Annu. Rev. Nutr. 2005. 25:9–35
doi: 10.1146/annurev.nutr.24.012003.132159

First published online as a Review in Advance on April 22, 2005

# DEFECTIVE GLUCOSE HOMEOSTASIS DURING INFECTION

Owen P. McGuinness
*Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0615; email: owen.mcguinness@vanderbilt.edu*



**Key Words** glucagon, insulin resistance, sepsis, nutritional support, enteral nutrition, parenteral nutrition, hyperglycemia, gluconeogenesis, lactate

■ **Abstract** Infection leads to profound alterations in whole-body metabolism, which is characterized by marked acceleration of glucose, fat and protein, and amino acid flux. One of the complications of infection, especially in the nutritionally supported setting, is hyperglycemia. The hyperglycemia is caused by peripheral insulin resistance and alterations in hepatic glucose metabolism. The defects in hepatic glucose metabolism include overproduction of glucose and a failure of the liver to appropriately adapt when nutritional support is administered. Investigators have suggested that multiple factors contribute to the observed defects. In this review, I focus primarily on alterations in carbohydrate metabolism, examining both the metabolic response to infection and inflammatory stress, the role of the accompanying neuroendocrine and inflammatory responses in the metabolic response, and the interaction between the endocrine response to infection and nutritional support.

## CONTENTS

## INTRODUCTION

Infection leads to profound alterations in whole-body metabolism, which is characterized by marked acceleration of glucose, fat and protein, and amino acid flux. This acceleration of flux per se is not detrimental except that it is accompanied by net protein loss and diabetic-like hyperglycemia. These two accompanying metabolic side effects, along with a number of other factors, influence the morbidity and mortality of the individuals with accompanying infections. Many of these patients receive nutritional support. Yet until recently the threshold for correcting hyperglycemia has been rather high (~200 mg/dl). Recent clinical trials indicate that aggressive management of glucose levels in the ICU setting (~100 mg/dl) has marked beneficial effects on morbidity and mortality (48, 56, 152, 159, 160). The primary option for management of hyperglycemia is the administration of exogenous insulin. While exogenous insulin can be a panacea in correcting hyperglycemia, recent evidence suggests that it may also modulate the underlying inflammatory response.

In this review, I focus primarily on alterations in carbohydrate metabolism. I begin with a discussion of the general metabolic response to infection and inflammatory stress and the factors that contribute to the acceleration of glucose flux. The neuroendocrine response is a major mediator of the changes in glucose flux during infection. To better understand how these hormones can contribute to the overall metabolic response to inflammation I first discuss how these hormones regulate hepatic metabolism both acutely and chronically in the absence of inflammation. This is followed by a discussion of how the presence of inflammation alters their normal interaction and the ability of insulin to modulate their action. In fact, inflammation impairs the responsiveness of the liver and other tissues to both anabolic and catabolic hormones. The net interaction of the underlying defects in hormonal responsiveness and the accompanying hormonal response determines the overall response, which is generally catabolic. Finally, I discuss the unique response of the body to nutritional support. The liver switches from a site of glucose production in the fasted state to a major site of glucose consumption during nutritional support, and inflammation blocks the liver's normal response. The failure of the liver to consume glucose efficiently during nutritional support aggravates the hyperglycemia that is seen.



## OVERALL CHANGES IN GLUCOSE FLUX DURING INFLAMMATION

One of the characteristic effects of infection is hyperglycemia (13). The magnitude of the hyperglycemia is influenced by the fasting state and the severity of the illness. Glucose utilization is increased during infection due to the combined increase in glucose clearance and glucose levels (mass action). In spite of the increase in glucose utilization, hyperglycemia occurs due to a combined increase in glucose

production and a failure of peripheral glucose clearance to increase in proportion to the increase in glucose production (49).

Hypoglycemia can be observed during inflammatory stress. A potent stimulator of the inflammatory response is endotoxin. Following the acute injection of endotoxin in humans there is a rapid rise in splanchnic glucose release and a gradual rise in arterial glucose levels (49). With increasing doses of endotoxin in other species, the increase in glucose production (two- to threefold) is more robust and is persistent (91). However, despite this increase, hypoglycemia can develop after a period of hyperglycemia. In fact, with very high doses of endotoxin the progression to hypoglycemia can be very rapid and can be accompanied by a fall, rather than a rise, in glucose production. The mechanism for this is discussed below.

During prolonged infection, as is seen in the intensive care unit, basal glucose production is increased [twofold (134, 143, 155)] after a brief fast in the presence or absence of hyperglycemia (Figure 1). This increase is seen in animal models as well (90, 106). The contribution of glycogenolysis and gluconeogenesis to the increase in glucose production is dependent upon the duration of the stress. Following the acute administration of endotoxin, glycogenolysis is the primary source of the glucose carbon (119), but during chronic infections, if glycogen stores are depleted, an increase in gluconeogenesis contributes to the enhancement of glucose production (90, 106). Although gluconeogenesis has not been directly measured in glycogen-replete states, both processes are likely increased.

In some ways, it is surprising that gluconeogenesis can increase during an inflammatory stress; however, this is dose and possibly species dependent. It is well known that prior exposure to endotoxin or infection decreases the capacity of the liver to synthesize glucose in vitro (14, 29, 47, 67, 123, 149, 162). Increases in gluconeogenic precursor supply and hormones that are known to enhance gluconeogenesis are ineffective in livers isolated from infected animals. Yet in vivo, except following very severe inflammatory stress where hypoglycemia can develop, gluconeogenesis is either maintained at baseline or increased. Presumably, the infection-induced increase in gluconeogenic substrate supply and the elevated levels of stress hormones combine to sustain, and in some cases augment, the gluconeogenic rate in vivo.



## GLUCONEOGENESIS AND SUBSTRATE AVAILABILITY DURING INFLAMMATION

Substrate availability has been promoted as a primary mechanism for the increase in glucose production during inflammatory stress. While adequate substrate availability is required to support elevated gluconeogenic rates, enhanced substrate delivery alone does not translate into an increase in glucose production. Acute increases in lactate or alanine do not increase glucose production (28, 38, 109), even in a glycogen-depleted setting where glucagon is markedly increased (110,

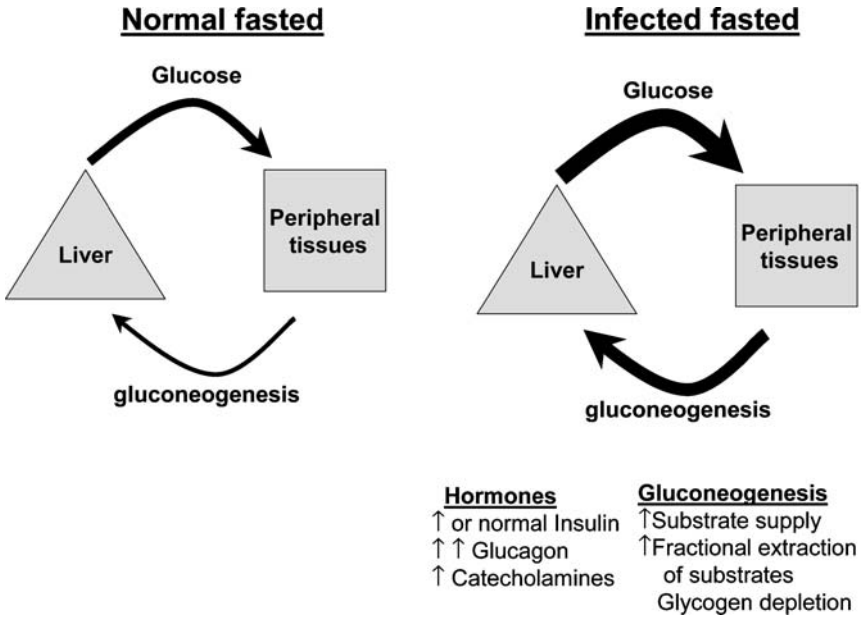


**Figure 1** Impact of inflammation on gluconeogenesis and hepatic glucose production in the fasted state.



167). An increase in gluconeogenic precursor availability, even in stressed states, does not impair insulin suppression of liver glucose production (155). Thus, gluconeogenic precursor availability per se is not an important determinant of glucose production.

