diabetes. Much of this confusion may be attributable to the presence of autonomic neuropathy, common in type I diabetes. In contrast, more consistent evidence supports the role of stress in type II diabetes. Although human studies on the role of stress in the onset and course of type II diabetes are few, a large body of animal study supports the notion that stress reliably produces hyperglycemia in this form of the disease. Furthermore, there is mounting evidence of autonomic contributions to the pathophysiology of this condition in both animals and humans.

"But if the degenerate, or depraved nervous liquor doth continually flow into the blood, it produces sometimes the unbloody dysentery, such as we have already described, sometimes the diabetes. . . ."

Thomas Willis
Pharmaceutis Rationalis, 1679

The notion that stress could contribute to the etiology of diabetes mellitus has a long history in medicine—as the 17th century physician Willis noted (1). By the 19th century, the role of stress in the etiology of diabetes had become established firmly in the medical literature. Henry Maudsley, considered by many to be the founder of modern psychiatry, wrote, "This we know: that diabetes is sometimes caused in man by mental anxiety . . . (2)." As Willis had before him, Maudsley observed that diabetes often followed the occurrence of a sudden trauma. He reported the story of a military officer, who, upon discovering that his wife was having an affair, immediately developed the disease. No less a figure than the great William Osler also subscribed to the notion that stress was involved in the etiology of some types of diabetes. In his landmark *Textbook of Medicine*, Osler differentiated between true diabetes and the less severe diabetes of obesity, probably analogous to what is called type II diabetes today: "In true diabetes, instances of cure are rare. On the other hand, the transient or intermittent glycosuria met with in stout overfeeders, or in persons who have undergone a severe mental strain, is very amenable to treatment (3)."

By the beginning of the 20th century, laboratory studies began to replace astute clinical observation as the principal source of medical knowledge. Commenting on existing clinical literature, Walter B. Cannon made the first appeal for the experimental study of how stress affects diabetes. "Although clinical evidence thus indicates an emotional origin of some cases of diabetes and glycosuria," Cannon wrote, "the intricacies of existence and the complications of disease in human beings throw some doubt on the value of that evidence. . . .it is desirable, therefore, that the question of an emotional glycosuria be tested under simpler and more controllable conditions." To study the problem experimentally, Cannon (4) provoked stress-induced hyperglycemia in normal cats. In this early investigation, 12 cats were confined in a holder for varying lengths of time, dependent on each animal's reaction to this novel situation. The cats were given a large quantity of water by stomach tube, and urine was drained promptly. In all cases, sugar was absent

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RECEIVED FOR PUBLICATION 26 AUGUST 1991 AND ACCEPTED IN REVISED FORM 31 MARCH 1992.

TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS; TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS; GH, GROWTH HORMONE; FFA, FREE FATTY ACID; EPI, EPINEPHRINE; STZ, STREPTOZOCIN; NE, NOREPINEPHRINE.

THIS ARTICLE IS ONE OF A SERIES PRESENTED AT THE MEETING ON THE BEHAVIORAL ASPECTS OF DIABETES MELLITUS.

from the urine before the animal became excited, but the stress intervention invariably resulted in glycosuria. Cannon observed an apparent relationship between the animal's emotional state and the onset of hyperglycemia. Specifically, animals that appeared frightened or enraged developed glycosuria more quickly than animals that responded to the confinement in a calm manner.

Cannon attributed this effect to the fight or flight response, which includes sympathetic discharge and elevations in circulating levels of catecholamines, glucocorticoids, and GH. The net effect of this response is energy mobilization. In that glucoregulation is compromised in diabetic individuals, the energy-mobilizing effects of stress can be deleterious to blood glucose control in a diabetic patient (5,6). Therefore, the extent to which environmental stress and other behavioral variables contribute to blood glucose control is theoretically important in the clinical management of this disorder.