Fatty acid availability and the hormonal environment can dictate the effectiveness of the increase in substrate supply. Combined increases in gluconeogenic precursor supply and fatty acids will increase hepatic glucose production (109). Increases in fatty acids impair insulin suppression of hepatic glucose production (147). They suppress the glycogenolytic and enhance the gluconeogenic effects of both glucagon and epinephrine (24, 61). Given that fatty acid availability is increased during infection and inflammatory stress (166, 169), this may help contribute to any observed increase in gluconeogenesis.

A reciprocal fall in net glycogen breakdown buffers the effect of a rise in gluconeogenic precursor supply on hepatic glucose production. Gluconeogenic precursor uptake increases as substrate supply increases. In a setting of fixed hormone levels, physiologic increases in alanine concentration proportionally increase net hepatic alanine uptake (38). Increases in lactate concentration increase net hepatic lactate uptake, but this is not a linear function of substrate delivery (28). Investigators who decreased substrate supply in septic rats and humans using dichloroacetic acid (DCA) (59, 86) observed a fall in lactate and a concomitant fall in glucose

production, which suggests substrate supply helps drive the rise in glucose production. In humans, infusion of DCA (73) will modulate glucose production in a setting where glycogen stores are depleted. Unfortunately, DCA may exert effects on the liver and peripheral tissues, which makes interpretations of the effects of substrate supply on liver glucose production suspect (39).

Although increased lactate production does contribute to the elevated lactate levels during inflammatory stress, this is not the only story. In fact, whole-body lactate flux increases to a lesser extent than lactate levels in septic patients, suggesting that lactate clearance falls. To address the potential role of hypoxia in the elevated lactate levels, DCA was administered to enhance pyruvate dehydrogenase activity in muscle (59). Using radiolabeled glucose and pyruvate, the investigators observed that DCA enhanced the fraction of pyruvate oxidized, despite a marked lowering of lactate and pyruvate levels, which suggests that anaerobic glycolysis may not be a significant contributor to elevated lactate levels during sepsis. That tissue hypoxia is not the primary mechanism for the lactic acidosis is supported by the fact that tissue levels of adenosine triphosphate, as assessed with phosphorus nuclear magnetic resonance in animals, are not decreased (71).

The two determinants of the gluconeogenic response are the delivery of gluconeogenic substrates to the liver (product of liver blood flow and substrate concentration) and the ability of the liver to extract the gluconeogenic precursors. Depending upon the magnitude of the stress and the specific gluconeogenic precursor, one or both may determine the gluconeogenic response in a given species. Although it is often stated that gluconeogenic precursor supply increases during infection, in fact this is not true for all gluconeogenic precursors. In humans (49), following a very low dose of endotoxin, gluconeogenic precursor delivery increased primarily because of a rise in lactate concentration, as the levels of other gluconeogenic precursors (alanine and glutamine) fell. This increase in lactate concentration, combined with the 50% increase in splanchnic blood flow, resulted in an increase in hepatic lactate delivery. The rise in lactate delivery primarily dictated the change in lactate uptake by the splanchnic bed, since splanchnic fractional extraction of lactate did not increase. Despite a fall in alanine and glutamine levels, net splanchnic uptake of both precursors increased because of a rise in fractional extraction by the splanchnic bed and the rise in splanchnic blood flow. The rise in gluconeogenic precursor uptake could account for approximately 50% of the endotoxin-induced rise in liver glucose production in the human after a very low dose of endotoxin. In other species where higher doses of endotoxin can be given, the rise in lactate is due in part to a decrease in whole-body lactate clearance (138); however, increases in lactate turnover contribute as well (165). Adrenergic blockade attenuated the rise in lactate concentration (64). Nevertheless, it is difficult to evaluate the role of the catecholamines, since hypoglycemia and hypotension developed during adrenergic blockade. With higher doses of endotoxin in a canine model, glycogen breakdown was the primary source of the increase in glucose production, despite the fact that the levels of lactate and alanine rose (119). The actual uptake of these substrates by the liver does not increase markedly in endotoxemia.

In the glycogen-depleted setting, the liver is a net consumer of lactate. However, following the administration of endotoxin, the net uptake of lactate decreases and in fact, the liver transiently switches to lactate release, in spite of a rise in arterial lactate levels. The switch to lactate release occurs because of a robust increase in hepatic glycolysis driven by a concomitant rise in hepatic glycogenolysis. In the case of alanine, arterial levels rise progressively. Yet the fractional extraction of alanine tends to fall, minimizing the rise in net hepatic alanine uptake. When combined with the fact that net hepatic uptakes of the other gluconeogenic amino acids (threonine, glutamine, serine, and glycine) do not rise, net hepatic uptake of gluconeogenic precursors [an index of gluconeogenesis (119)] does not rise following the administration of endotoxin.

With chronic infections, gluconeogenesis is likely increased. An increase in gluconeogenesis has been directly assessed in animal models (106). Although it likely increased in humans (143), gluconeogenesis has not been accurately quantified. The method used to assess gluconeogenesis (tracer-determined alanine conversion to glucose) is prone to errors and does not yield a quantifiable measure of gluconeogenesis (81). Moreover, this method does not separate the contributions of the kidney and the liver to whole-body gluconeogenesis. Normally renal gluconeogenesis is a minor contributor to whole-body glucose flux (20). However, the kidney can be a significant site of lactate removal in stressful settings (6). As with an acute inflammation, the relationship between increases in lactate levels and net splanchnic lactate uptake in chronic infection are not straightforward. In severely septic patients, the splanchnic bed is not a significant producer or consumer of lactate (32) despite marked elevations in lactate levels. The net balance of lactate in patients who were consumers of lactate could at most account for less than 1% (0.01 mg/kg/min) of the predicted net splanchnic glucose output ($\sim$2 mg/kg/min). With lethal doses of endotoxin, the impairment in gluconeogenic capacity of the liver is so marked that total glucose production rapidly falls and hypoglycemia ensues once hepatic glycogen stores are depleted. In that setting, the liver is not a significant consumer or producer of lactate (23). Thus, despite the increased availability of lactate and in many cases other gluconeogenic substrates during infection and inflammation, the relative importance of gluconeogenesis and glycogenolysis to the total rate of glucose production is difficult to predict.



## NORMAL INTERACTION BETWEEN COUNTERREGULATORY HORMONES AND HEPATIC METABOLISM

The alteration in metabolism that accompanies inflammation represents an integration of three separate but interrelated biological responses: (*a*) activation of the neuroendocrine system, (*b*) release of cytokines from the activated immune system, and (*c*) release of lipid mediators from multiple cell types (84). The differing metabolic responses to acute endotoxin administration and chronic infection can

be explained in part by the differing acute and chronic responses of the liver to stress hormones.

Since Shamoon et al. (139) conducted their original studies, it has been hypothesized that many of the metabolic responses observed during infection could be explained by a synergistic interaction between the accompanying hormonal responses to inflammation. In these seminal studies, Shamoon and colleagues demonstrated that the hyperglycemic response to a hormone could be amplified if other counterregulatory hormones were also infused. In those studies (139), it was observed that over the course of 5 to 7.5 hours of hormone infusion, epinephrine (13x basal)-amplified glucagon stimulated glucose turnover. The addition of cortisol (4x basal) further enhanced stimulation of glucose turnover, such that the response was greater than the sum of their individual effects. Unfortunately, defining how these hormones interact acutely as well as chronically to control the metabolic response is complex. Moreover, it is even more complex, given that during infection these hormones have to interact with the immune response. To explain how these hormones might interact, the discussion below first describes some of the known effects of these hormones when they are infused acutely in isolation, and then relates what is known about how some of them interact.

Glucagon is a potent stimulator of glucose production; its effect wanes with time (19, 21). The effect of glucagon on glucose production has been shown to result primarily from a rapid, potent, time-dependent effect on glycogenolysis, and to a lesser extent, from a less potent, slower effect on gluconeogenesis (22, 104). In fact, glucagon has been shown to acutely increase hepatic gluconeogenic efficiency in vivo (154), yet the contribution of the rise in gluconeogenesis to the increase in glucose production was small. This paradox may be explained by the fact that glucagon has little effect on gluconeogenic substrate mobilization from muscle or fat. Thus, any enhancement of gluconeogenic flux would initially increase gluconeogenesis, but then the gluconeogenic substrate levels in blood would fall and the gluconeogenic contribution to glucose production would return toward its basal rate.

Epinephrine can also increase glucose production in a rapid, time-dependent manner, albeit with a decreased sensitivity on a molar basis compared with glucagon (26, 153). The effect of epinephrine on glucose production results from a stimulation of both gluconeogenesis and glycogenolysis. The increase in gluconeogenesis is due to the indirect action of the hormone on peripheral substrate release, whereas enhancement of glycogenolysis is due to the direct action of epinephrine on the liver (25, 27). Subsequent studies (61) demonstrated that when the hormone increased the gluconeogenic precursor supply, it caused a compensatory decrease in its glycogenolytic action, implying a reciprocal relationship between the two processes. Increasing the gluconeogenic precursor supply to the liver increased gluconeogenesis but did not increase total glucose production, thereby implying a decrease in glycogenolysis. Studies examining the interaction between epinephrine, cortisol, and glucagon clearly demonstrate that they can have an additive effect on glucose production (60, 61, 100), with little evidence of synergy. Moreover,

the mobilization of gluconeogenic substrates by epinephrine only increases the contribution of gluconeogenesis to whole-body glucose production.

In summary, although the studies of Shamoon et al. (139) would suggest potential synergy between counterregulatory hormones in the acute setting, in subsequent well-controlled studies there was little evidence of synergy. Moreover, although these hormones may differentially regulate gluconeogenic precursor supply and consequently the contribution of gluconeogenesis to total glucose production, gluconeogenic precursor supply does not determine the overall rate of glucose production.

For many types of inflammatory stressors, the endocrine response persists for multiple days. The metabolic response to a chronic elevation in hormones may differ markedly from that seen in the acute setting. Studies (7, 54) in humans observed that a combined infusion of glucagon, epinephrine, and cortisol (5- to 20-fold and 4-fold, respectively) for three days could lead to sustained hyperglycemia and elevated glucose production. Subsequent studies in dogs (111), using a three-day infusion of glucagon, epinephrine, norepinephrine, and cortisol, produced a metabolic response similar to that in humans. The sustained increase in liver glucose production was due primarily ($\sim$70%) to an increase in gluconeogenesis.

Additional studies examined the contribution of the individual hormones to the overall response to chronic (three days) stress hormone infusion (SHI). Initial studies examined the impact of the acute discontinuation of a specific hormone after a chronic SHI. Acute removal of glucagon (three hours) markedly decreased net hepatic glucose output and hepatic glycogenolysis (115). Net hepatic gluconeogenic precursor uptake was not altered; the majority of the gluconeogenic carbon was diverted to glycogen synthesis. A similar response was observed when the chronic epinephrine infusion was discontinued (117). Net hepatic glucose output was completely suppressed, whereas net hepatic gluconeogenic precursor uptake was minimally affected. These data could be interpreted to suggest that both epinephrine and glucagon have no impact on gluconeogenesis and primarily affect hepatic glycogen metabolism. Thus, another hormone (e.g., cortisol or norepinephrine) must drive the rise seen in gluconeogenesis during chronic SHI. Yet chronic infusion of cortisol alone has only modest effects on gluconeogenesis (58), and acute removal of norepinephrine had little, if any, impact. The impact of acute removal of a hormone may not reflect its role in a chronic process such as SHI.

The impact of the absence of a chronic elevation of a single hormone on the overall metabolic response to SHI was also evaluated. The absence of an increase in glucagon during SHI nearly completely prevented the SHI-induced increase in net hepatic glucose output (107). Interestingly, despite chronic elevations in cortisol and catecholamines, futile cycling of glucose into and out of the liver was enhanced, which suggests that glucagon can serve as a brake to limit hepatic glucose entry in a setting of hyperglycemia and thus sustain the hyperglycemia. Moreover, the rise in gluconeogenesis was absent despite marked elevations in gluconeogenic substrate (e.g., lactate and alanine) concentrations. The most dramatic effects were a failure

of the liver to revert to lactate consumption despite elevated lactate concentrations and a failure of net hepatic alanine fractional extraction to increase. Conversely, the absence of an increase in epinephrine also blunted the hyperglycemia, but it had little impact on gluconeogenesis or gluconeogenic precursor supply (116). This is in marked contrast to the acute effects of epinephrine, which enhances gluconeogenic supply and gluconeogenesis. In contrast to epinephrine, the lack of a rise in norepinephrine had little impact on the overall metabolic response to SHI. Interestingly, the absence of a rise in cortisol eliminated the SHI-induced increase in gluconeogenesis, primarily by decreasing substrate supply (51). The enhanced extraction of gluconeogenic substrates by the liver persisted. Moreover, hepatic glycogen stores, which in fact tended to rise during SHI, were markedly depleted by SHI when a rise in cortisol was absent. This is consistent with the observed increase in hepatic glycogen content when cortisol was increased chronically in the absence of a rise in the other counterregulatory hormones (58).

Thus, in the context of elevations in multiple counterregulatory hormones, these hormones work in concert to maintain hyperglycemia by increasing hepatic glucose production (both glycogenolysis and gluconeogenesis; Figure 1). The synergy that can occur between the hormones in augmenting net hepatic glucose production is accomplished by targeting one of four cellular processes: (*a*) substrate supply, (*b*) the capacity of the liver to take up gluconeogenic precursors, (*c*) mobilization of glycogen stores, or (*d*) facilitation of glucose release by the liver while minimizing hepatic glucose entry.



## HORMONAL CONTROL OF THE METABOLIC RESPONSE TO INFLAMMATION

The metabolic response to inflammation is complex. The alterations that accompany infection represent an integration of three separate but interrelated biological responses: (*a*) activation of the neurohumoral system, (*b*) production of cytokines, and (*c*) release of lipid mediators from multiple cell types. The intertwining of these systems has made it difficult to differentiate between the primary and the secondary events, which direct the metabolic response to infection.

Activation of the adrenergic system appears to be one of the primary mechanisms for the rapid increase in hepatic glucose production that occurs following acute endotoxin administration (64). Combined ($\alpha$ and $\beta$) adrenergic blockade prevented the increase in hepatic glucose production in the conscious rat. Interestingly, blockade of either $\alpha$ or $\beta$ adrenergic receptors did not completely attenuate the response to endotoxin.

The rise in glucagon may also contribute to the rise in hepatic glucose production. Glucagon is markedly elevated during infection and inflammation (8, 12, 30, 49, 88). The increase in glucagon levels is generally greater than one might see during hypoglycemia (9). Moreover, although the rise in glucagon secretion has not been directly measured during inflammation, it is substantially greater than the rise

in the arterial levels (70). The glucagon assay detects both the biologically active glucagon and a large molecular-weight glucagon that is thought to be derived from the intestine (161). As much as 50% of the basal immunoreactive glucagon is not biologically active. Consequently, a doubling of immunoreactive glucagon levels (50 to 100 pg/ml) can represent a more than fourfold rise in glucagon secretion.