It is now widely accepted that the autonomic/adrenocortical systems play a major role in the regulation of carbohydrate metabolism (Fig. 1). The effects of the autonomic nervous system on insulin action is both facilatory and inhibitory. Branches of the parasympathetic right vagus nerve innervate the pancreatic islets, and stimulation of the right vagus causes increased insulin secretion. Adrenergic stimulation of pancreatic islet cells can lead to either facilitation or inhibition of insulin secretion. β-adrenergic stimulation at low levels is facilatory to insulin output, whereas high levels of β-adrenergic stimulation or α-2 adrenergic stimulation is inhibitory. β-adrenergic stimulation also stimulates glucagon release from the pancreatic α-cells. Glucagon, in turn, stimulates glucose production in the liver. Thus, sympathetic and parasympathetic innervation of the pancreas modulates the normal regulation of carbohydrate metabolism (7–9). β-adrenergic stimulation also promotes the conversion of glycogen to glucose in the liver and fat to FFAs in adipose tissue. FFAs further are metabolized to ketoacids in the liver. Circulating EPI can stimulate glycogenolysis (7), whereas vagal stimulation can inhibit hepatic glucose production (10). Thus, the autonomic nervous system has both direct neural and indirect hormonal control pathways in the regulation of glucose metabolism (8).

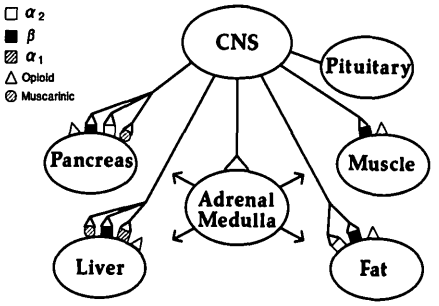

Figure 1—*Schematic of pathways by which the central nervous system (CNS) can influence glucose metabolism. Adrenergic (α and β), cholinergic (muscarinic), and opioidergic pathways are shown. Adrenal cortical pathways are not shown.*

Stressful stimuli can activate several other neuroendocrine responses that can result in elevated blood glucose levels. Activation of the hypothalamic-pituitary-adrenocortical axis causes release of increased amounts of glucocorticoids, enhances gluconeogenesis in the liver, and diminishes cellular glucose uptake. Stress-induced release of GH also can decrease glucose uptake, and β-endorphin can suppress insulin secretion and elevate glucose levels (11). Therefore, stressful stimuli can impact on glucose levels through numerous pathways. The adaptive benefit of stress-induced energy mobilization in healthy, nondiabetic individuals is obvious. However, in diabetes mellitus, where glucose metabolism is compromised, these stress effects can be problematic. Finally, elevated blood glucose levels can, by themselves, eventually impair the pancreas' ability to respond to a glucose stimulus (12). Thus, glucose toxicity resulting from chronic, intermittent, stress-induced elevations in blood glucose could produce a permanent effect on pancreatic secretory ability.

THE ROLE OF STRESS IN THE ONSET OF TYPE I DIABETES

— Animal research has provided some objective evidence to suggest that stress affects the onset of type I diabetes. Animals that were partially pancreatectomized surgically have been shown to develop either transient or permanent diabetes after restraint stress (13). Although these animals do not develop diabetes spontaneously, restraint stress produced transient or permanent diabetes in 25–28% of pancreatectomized animals, but none of the control animals developed diabetes. Some animals who were not altered surgically became hyperglycemic after the stressor, but none became diabetic. More recently, chemical pancreatectomy with β-cell cytotoxins, such as alloxan and STZ, have been used instead of surgical procedures. By controlling the dosage of these cytotoxic agents, partial or complete destruction of pancreatic β-cell mass can be produced, mimicking the clinical picture of type II and type I diabetes, respectively. Huang et al. (14) found that light-shock stimulation could inhibit the development of STZ-induced diabetes in young mice that received a single dose of STZ. Although the mechanism of this effect was not defined, other researchers have found that administration of exogenous steroids can inhibit the development of another STZ-induced model of diabetes (15). It is possible, therefore, that the protective effect of shock on the development of diabetes observed in animals treated with a single dose of STZ may have been mediated through the adrenal corticotrophic effects of stress.

The diabetes-prone BB Wistar rat (16) provides a genetic model for Type I diabetes. A significant percentage of these animals spontaneously develop an autoimmune insulitis that results in dia-

betes by the time they are 5 mo old. The effects of stress on BB rats have been demonstrated by Carter et al. (17). A combination of behavioral stressors, such as restraint and crowding, were found to lower the age of onset of diabetes. Lehman et al. (18) found that a greater percentage of animals became diabetic after stress, compared with unstressed controls. Because BB rats possess other endocrine and immune abnormalities, one must be cautious in generalizing these findings to humans.