The rise in glucagon may also contribute to the rise in hepatic glucose production following endotoxin administration. The endotoxin-induced rise in glucagon persisted in the presence of adrenergic blockade, yet an increase in hepatic glucose production was absent (64). This led the authors to conclude that the rise in glucagon does not contribute to the endotoxin-induced rise in hepatic glucose production. In a normal setting, the rise in glucagon observed during endotoxemia would markedly increase hepatic glucose metabolism (154). It is likely that if glucagon had not increased, hepatic glucose production would have fallen below basal rates because of the concomitant rise in insulin or more likely because of an underlying impairment in hepatic metabolism. As a result, hypoglycemia would have developed. In fact, one of the hallmarks of a rise in glucagon is a rise in the fractional extraction of alanine by the liver (154). Following endotoxin administration, hepatic fractional extraction of alanine did not increase, consistent with an impairment in glucagon action during endotoxemia (119). At present, no studies have assessed the role of glucagon in the response to endotoxin.

A number of investigators have examined the role of catecholamines and glucagon in the overall hepatic response to chronic stress. In one of the first studies (72), which was done in burn patients, somatostatin was infused with replacement of insulin with or without glucagon replacement. When glucagon was not replaced, endogenous glucose production and arterial glucose concentration decreased markedly. Exogenous glucose had to be infused to prevent hypoglycemia. Subsequent studies in dogs (113, 168) and rats (88) with an infection also demonstrated that acute correction of the hyperglucagonemia decreased hepatic glucose production due to a fall in hepatic glycogenolysis.

We (113) observed, using a combination of tracer and arterio-venous difference techniques, that suppression of the hyperglucagonemia did not alter net hepatic gluconeogenic precursor uptake. In the specific case of alanine, the fall in net hepatic fractional extraction of alanine after lowering the glucagon concentration was offset by a gradual elevation of arterial alanine concentration. This is consistent with the known potent effect of glucagon on hepatic amino acid transport (75). The fall in glucose production was due to a diversion of the gluconeogenic carbon to glycogen rather than release as glucose. In many ways, this is reminiscent of the effects observed when glucagon was acutely discontinued during SHI (115). The lack of a detectable effect on the gluconeogenic process may indicate that the impact of the acute removal of glucagon does not reflect its chronic role during an infection. If the glucagon response was simulated in noninfected animals, liver glucose production was not augmented (114). However, when the chronic glucagon infusion was acutely discontinued, a comparable fall in hepatic glucose output was observed and hepatic gluconeogenic precursor uptake was unaltered

(114). The chronic hyperglucagonemia markedly augmented the capacity of the liver to take up gluconeogenic precursors. Yet this did not enhance net hepatic gluconeogenic precursor uptake and glucose output, presumably because the arterial gluconeogenic substrate concentrations decreased (109). In fact, this up-regulation in the capacity to take up gluconeogenic precursors (specifically alanine) far exceeded that seen when an infection accompanied the hyperglucagonemia (106). Thus, a defect in glucagon action may limit glucagon effectiveness in augmenting the gluconeogenic process when an infection is present.

Catecholamines also contribute to the increase in hepatic glucose production during infection; however, their importance is dependent upon the severity of the stress. Following a mild infection in which basal catecholamines were minimally elevated, combined adrenergic blockade had no effect on hepatic glucose production (63). When sympathetic outflow was markedly elevated, combined adrenergic ($\alpha$ and $\beta$) blockade prevented the sepsis-induced (168) as well as the endotoxin-induced (64, 82) increase in hepatic glucose production. The elevated lactate levels seen during chronic infection were not altered by adrenergic blockade (82). However, they were attenuated following an acute administration of endotoxin (64).

Glucocorticoids increase markedly following endotoxemia (46, 119, 136, 156). Their acute role in sustaining liver glucose production is likely modest. Adrenalectomy increases the susceptibility to hypoglycemia (105). Acute elevations in cortisol have minimal effects on hepatic glucose production or gluconeogenesis (57). As mentioned above, cortisol may amplify the effects of the other counterregulatory hormones.

Interpreting the roles of the endocrine hormones is difficult in a setting where insulin is ever changing and its ability to antagonize the hormones may be modified by the accompanying illness. Thus, quantifying the role of a given classical counterregulatory hormone in the overall metabolic response of the liver is difficult. Moreover, as is discussed below, since the accompanying cytokine response to inflammatory stress interacts with and may actually blunt the effectiveness of the stress hormones as well as insulin, defining the specific role of a hormone may be difficult.



## INSULIN RESISTANCE AND INFLAMMATION

Insulin resistance is characteristic of sepsis and inflammation. It is reversible once the injury or inflammation has been resolved. Many tissues are involved, including the muscle, liver, and adipose, and the inflammatory cells themselves. Because of the multiple cellular targets and the difficulty in controlling for variables such as duration of fasting, age, glycemia, severity of injury, and drug treatment, quantifying the extent of the glucose intolerance was initially difficult (103). An additional confounding response was that of endotoxemia, where hypoglycemia can occur, and initially investigators suggested either insulin action was enhanced or endotoxin induced insulin-like effects (47, 96).

Using the euglycemic hyperinsulinemic clamp or the hyperglycemic clamp techniques, investigators were able to quantify the extent of insulin resistance during infection and endotoxemia in multiple species. It was clear from the studies that overt insulin resistance was present in infection. The extent of the insulin resistance varied but in the presence of physiologic hyperinsulinemia, the glucose requirements were decreased by approximately 50% (82, 93, 95, 98, 134, 163). When indirect calorimetry was combined with the technique, the primary defect was not glucose oxidation but glucose storage (134). This differs somewhat from the insulin resistance of obesity and diabetes, where both oxidation and storage are negatively impacted (31). The complexity of this is exemplified by the fact that augmentation of pyruvate dehydrogenase activity (140) alone could not explain the isolated impairment in glucose storage (141), and did not improve insulin-stimulated glucose disposal in septic humans and rats. Thus, multiple defects may be present (impairments in glucose delivery, cellular glucose transport, and phosphorylation, as well as glycogen synthesis).

In a series of studies, Lang et al. (83, 96–98, 120, 121) clarified the sites for the insulin-like activity of inflammation and infection as well as the sites of impaired glucose disposal and the role of the adrenergic system in the augmentation of tissue glucose utilization. In the absence of an increase in insulin, infection increases whole-body glucose utilization despite marked peripheral insulin resistance. The increase occurs in multiple tissues, especially in macrophage-rich tissues (e.g., spleen, liver, intestine). This increase occurs independently of insulin and is linked to the cytokine response that accompanies inflammation. No one cytokine controls the metabolic response to endotoxin. Injection of high doses of TNF can re-create the metabolic response to endotoxin (151). Yet neutralization of TNF prior to endotoxin injection does not significantly attenuate the metabolic response to endotoxin, even though it attenuates the lethality of the endotoxin (99). The elevations in body temperature, synthesis of eicosanoids, and fever (85, 87) also do not play an essential role in the metabolic response to endotoxin.

The insulin resistance in infection and inflammation has been attributed to elevated levels of cytokines. Studies have revealed that elevated concentrations of cytokines, such as interleukin-6 and TNF-$\alpha$, can induce insulin resistance (76, 78). Further complicating the issue is that cytokines may be synthesized locally in muscle, so that circulating levels of the cytokines may not reflect the true cellular exposure (50). In addition, infusion of insulin can amplify the cytokine response to endotoxin (79, 148).

Several mechanisms may play a role in cytokine-induced insulin resistance. TNF-$\alpha$ stimulation increases serine phosphorylation of insulin receptor substrate 1, decreasing its tyrosine phosphorylation by the insulin receptor kinase (1, 68, 69). Although these phosphorylation events are very rapid, full TNF-$\alpha$- and endotoxin-mediated insulin resistance is slow to develop (11, 44). A family of protein suppressors of cytokine signaling have been suggested to be involved (74, 78, 157, 158). As with many of these signaling events, their importance in the actual

phenotypic expression of the insulin resistance observed during infection is difficult to quantify.

Although it is clear that insulin resistance is a major contributor to the pathology of hyperglycemia during infection, it is still unclear how this insulin resistance interacts with the neuroendocrine environment of inflammation, when the effectiveness of these hormones is also impaired. Glucagon, growth hormone, and adrenergic signaling are all impaired during inflammatory stress (33, 55, 132, 133).

## INTERACTION BETWEEN NUTRITIONAL SUPPORT AND INFLAMMATION



The defects in whole-body glucose metabolism are most evident when exogenous glucose either is administered alone or as part of parenteral nutrition. In response to an acute infusion of glucose, the liver removes less than one third of the exogenous glucose, and the remaining tissues, primarily muscle, are the major sites of glucose disposal. Hepatic glucose uptake can reach one third of the load if the glucose is given orally (127). During intravenous glucose delivery, suppression of liver glucose production rather than stimulation of liver glucose uptake is the major way the liver contributes to glucose homeostasis. Following the administration of endotoxin, the depleted hepatic glycogen stores are resistant to repletion by the administration of exogenous glucose (89, 112). This is due to both a failure to suppress endogenous glucose production as well as to a failure to augment glycogen synthesis. An elevated glycogen phosphorylase activity and a failure to suppress phosphorylase during glucose infusion, rather than a defect in glycogen synthase activation, contribute to the impaired hepatic glycogen synthesis (10). The role of the liver in glucose homeostasis changes dramatically during chronic nutritional support.

The clinical perception that the liver is a significant site of glucose disposal in the nutrition-support patient only when hyperglycemia is present is no longer well-founded (164). This belief is based on (*a*) limited uptake of glucose by the liver in the acute setting in the absence of hyperglycemia, (*b*) a respiratory exchange ratio greater than 1 in nutrition-support patients who develop hyperglycemia, and (*c*) increased incidence of the hepatic steatosis seen with hyperglycemia. In fact, de novo lipogenesis (i.e., glucose to lipid) rarely occurs except in cases of carbohydrate feeding in excess of the energy requirements (65). The major substrate for hepatic lipogenesis is circulating free fatty acids and not glucose (145). In the presence of near-normal glucose levels in nonseptic individuals receiving nutritional support, the splanchnic bed was a significant site of glucose utilization; fractional splanchnic extraction of glucose was ~20% (144). The role of the liver has not been directly assessed in humans because of lack of access to the hepatic and portal veins. In the dog administered chronic total parenteral nutrition (TPN) into a peripheral vein for four days, the liver took up ~50% of the exogenous glucose delivered; hepatic extraction of glucose was ~20% (108). Nearly

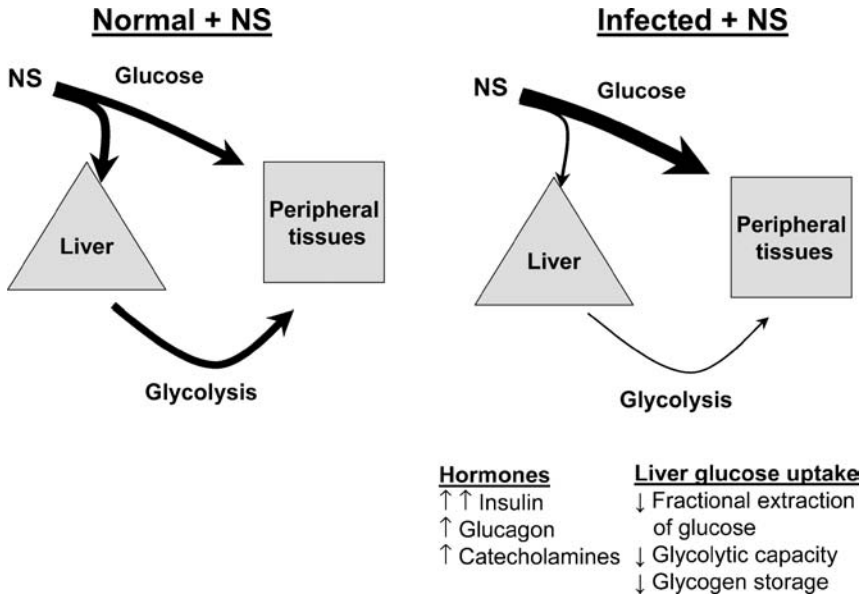


**Figure 2** Impact of inflammation on glucose uptake by hepatic and peripheral tissues during nutritional support (NS).



75% of the glucose taken up was released as lactate and delivered to peripheral tissues (i.e., reverse Cori cycle). Since removal of lactate by peripheral tissues is more efficient than glucose and is not dependent upon insulin (28), the response of the liver limits the severity of the hyperglycemia and hyperinsulinemia that otherwise would occur (Figure 2). Clearly then, any defect in hepatic glucose uptake during TPN would predispose the individual to hyperglycemia and/or hyperinsulinemia.

Interestingly, the rate of glucose uptake by the liver during chronic TPN is greater than that which would have been predicted based upon acute studies. The liver of the normal animal receiving chronic TPN consumes a substantial net quantity of glucose ($\sim$4.5 mg/kg$^{-1}$/min$^{-1}$) in the presence of normal glucose levels (120 mg/dl) and only mild hyperinsulinemia (15 $\mu$U/ml) (108). In the acute setting, these levels of insulin and glucose would not initiate net hepatic glucose uptake (NHGU). Three factors regulate NHGU acutely: the hepatic glucose load (blood flow $\times$ glucose level), the hormonal milieu (insulin and glucagon levels), and the route of glucose delivery (portal signal). Physiologic increases in glucose alone will not induce NHGU. However, in the presence of elevated glucose, insulin increases NHGU in a dose-dependent manner. It is enhanced further if the glucose is administered into the portal vein (which activates the portal signal) (125, 127). To induce NHGU of the magnitude seen in the normal animal during TPN ($\sim$4 mg/kg$^{-1}$/min$^{-1}$), the arterial plasma glucose levels would have to be greater

than 200 mg/dl and the arterial insulin levels would have to exceed 170 $\mu$U/ml (125). In fact, to obtain substantial NHGU with more physiologic insulin levels ($\sim$30 $\mu$U/ml), the glucose would have to be infused into the portal vein to activate the portal signal and the arterial glucose levels would have to exceed 200 mg/dl. Thus, the liver of the TPN-adapted dog increased its capacity to consume glucose. A potential explanation is an increase in glucokinase activity (5, 126), possibly initiated by the prolonged exposure to mild hyperinsulinemia and to the very low glucagon levels seen during TPN. However, this likely is not the sole explanation.

The acute versus chronic modulation of liver glucose uptake in the setting of continuous nutritional support varies markedly. Glycogen synthesis is the primary fate of glucose taken up by the liver following a meal (127). Surprisingly, despite the large activation of glycolysis following TPN, acute increases in glucose and insulin or direct activation of glucokinase primarily divert the additional glucose carbon to glycogen rather than to lactate (17, 41). The preferential diversion of glucose carbon to glycogen may be explained by a property of glucokinase (i.e., hexokinase IV). Overexpression of glucokinase, but not hexokinase I, diverts glucose to glycogen. In contrast, overexpression of hexokinase I diverts the glucose to glycolysis (137). The fact that acute manipulation of glucose and insulin, as well as glucokinase, diverts glucose away from a very active glycolytic pathway during TPN is consistent with this observation. Thus, glycogen synthesis is the preferred site for glucose disposal when acute manipulations are made, irrespective of the liver's metabolic state.