Stress also has been suspected to play a role in the onset of type I diabetes in humans. Studies have shown that diabetic patients are more likely to suffer a major family loss before the onset of symptoms (19–21). However, these studies tend to be poorly controlled, and/or they rely on recall of specific life events. Robinson and Fuller (19) did compare diabetic patients with nondiabetic siblings of similar age and a matched neighborhood control group. The diabetic subjects had significantly more severe life events within the 3 yr before diagnosis than either control group. Severe life events were defined based on the degree of short-term or long-term threat to the subject. This study is limited by its small sample size, and it fails to give specific examples of severe life events. Although these studies are far from conclusive, it must be noted that only 50% of identical twins are concordant for type I diabetes. Although both show evidence of autoimmune abnormalities, the disease develops in only 50% of the pairs. It has been postulated, therefore, that some environmental stimulus is necessary for the overt expression of the disease. Therefore, stress may affect the onset of type I diabetes by directly or indirectly triggering this autoimmune abnormality. However, conclusive evidence for this mechanism is lacking.

STRESS AND GLUCOSE CONTROL IN TYPE I DIABETES— The literature on the relationship between stress, autonomic arousal, and glucose control in diabetes is more extensive. Lee et al. (22) have demonstrated that not all rats with chemically induced diabetes respond to stress in the same way. After either alloxan or STZ injections, ~50% of the animals demonstrated elevated baseline plasma EPI levels (reactive responders) whereas the other 50% (nonreactive responders) did not differ from controls in terms of plasma EPI. After footshock, the reactive animals had plasma EPI levels >5460 pM, whereas the nonreactive and control rats were <3276 pM. The three groups did not differ in terms of NE response to stress. Reactive and nonreactive animals had elevated blood glucose at baseline (>11.2 mM) relative to controls (<5.6 mM), and all groups showed increased blood glucose in response to stress. This suggests that the reactive animals have an increased secretion of EPI from the adrenal medulla rather than a decreased rate of removal of EPI from the blood (22). On the other hand, Bellush and Rowland (23) found that all STZ rats had reliably higher NE than controls, both before and after stress. EPI was found to increase in diabetic animals after stress and decrease in controls. In this study, 24-h urinary catecholamine excretion was used rather than plasma levels. The authors conclude that the elevated NE levels in the diabetic rats suggest greater sympathetic activity in those animals. These studies highlight the complex nature of the relationship between environmental stimulation and diabetes in animals rendered susceptible to the disease.

Models that produce artificially induced diabetes do have some problems. First, pancreatectomized animals undergo potentially stressful procedures that differ from type I diabetes onset in humans (24). The stress of the sudden onset of the condition in these animal models may lead to changes in catecholamines, independent of the effects of experimental stressors on the condition itself (22). Second, the animals used in these studies often have chronic hyperglycemia that is not being controlled by insulin. Therefore, it may not be appropriate to generalize these findings to humans with type I diabetes, who often are in reasonable glycemic control with insulin.

In humans, several physical stressors such as illness, trauma, or rapid metabolic changes have been shown to cause hyperglycemia and eventual ketoacidosis in type I diabetes (25). McLesky et al. (26) found a clear hyperglycemic response in both type I and type II diabetic patients during a surgical stress. Furthermore, insulin-dependent diabetic children have been shown to demonstrate elevated blood glucose and more rapid ketone release after EPI infusion compared with normal children (27).

The experimental study of the effects of psychological stress on glucose metabolism in diabetic patients was undertaken first by Hinkle et al. (28–30). Their studies of diabetic patients demonstrated increases in blood glucose and ketones after stressful psychiatric interviews. However, their work was poorly controlled and difficult to interpret. Vandenbergh et al. (31) examined the impact of hypnotically induced emotion on predominantly IDDM subjects, in a controlled fashion. Coincident with nonsignificant increases in plasma FFAs, they observed decreases in blood glucose. These findings were replicated in a subsequent study (32). However, these researchers did not fully document whether or not their subjects had endogenous insulin reserves. Recent negative life events also have been shown to have an influence on diabetic control. Chase and Jackson (33) found that life stress, as defined by a list of events requiring psychosocial readjustment, is correlated with both GHb and blood glucose. This suggests that stress has an impact on both long-term and short-term indexes of glycemic control. Brand et al. (34), on the other hand, found life stress to be correlated only with urinary ketone levels in males. As with most studies in this

area, specific examples of stressors were not provided. These studies used different measures of life stress and neither investigated whether the findings suggest a direct effect of stress on glycemic control or an indirect effect based on poorer compliance.

Not all studies have demonstrated that laboratory stress leads to blood glucose changes in type I diabetic patients. In one study, type I diabetic patients in good glycemic control were compared with individuals in an acute state of insulin insufficiency. After mental-arithmetic and public-speaking stressors, neither group showed significant changes in blood glucose levels (35). Because artificially induced insulin deficiency may not be comparable with chronic poor glycemic control, Gilbert et al. (36) compared patients in good glycemic control with those who had a history of poor control as measured by GHb. Neither group showed a significant change in blood glucose after a public speaking stressor, although the poorly controlled diabetic subjects had higher poststress urine glucose levels.

Other studies have found idiosyncratic changes in blood glucose after laboratory stressors. Bradley (37) reported that noise stress increased blood glucose in initially hyperglycemic diabetic subjects and decreased blood glucose in initially hypoglycemic diabetic subjects. Some have found that mental arithmetic can produce either increases or decreases in blood glucose (38) in type I diabetic patients, and that the direction of blood glucose change is idiosyncratic. Stabler et al. (39) examined the relationship between glycemic response to stress and behavior patterns of type A personality individuals. They found that type A children showed elevated blood glucose levels after playing a stressful video game, whereas type B children exhibited decreased blood glucose levels. Although the differences in blood glucose were small and probably not clinically significant, type A children had higher GHb levels than type B children. A subsequent study failed to replicate the GHb differences between type A and type B children, although glucose reactivity to stress was not assessed (40). Thus, some of the studies investigating the impact of psychological stress on blood glucose in human diabetes report that stress has a hyperglycemic effect, whereas others find that the response is idiosyncratic, with some patients showing hyperglycemia and some showing hypoglycemia in response to stressful stimuli. Stabler et al.'s study (39) is notable in that it suggests that these differences in response to stress could be related to some personality variable. The issue of how individuals differ in metabolic response to stress has significant clinical implications and should be studied further.

Although the effects of stressful behavioral manipulations on blood glucose are somewhat contradictory, the data on the role of stress hormones (catecholamines, cortisol, GH) in the development of hyperglycemia and ketosis in type I diabetes appears to be more consistent. Fernqvist et al. (41) studied the effects of different doses of EPI on the absorption of subcutaneous insulin. Both healthy, nondiabetic and diabetic subjects exhibited decreased absorption of insulin, even though subcutaneous blood flow remained stable or increased. At high levels of EPI (0.3 nmol $\cdot$ kg^{-1} $\cdot$ min^{-1} intended to mimic moderate physical stress, insulin absorption was retarded by as much as 50%. One problem with this study was that not all of the subjects may have had Type I diabetes, so some may have had an endogenous insulin supply. In a series of well-controlled studies, Sherwin et al. (42) examined the effects on plasma glucose of infusions of EPI, glucagon, and cortisol, both alone and in combination in normal subjects and type I diabetic patients. The type I diabetic patients received insulin infusions for several hours before injection of the hormones. After EPI infusion, the elevation of blood glucose was 4–6 times greater in type I diabetic patients compared with normal control subjects. This increase was sustained in type I diabetic patients over a 5-h period, but lasted <2 h in the control subjects. Cortisol infusions produced a 5–7 times greater increase in blood glucose in the type I diabetic patients compared with normal control subjects. An increase in hepatic glucose production was observed only in the type I diabetic patients.

The apparently contradictory results in studies on the effects of stress in type I diabetic patients and the more consistent results on the stress hormone-induced hyperglycemia probably are attributable to several factors. First, the term stress is used to describe an enormous variety of both experimental stimuli (e.g., noise) and responses (e.g., mental arithmetic). In the studies just cited, no two groups of researchers used the same stress, hence, the disparity of results is not surprising. Furthermore, many of these studies did not describe the nature of their subjects' diabetes carefully. The effects of a given environmental stimulus on a patient with some endogenous insulin could be quite different than if applied to a patient without endogenous insulin. Finally, disruptions in autonomic nervous system activity, because of diabetic neuropathy, can lead to decreased sympathetic responses in diabetic patients (43). In patients with known autonomic neuropathy, mental-arithmetic stress does not produce the typical changes in skin temperature and heart rate that are found in both diabetic patients without neuropathy and nondiabetic control subjects (44). Because these sympathetic nervous system defects are common in diabetes, Cryer (43) has argued that increased sympathetic nervous system activity is not likely to be responsible for hyperglycemia in type I diabetes. Variations in autonomic status among diabetic patients may account for the different stress effects found in various studies and also explain why exogenously administered stress hormones

produce more reliable hyperglycemic effects.