The mechanism whereby glycogen is no longer a major metabolic fate during TPN is unknown. Overexpression of glucokinase improves hepatic glucose utilization (137). Because glucokinase preferentially diverts glucose to glycogen, this casts doubt on activation of glucokinase as the sole explanation for the increased rate of glucose uptake and lactate release during TPN. Glycogen synthesis may be suppressed by accumulating glycogen stores (37). However, glycogen synthase activity does not decrease in glycogen-replete rats (53), and acute activation of glucokinase is very effective in augmenting liver glucose uptake (42) in the TPN-adapted state. Glycogenolysis may increase to equal the rate of glycogen synthesis, leading to rapid cycling of glucose through glycogen. Consistent with this, while 75% of NHGU is released as lactate during TPN, only 30% of U-$^{14}$C glucose taken up by the liver is diverted to lactate. The remainder of the U-$^{14}$C glucose either accumulates in glycogen or is oxidized. However, a net decrease in glycogen synthesis alone likely will not explain the preferential diversion to lactate. A specific activation of glycolysis, possibly mediated by a rise in fructose 2,6-bisphosphate, an activator of phosphofructokinase, and pyruvate kinase, likely contributes (131).

In response to infection, the ability of the liver to remove an exogenous glucose load acutely delivered into a peripheral vein is decreased (112). We have observed a similar response in infected animals adapted to TPN (108). The infection-induced decrease in NHGU during an acute peripheral glucose infusion was due to both an impaired stimulation of hepatic glucose uptake and an impaired suppression of

hepatic glucose production (112). The impaired suppression of glucose production is a characteristic of infection in humans (11, 142). In the TPN-adapted animal, an impairment in hepatic glucose uptake (Figure 2) is the primary contributor to the defect during infection; however, glucose production would be elevated as well were it not for the compensatory hyperinsulinemia (40). The mechanism(s) for this is (are) unknown.

Elevated glucagon concentrations likely contribute to the impaired net liver glucose uptake during infection. Chronic elevations in glucagon may also explain the need for additional insulin to restrain hepatic glucose production. Acute increases in glucagon antagonize liver glucose uptake by stimulating hepatic glucose production and inhibiting glycogen synthesis (66). However, the acute and chronic effects of glucagon are markedly different. Acutely, glucagon regulates glycogen metabolism, but chronically it regulates gluconeogenesis (107, 115). As mentioned above, chronically it can limit cortisol-induced enhancement in liver glucose uptake and facilitate glucose production (51). It is most effective in increasing gluconeogenesis when an adequate supply of gluconeogenic amino acids and lipids, both of which are supplied in TPN, are present (102, 112). One possible mechanism by which glucagon could limit liver glucose uptake is inhibition of glucokinase (129, 130). However, chronic activation of glucokinase (chronic fructose infusion) alone cannot correct the infection-induced impairment in liver glucose uptake (43). This suggests that the infection-induced impairment in liver glucose uptake may be due to defects at multiple sites. Glucagon is a potent inhibitor of phosphofructokinase and pyruvate kinase (129, 130). Thus, combined decreases in glucokinase, phosphofructokinase, and pyruvate kinase could explain the decrease in liver glucose uptake and the lactate release seen during infection. A host of other factors (including cytokines, prostaglandins, and nitric oxide) may contribute to the alterations in hepatic glucose production. However, many of their effects on glucose metabolism are mediated both directly and indirectly via their activation of the neuroendocrine system (3, 87, 92, 94, 150). Inhibition of nitric oxide does not alter liver glucose uptake during infection (16). Catecholamines can inhibit liver glucose uptake (108), but significant impairment in the hepatic response to TPN is seen in models with very little elevation in catecholamine levels.

Correction of the infection-induced hyperglycemia by administration of insulin may not necessarily improve liver glucose uptake. Although administering insulin can facilitate NHGU, the concomitant lowering of glucose levels will counteract this effect. As mentioned above, two of the three major determinants of NHGU are the insulin and glucose levels. Increases in insulin not only improve NHGU, they also increase muscle glucose uptake (170). Based upon the studies of Myers et al. (125) in 42-hour fasted dogs, ~15% of the exogenous glucose delivered into a peripheral vein was disposed of by the liver in the presence of acute moderate elevations of insulin and glucose levels. Further increases in the insulin level did not alter this percentage. This is in marked contrast with the response seen following TPN in the normal dog, where the liver removed 45% of the exogenous glucose in the absence of hyperglycemia (15). Interestingly, when glucose levels in

42-hour fasted dogs were increased in a stepwise manner in the presence of fixed elevated insulin levels (~33 $\mu$U/ml), the glucose disposed by the liver increased progressively from 14% to 29% (124). Thus, acute hyperglycemia tends to shift glucose carbon to the liver and away from the periphery. In fact, our data indicate that acute increases in arterial glucose levels in the TPN-adapted state have a much greater impact on liver glucose uptake than do proportional increases in insulin (17, 41).

Predicting the impact of correcting infection-induced hyperglycemia on liver glucose uptake is difficult; infection impairs both insulin- and glucose-dependent liver glucose uptakes. Infection impairs the slope of the relationship between glucose levels and NHGU ($\downarrow$ ~45%). Despite this impairment, NHGU is still more responsive to increases in glucose concentration than to insulin concentrations (40), and increases in insulin above the already elevated insulin level did not improve liver glucose uptake. Thus, in the clinical setting, correction of hyperglycemia by exogenous infusion of insulin could decrease net liver glucose uptake in individuals who are already able to mount an insulin response, even if it is inadequate to maintain euglycemia. If the liver's contribution to whole-body glucose disposal decreases as insulin levels are increased and glucose levels are decreased, glucose utilization by peripheral tissues becomes the predominant mechanism for the lowering of glucose levels. Individuals with pre-existing insulin resistance are at greatest risk for the complications of hyperglycemia during nutritional support, especially when an infection is present (18, 31, 34). The combination of the infection-induced peripheral insulin resistance and the unresponsiveness of the liver to additional insulin contribute to the very high insulin requirements in these populations (118). Thus, these studies suggest that the acute correction of infection-induced hyperglycemia by administering exogenous insulin does not improve, and may even exacerbate, the infection-induced impairment in liver glucose uptake.

A body of evidence suggests that total enteral nutrition (TEN) may be more efficacious than TPN in reducing secondary infections and decreasing mortality (80). One proposed benefit of TEN is the preservation of the gut "barrier." TEN is reported to prevent translocation of bacteria into the portal and possibly the systemic circulation (35, 135). During TPN, gut atrophy occurs (4), which may allow translocation (62, 101). Support for the "translocation hypothesis" in animal models has been documented; however, there is no direct or convincing indirect evidence that it modifies or prevents bacterial translocation in humans (146). TEN may modify the gut inflammatory response, which in turn alters the general response to injury (36). TEN is beneficial to the gut; whether this is the sole mechanism by which it improves patient outcome is unclear.