THE ROLE OF STRESS IN THE ONSET OF TYPE II DIABETES

— Although it is now known that type I diabetes results from autoimmune destruction of the pancreatic β-cells, the pathophysiology of type II diabetes remains obscure. Conventional theories suggest that type II diabetes is caused by either a primary defect in the β-cell, making it less responsive to glucose stimulation, or by the severe insulin resistance that eventually exhausts β-cell function (45). However, attempts to find such a defect in the β-cell or such a mechanism for insulin resistance in somatic cells has been frustrating. Examination of genes that code for insulin production or insulin-receptor expression have failed to identify defects in these functions (46).

Over the past 10 years, there has been speculation that the autonomic nervous system is involved in the pathophysiology of type II diabetes (11,47–50). This possibility was foreseen by Claude Bernard, who found that hyperglycemia could be produced in normal, nondiabetic rabbits by lesioning the area of the hypothalamus. More recently, several researchers have shown that hyperglycemia can be produced by chemical stimulation of the brain with morphine and by a variety of endogenous neuropeptides, and that it can be abolished by bilateral adrenalectomy (11,51). Hyperglycemia also has been found to occur from a slow intravenous infusion of EPI (52) and from the type of stress that results in prolonged sympathetic discharge (53). Autonomic activity that leads to metabolic decompensation could be stimulated by stress (50) or by the effects of dietary fat and carbohydrate on sympathetic outflow (54–55).

One of the first observations that stress could contribute to the expression of hyperglycemia in an animal model of spontaneously occurring type II diabetes was made during metabolic studies of the sand rat (*psammomys obesus*) (57). The sand rat is a north African rodent that eats an exclusively low calorie diet of succulent plants in its natural habitat. Sand rats that are maintained on a low-calorie, low-carbohydrate diet do not develop diabetes. However, when they are fed laboratory chow and allowed to become obese, a significant percentage of the animals develop an analog of type II diabetes (56). Mikat et al. (57) have shown that stress, diet, and obesity each may play a role in the expression of hyperglycemia in these animals. The researchers maintained sand rats on a low-calorie, low-carbohydrate diet of vegetables and saline, so that they remained euglycemic. Glucose or saline then was administered to rats either through an esophageal tube or intraperitoneally by injection. Similar procedures were carried out on a group of Sprague-Dawley rats. Blood samples were drawn from all of the animals at 30- and 120-min intervals, and analyzed for glucose and insulin. Sand rats that received glucose via an intraperitoneal injection (not intubated) showed normal glucose tolerance values. However, sand rats with esophageal intubation showed the abnormal glucose tolerance that would be considered typical of diabetes. In contrast, in the Sprague-Dawley rats, intubation did not alter normal glucose tolerance values. Thus, it appears that stress, such as that of intubation, precipitates glucose intolerance even in lean, euglycemic sand rats genetically predisposed towards developing diabetes.

The genetically obese mouse (C57BL/6J, *ob/ob*) is a more commonly used model of type II diabetes. This animal is a good model of type II diabetes because it is characterized by a syndrome of obesity, hyperinsulinemia, insulin resistance, hyperglycemia, and glucose intolerance (56). However, some controversy has existed over the degree to which the obese mouse is hyperglycemic. Different laboratories have reported varying basal plasma glucose levels, ranging from 7.28 mM to >16.8 mM

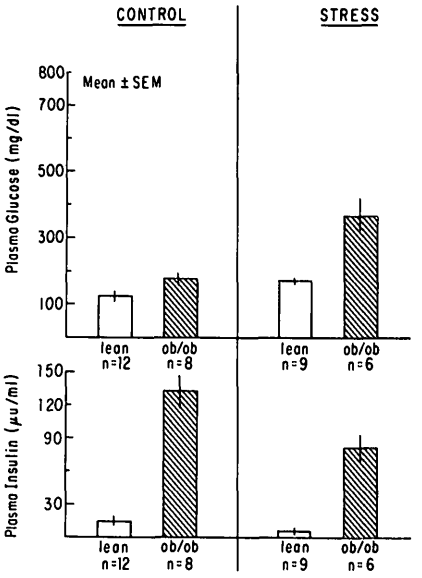

Figure 2—*Mean ± SE effects of stress on plasma glucose and insulin in C57BL/6J ob/ob mice and their lean littermates. From Surwit et al. (61). © by the American Diabetes Association.*

(58–60). Surwit et al. (61) have shown that the degree of hyperglycemia is dependent, in part, on whether the animal is exposed to stressful environmental stimuli. In one experiment, blood samples were drawn from obese and lean mice after either a rest period or exposure to stress. Stress consisted of restraint in a wire-mesh cage for 60 min, punctuated by a 5-min period of shaking. Both lean and obese animals had an increase in plasma glucose levels produced by the stress. This effect was significantly greater in the obese animals than in their lean littermates (Fig. 2). Similarly, even though plasma insulin decreased in all animals after stress, the decrease was significantly greater in obese animals. In a later study, this same group found that stress-induced hyperglycemia easily could be conditioned classically in C57BL/6J *ob/ob* mice, but not in a nondiabetic control strain (62). Taken together, these data argue that the expression of hyperglycemia in this genetic model of type II diabetes is dependent on exposure to stressful stimuli.

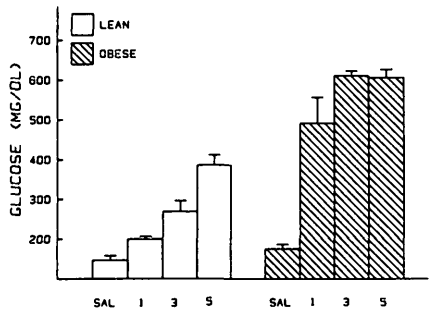

Figure 3—*Effects of increasing dose of EPI in plasma glucose in C57BL/6J ob/ob mice and their lean littermates. SAL, saline-injected controls. Dose is expressed as μg salt/10 g body wt. Results are means ± SE glucose (mg/dl). From Kuhn et al. (63). © by Physiology Biochemistry and Behavior.*

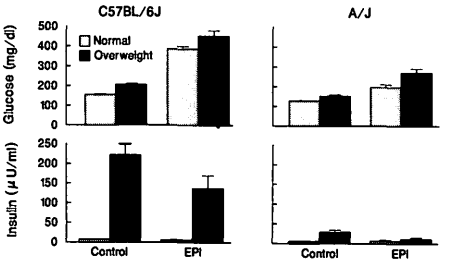

Figure 4—*Effects of diet-induced obesity and strain on serum glucose response to EPI in C57BL/6J (diabetes-prone) and A/J (diabetes-resistant) mice. EPI was injected subcutaneously (0.5 μg/10 g body wt). Control mice received equal volume injections of saline. Results are means ± SE. From Surwit et al. (65). © by the American Diabetes Association.*

The mechanism by which stress appears to disregulate glucose metabolism in obese mice was studied by Surwit et al. (61). In one study, Surwit's group studied the effects of EPI on plasma glucose and insulin in both lean and obese animals. The experimental group received an injection of EPI bitartrate, and control animals were injected with saline. Blood samples were drawn 1 h after injection. The results indicated that the effects of EPI were analogous to those of stress. That is, EPI produced an increase in plasma glucose in all animals, with obese mice showing a greater response than their lean littermates. Likewise, EPI decreased plasma insulin only in obese mice. In a follow-up study, Kuhn et al. (63) investigated the contribution of altered peripheral sympathetic function to the exaggerated glycemic response of *ob/ob* mice to stress. Obese mice and their lean littermates were injected with one of three doses of EPI bitartrate or phentolamine mesylate. EPI was administered in the dose range from 1–5 μg/10 g body weight, whereas plasma glucose responses were maximal at the lowest dose of EPI tested in the obese mice, suggesting that the dose-response relationship is altered in obese animals (Fig. 3). Moreover, phentolamine, an α-adrenergic antagonist, produced a greater increase in plasma insulin in *ob/ob* mice than the lean littermates. This suggests that increased sensitivity to catecholamines may be largely α-adrenergic. Altered peripheral responses to sympathetic stimuli are therefore important in the exaggerated glycemic responses of *ob/ob* mice to stress and may be an etiological factor in the development of diabetes in these animals. Fujimoto et al. (64) observed a similar exaggerated sensitivity to EPI in the KK mouse, another animal model of type II diabetes. Furthermore, they observed that α-adrenergic blockade with phentolamine could provoke an exaggerated insulin response in KK mice compared with control mice, suggesting that KK, like *ob/ob* mice, have altered adrenergic sensitivity.