One possible benefit of TEN, especially on hepatic function, is the direct delivery of the nutrients into the portal circulation. In fact, infusion of nutrients into the portal circulation was more effective in improving plasma protein levels in stressful situations than was the peripheral route (36, 128, 171). However, in nonstressed animals, portal nutrition was no more beneficial than was a peripheral

route (45, 77). The improvement in hepatic metabolism following portal nutrient delivery in stress situations indicates that factors in addition to improved gut function contribute to the improved outcome of enterally fed patients. The accretion of hepatic glycogen may help protect the liver from periods of hepatic microcirculatory ischemia commonly seen during infection (2). In addition, increased amino acid delivery to the liver may also be beneficial in meeting the increased protein synthetic needs of the liver. In normal animals, acute delivery of glucose via the portal vein amplifies hepatic glucose uptake and glycogen repletion (127). Thus, we expected that during TEN, liver glucose uptake would be higher than during TPN; however, that was not the case (15). In fact, when identical nutrient solutions were given to dogs as TEN and TPN, the liver removed a similar amount of glucose. However, insulin levels were higher with TEN than TPN, and peripheral glucose uptake was lower in TEN. Since the portal signal inhibits peripheral glucose uptake in addition to stimulating NHGU (52), it may explain the impaired peripheral glucose uptake and higher insulin requirements seen during TEN. The possible explanations as to why TEN did not enhance NHGU further include (*a*) portal delivery of nonglucose substrates (amino acids) inhibits the effect of the portal signal on NHGU (122), (*b*) the portal signal is ineffective at the liver in the chronic nutritionally supported state (52), and (*c*) endocrine alterations, such as elevated glucagon levels, during TEN limit the rise in NHGU. Amino acids delivered enterally directly enter the portal circulation and may inhibit liver glucose uptake. Portal, but not peripheral, delivery of gluconeogenic amino acids inhibits the effect of the portal signal (122). Another possibility is that the portal signal is ineffective in the background of the large adaptations seen during TPN. This is likely, given that an acute, but not chronic, increase in fructose is effective (42, 43), and fructose is thought to act on the same enzymes as the portal signal.



## SUMMARY

Infection and inflammation result in profound activation of the glucoregulatory system. In many other types of acute stressors, such as exercise and hypoglycemia, the tissue responses to hormones are generally amplified or at least sensitized, allowing rapid adjustments to be made during the stress. By contrast, in the setting of inflammation nearly all organs become hyporesponsive, shifting the body to a state of metabolic inflexibility. The root cause of this inflexibility is unclear but is likely dependent upon the inflammatory response rather than simply the neuroendocrine response. One consequence of this metabolic inflexibility is hyperglycemia, especially during nutritional support.

## ACKNOWLEDGMENTS

This work was supported by NIH Grant DK-43748 (P.I., Owen McGuinness), Clinical Nutrition Research Unit Grant P30-DK-26657, and the Vanderbilt Diabetes Training and Research Center Grant (DK-20593).

**The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org**

## LITERATURE CITED


1. Aguirre V, Werner ED, Giraud J, Lee YH, Shoelson SE, White MF. 2002. Phosphorylation of Ser307 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action. *J. Biol. Chem.* 277:1531–37
2. Asher EF, Garrison RN, Ratcliff EJ, Fry DE. 1983. Endotoxin, cellular function, and nutrient blood flow. *Arch. Surg.* 118:441–45
3. Bagby GJ, Lang CH, Skrepnik N, Spitzer JJ. 1992. Attenuation of glucose metabolic changes resulting from TNF-alpha administration by adrenergic blockade. *Am. J. Physiol.* 262:R628–35
4. Barber AE, Jones WG 2nd, Minei JP, Fahey TJ 3rd, Lowry SF, Shires GT. 1991. Bacterial overgrowth and intestinal atrophy in the etiology of gut barrier failure in the rat. *Am. J. Surg.* 161:300–4
5. Barzilai N, Rossetti L. 1993. Role of glucokinase and glucose-6-phosphatase in the acute and chronic regulation of hepatic glucose fluxes by insulin. *J. Biol. Chem.* 268:25019–25
6. Bellomo R. 2002. Bench-to-bedside review: lactate and the kidney. *Crit. Care* 6: 322–26
7. Bessey PQ, Aoki TT, Wilmore DW. 1985. Fuel utilization following injury: relationship to hormonal environment. *J. Surg. Res.* 38:484–93
8. Bessey PQ, Lowe KA. 1993. Early hormonal changes affect the catabolic response to trauma. *Ann. Surg.* 218:476–89
9. Biggers DW, Myers SR, Neal D, Stinson R, Cooper NB, et al. 1989. Role of brain in counterregulation of insulin-induced hypoglycemia in dogs. *Diabetes* 38:7–16
10. Buday AZ, Lang CH, Bagby GJ, Spitzer JJ. 1986. Glycogen synthase and phosphorylase activities during glycogen repletion in endotoxemic rats. *Circ. Shock* 19:149–63
11. Carlson GL. 2004. Hunterian Lecture. Insulin resistance in human sepsis: implications for the nutritional and metabolic care of the critically ill surgical patient. *Ann. R. Coll. Surg. Engl.* 86:75–81
12. Caruana JA, Camara DS, Schneeberger GJ, Nolan JP. 1984. The clearance capacity of the canine liver for a portal vein endotoxin infusion. *J. Surg. Res.* 37:197–201
13. Cely CM, Arora P, Quartin AA, Kett DH, Schein RM. 2004. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest* 126:879–87
14. Ceppi ED, Knowles RG, Carpenter KM, Titheradge MA. 1992. Effect of treatment in vivo of rats with bacterial endotoxin on fructose 2,6-biphosphate metabolism and L-pyruvate kinase activity and flux in isolated liver cells. *Biochem. J.* 284:761–66
15. Chen SS, Donmoyer C, Zhang Y, Hande SA, Lacy DB, McGuinness OP. 2000. Impact of enteral and parenteral nutrition on hepatic and muscle glucose metabolism. *J. Parenter. Enteral Nutr.* 24:255–60
16. Chen SS, Donmoyer CM, Ejiofor J, McCay J, Archuletta R, et al. 2002. Impact of intraportal N(omega)-nitro-L-arginine infusion on hepatic glucose metabolism in total parenteral nutrition-adapted dogs: interaction with infection. *Metabolism* 51: 274–83
17. Chen SS, Donmoyer CM, Pearson DA, Poole A, Zhang Y, et al. 2004. Impact of infection on glucose-dependent liver glucose uptake during TPN: interaction with insulin. *Am. J. Physiol.* 286:E286–95
18. Chen Y-D, Swislocki ALM, Hellenbeck CB, Wu M-S, Reaven GM. 1988. Relationship between plasma glucose and insulin concentration, glucose production and glucose disposal in normal subjects