Surwit et al. (65) also have shown that altered adrenergic sensitivity might be a biological marker for the development of type II diabetes in the background strain for the *ob/ob* mutation. They demonstrated that lean, nondiabetic C57BL/6J mice also show exaggerated glucose response to EPI compared with several other strains (Fig. 4). Furthermore, they showed that these mice develop type II diabetes when allowed to become obese on a high-fat, high-simple-carbohydrate diet. That research team thus speculated that altered sensitivity to adrenergic stimulation in the pancreas, liver, and possibly other sites may be related to the pathophysiology of type II diabetes (50).

Finally, exaggerated glycemic reactivity to behavioral stress also appears to be characteristic of at least some individuals who are predisposed to developing type II diabetes. Pima Indians are at high risk for developing type II diabetes. Approximately 60% of Pima Indians eventually develop type II diabetes in adulthood, compared with 5% of the white population. In a previous study (66), young, euglycemic Pima Indians showed a disturbed glycemic response to behavioral stress compared with whites. Pima Indians and whites were given a mixed meal, which was followed 2 h later by a 10-min mental-arithmetic stressor. Although both groups showed almost identical normal glucose tolerance in response to the meal (2 h pc glucose, 5.6 mM), 10 of 13 Pima Indians showed a small rise in glucose after a mental-arithmetic stressor, whereas 7 of 8 white control subjects did not (difference in blood glucose between Pima Indians and white control subjects after stress was 1 mM). In that both groups showed similar cardiovascular and neuroendocrine responses to the stress, it appears as though the diabetes-prone Pima Indians have a specific glucoregulatory defect that becomes apparent during such stimulation. As a marker for the development of type II diabetes, the direction of glycemic response to this stressor has a sensitivity of 76% and a specificity of 87%. In that only ~60% of our Pima Indian sample will develop type II diabetes, the sensitivity of the test may be much higher. These findings suggest that environmental stress, which activates the sympathetic nervous system, may be particularly deleterious to patients with type II diabetes, and that methods to reduce the effects of stress may have some clinical utility in this disease (50).

No controlled studies have been

conducted on how stress might affect the initial onset of type II diabetes in humans. However, as noted previously, the earliest recognition of how stress seemingly interacts with this disease was from anecdotal reports of diabetes being precipitated by acute life stress (1,2,3). Osler (3), in particular, appeared to differentiate type I from type II diabetes, in that the latter form of the disease was particularly responsive to stress. Since the first awareness of the relationship between stress and diabetes, numerous physiological mechanisms have been postulated to explain how stress disrupts glucose metabolism in diabetes. One line of research has focused on how glucose intolerance can be induced by stress hormones or by stress itself in nondiabetic individuals. Hamburg et al. (67) gave normal volunteers a low-dose EPI infusion that produced elevations in plasma EPI similar to those associated with the stress of a minor viral illness. They demonstrated that under these conditions, the deterioration in glucose tolerance was significant. Using a different type of experimental paradigm, Wing et al. (68) investigated the effect of a standardized psychological stressor on the use of a carbohydrate load in normal individuals. Subjects were fed a carbohydrate load, and then were exposed to a stressor that involved participation in competitive tasks. They found that an acute psychological stressor delayed the peak glucose response, and, therefore, apparently altered the ability of the subjects to absorb carbohydrates. In a subsequent study, this group demonstrated that this altered metabolic response was attributable to a stress-induced delay in gastrointestinal transit time (69).

STRESS AND GLUCOSE CONTROL IN TYPE II DIABETES— A modest amount of literature on the effects of stress on control of type II diabetes has accumulated over the past 15 yr. Grant et al. (70) looked at the role of stress in terms of the relationship between actual life events and fluctuations in the course of diabetes mellitus. Subjects included 15 patients with type I diabetes and 22 patients with type II diabetes. Life events were measured with a modified version of the Schedule of Recent Events (71). Their results suggested a relationship between life events, particularly those of a negative nature, and changes in diabetic symptomatology. Based on their results, they suggested that there may be life-event-responsive diabetic patients. However, no attempt was made to differentiate stress responding in type I and type II diabetic patients. McClesky et al. (26) investigated the effect of a physical stressor, namely surgery and anesthesia, on glucagon levels in both normal, nondiabetic subjects and diabetic patients—all of whom were undergoing elective surgery. Serum glucagon and glucose levels were repeatedly sampled during the pre-, intra-, and postoperative periods. Throughout the sampling period, the diabetic patients showed a clear hyperglycemic response to the surgical stress.

Although the mechanism of this stress responsivity in diabetic patients has not been studied directly, some evidence has accumulated for the altered adrenergic sensitivity and responsivity in patients with type II diabetes, and in animal models of the disease. Linde and Deckert (72) and Robertson et al. (73) observed that α-adrenergic blockade with phentolamine increased glucose-stimulated insulin secretion in type II diabetic patients; the latter group showed that this increase is 5 times greater in type II diabetic patients than in normal, nondiabetic control subjects. This suggests that α-adrenergic stimulation may have a greater effect on insulin release in diabetic patients than in normal subjects. Most recently, Kashiwagi et al. (74) demonstrated that selective blockade of α-2 receptors increased both insulin secretion and glucose disposal rate after a mixed meal in type II diabetic patients. Also, it has been reported that glyburide, one of the sulfonylurea oral agents used to treat type II diabetes, binds to α-2 receptors in the pancreas, suggesting that one effect of this drug on insulin secretion may be caused by antagonism of adrenergic activity (75). The various adrenergic effects on glucose metabolism are summarized in Fig. 1.

SUMMARY— For at least 300 years, physicians and patients have noted that the onset of diabetes often is preceded by some significant life stress. This perceived relationship may simply be assignable to the fact that two uncommon and salient life events often are perceived as related more frequently than two more common events. However, some evidence does suggest that stress may precipitate the onset of the disease or compromise glycemic control once the disease is established. Glucose toxicity that results from chronic, intermittent, stress-induced elevations in blood glucose further may compromise pancreatic secretory ability (12), leading to the progression of the disease.

However, the literature on the effects of stress in both experimental models and in human type I diabetes is complicated and often contradictory, and does not allow us to reach a clear conclusion about how stress impacts on the disease. In animal models, the effects of stress appear to depend on the type of stress and the particular model studied. Also, because animal models of type I diabetes rarely are treated with insulin, the relevance of these studies to clinical problems is not immediately apparent. Human studies are confusing, with some studies showing hyperglycemic effects, some showing no effects, and some showing idiosyncratic effects, with patients demonstrating either hyper- or hypoglycemia in response to the same stressor. These inconsistencies may reflect true individual differences in metabolic response to stress that could be related to other behavioral variables (e.g., type A personality). On the other hand, confounding conditions, such as autonomic neuropathy, which develops over time and would compromise any sympathetic nervous system response to stress,

also may contribute to these apparent idiosyncratic responses to stress on the part of different patients. At the moment, we can draw only limited conclusions about the effects of stress on type I diabetes control or how these effects would best be treated. Clearly, more research is needed to determine the role of stress in type I diabetes. Further studies should carefully exclude patients with symptoms of autonomic neuropathy and should test patients on multiple occasions to detect idiosyncratic patterns.

The potential role of stress in type II diabetes was noted a century ago by William Osler (3), and stress-reducing maneuvers were recommended as treatment for this form of the disease. More recently, a theoretical rationale for the importance of stress effects on glycemic control in type II diabetes has emerged from animal studies. These uniformly suggest that stress can affect glycemic control adversely in type II diabetes. Evidence from both animals and humans suggests that individuals with type II diabetes have altered adrenergic sensitivity in the pancreas, and perhaps other sites as well, which could make them particularly sensitive to stressful environmental stimulation. Other stimuli of sympathetic activity, such as dietary fat and simple carbohydrates, also may contribute more to the development of diabetes through this adrenergic mechanism. But, although substantial data exists to show the theoretical importance of stress in type II diabetes, no direct evidence demonstrates that stress plays a clinically significant role in the expression or control of the human disease. As in type I diabetes, clinical studies rarely have attempted to assess the role of individual behavioral differences in identifying those patients who show stress hyperglycemia or who may be particularly responsive to stress management. Few studies have followed patients long enough for generalizations on clinical outcome to be made. More clinical research is needed to determine the degree to which stress affects the onset and course of diabetes.

Acknowledgments— Preparation of this manuscript was supported, in part, by Grant 5K02 MH 00303 from the National Institute of Mental Health and Grants 1R01 DK 42923 and 1R01 DK 43106 from the National Institute of Diabetes, Digestive and Kidney Diseases to R.S.S.

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