and patients with non-insulin-dependent diabetes. *J. Clin. Invest.* 67:1084–89
19. Cherrington AD, Diamond MP, Green DR, Williams PE. 1982. Evidence for an intrahepatic contribution to the waning effect of glucagon on glucose production in the conscious dog. *Diabetes* 31:917–22
20. Cherrington AD, Wasserman DH, McGuinness OP. 1994. Renal contribution to glucose production after a brief fast: fact or fancy? *J. Clin. Invest.* 93:2303
21. Cherrington AD, Williams PE, Shulman GI, Lacy WW. 1981. Differential time course of glucagon's effect on glycogenolysis and gluconeogenesis in the conscious dog. *Diabetes* 30:180–87
22. Chhibber VL, Soriano C, Tayek JA. 2000. Effects of low-dose and high-dose glucagon on glucose production and gluconeogenesis in humans. *Metabolism* 49:39–46
23. Chrusch C, Bands C, Bose D, Li X, Jacobs H, et al. 2000. Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis. *Am. J. Respir. Crit. Care Med.* 161:517–26
24. Chu CA, Galassetti P, Igawa K, Sindelar DK, Neal DW, et al. 2003. Interaction of free fatty acids and epinephrine in regulating hepatic glucose production in conscious dogs. *Am. J. Physiol.* 284:E291–301
25. Chu CA, Sindelar DK, Neal DW, Allen EJ, Donahue EP, Cherrington AD. 1997. Comparison of the direct and indirect effects of epinephrine on hepatic glucose production. *J. Clin. Invest.* 99:1044–56
26. Chu CA, Sindelar DK, Neal DW, Cherrington AD. 1996. Direct effects of catecholamines on hepatic glucose production in conscious dog are due to glycogenolysis. *Am. J. Physiol.* 271:E127–37
27. Chu CA, Sindelar DK, Neal DW, Cherrington AD. 1997. Portal adrenergic blockade does not inhibit the gluconeogenic effects of circulating catecholamines on the liver. *Metabolism* 46:458–65
28. Connolly CC, Stevenson RW, Neal DW, Wasserman DH, Cherrington AD. 1993. The effects of lactate loading on alanine and glucose metabolism in the conscious dog. *Metabolism* 42:154–61
29. Cornell RP, Filkins JP. 1974. Characterization of gluconeogenesis in enzymatically isolated parenchymal cells of rat liver. *Proc. Soc. Exp. Biol. Med.* 145:203–9
30. Dahn MS, Lange P. 1982. Hormonal changes and their influence on metabolism and nutrition in the critically ill. *Intensive Care Med.* 8:209–13
31. Davis SN, McGuinness OP, Cherrington AD. 1990. Insulin action in vivo. In *Diabetes Annual IV*, ed. KGMM Alberti, LP Krall, pp. 585–602. Amsterdam: Elsevier Sci.
32. De Backer D, Creteur J, Silva E, Vincent JL. 2001. The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. *Crit. Care Med.* 29:256–61
33. Defalque D, Brandt N, Ketelslegers JM, Thissen JP. 1999. GH insensitivity induced by endotoxin injection is associated with decreased liver GH receptors. *Am. J. Physiol.* 276:E565–72
34. Defronzo RA, Ferrannini E, Simonson DC. 1989. Fasting hyperglycemia in non-insulin dependent diabetes mellitus: contribution of excessive hepatic glucose production and impaired tissue glucose uptake. *Metabolism* 38:387–91
35. Deitch EA. 1992. Multiple organ failure pathophysiology and potential future therapy. *Ann. Surg.* 216:117–34
36. Deitch EA, Xu D, Franko L, Ayala A, Chaudry IH. 1995. Evidence favoring the role of the gut as a cytokine-generating organ in rats subjected to hemorrhagic shock. *Shock* 1:141–46
37. DeWulf H, Hers HG. 1968. The interconversion of liver glycogen synthase a and b in vitro. *Eur. J. Biochem.* 6:552–57

38. Diamond MP, Rollings RC, Steiner KE, Williams PE, Lacy WW, Cherrington AD. 1988. Effect of alanine concentration independent of changes in insulin and glucagon on alanine and glucose homeostasis in the conscious dog. *Metabolism* 37:28–33
39. Diamond MP, Suhrer JH Jr, Williams PE, Lacy WW, Cherrington AD. 1982. Contribution of the liver and extrasplanchnic tissues to the hypoglycemic action of dichloroacetate in the conscious dog. *Diabetes* 31:(Pt 1):326–32
40. Donmoyer CM, Chen S-S, Hande SA, Lacy DB, Ejiofor J, McGuinness OP. 2000. Hyperinsulinemia compensates for infection-induced impairment in net hepatic glucose uptake during TPN. *Am. J. Physiol.* 279:E235–43
41. Donmoyer CM, Chen S-S, Lacy DB, Pearson DA, Poole A, et al. 2003. Infection impairs insulin-dependent hepatic glucose uptake during total parenteral nutrition. *Am. J. Physiol.* 284:E574–82
42. Donmoyer CM, Ejiofor J, Lacy DB, Chen S-S, McGuinness OP. 2001. Fructose augments infection-impaired net hepatic glucose uptake during TPN administration. *Am. J. Physiol.* 280:E703–11
43. Donmoyer CM, Lacy DB, Zhang Y, Chen S-S, McGuinness OP. 2002. Impact of chronic fructose infusion on hepatic metabolism during TPN administration. *Am. J. Physiol.* 283:E1151–58
44. Engelman JA, Berg AH, Lewis RY, Lisanti MP, Scherer PE. 2000. Tumor necrosis factor alpha-mediated insulin resistance, but not dedifferentiation, is abrogated by MEK1/2 inhibitors in 3T3-L1 adipocytes. *Mol. Endocrinol.* 14:1557–69
45. Fairman RM, Crosby LO, Stein TP, Buzby GP, Mullen JL. 1983. Prehepatic total parenteral nutrition in the chair-adapted primate. *J. Parenter. Enteral Nutr.* 7:237–43
46. Feuerstein G, Hallenbeck JM, Vanatta B, Rabinovici R, Perera PY, Vogel SN. 1990. Effects of gram-negative endotoxin on levels of serum corticosterone, TNF$\alpha$, circulating blood cells, and the survival of rats. *Circ. Shock* 30:265–78
47. Filkins JP, Cornell RP. 1974. Depression of hepatic gluconeogenesis and the hypoglycemia of endotoxin shock. *Am. J. Physiol.* 227:778–81
48. Finney SJ, Zekveld C, Elia A, Evans TW. 2003. Glucose control and mortality in critically ill patients. *JAMA* 290:2041–47
49. Fong YM, Marano MA, Moldawer LL, Wei H, Calvano SE, et al. 1990. The acute splanchnic and peripheral tissue metabolic response to endotoxin in humans. *J. Clin. Invest.* 85:1896–904
50. Frost RA, Nystrom GJ, Lang CH. 2002. Lipopolysaccharide regulates proinflammatory cytokine expression in mouse myoblasts and skeletal muscle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283: R698–709
51. Fujiwara T, Cherrington AD, Neal DW, McGuinness OP. 1996. Role of cortisol in the metabolic response to stress hormone infusion in the conscious dog. *Metabolism* 45:571–78
52. Galassetti P, Shiota M, Zinker BA, Wasserman DH, Cherrington AD. 1998. A negative arterial-portal venous glucose gradient decreases skeletal muscle glucose uptake. *Am. J. Physiol.* 275:E101–11
53. Gannon MC, Nuttall FQ. 1997. Effect of feeding, fasting, and diabetes on liver glycogen synthase activity, protein, and mRNA in rats. *Diabetologia* 40:758–63
54. Gelfand RA, Matthews DE, Bier DM, Sherwin RS. 1984. Role of counterregulatory hormones in the catabolic response to stress. *J. Clin. Invest.* 74:2238–48
55. Gibson FA, Hinds CJ. 1997. Growth hormone and insulin-like growth factors in critical illness. *Int. Care Med.* 23:369–78
56. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. 1999. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 22:1408–14

57. Goldstein R, Palmer B, Liu R, Massillon D. 1995. The effects of chronic hypercortisolemia on gluconeogenesis assessed using two independent methods in vivo. *Diabetes* 44(Suppl. 1):201
58. Goldstein RE, Wasserman DH, McGuinness OP, Lacy DB, Cherrington AD, Abumrad NN. 1993. Effects of chronic elevation in plasma cortisol on hepatic carbohydrate metabolism. *Am. J. Physiol.* 264:E119–27
59. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. 1996. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann. Surg.* 224:97–102
60. Gustavson SM, Chu CA, Nishizawa M, Farmer B, Neal D, et al. 2003. Interaction of glucagon and epinephrine in the control of hepatic glucose production in the conscious dog. *Am. J. Physiol. Endocrinol. Metab.* 284:E695–707
61. Gustavson SM, Chu CA, Nishizawa M, Farmer B, Neal D, et al. 2003. Glucagon's actions are modified by the combination of epinephrine and gluconeogenic precursor infusion. *Am. J. Physiol. Endocrinol. Metab.* 285:E534–44
62. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. 1995. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am. J. Respir. Crit. Care Med.* 152:1545–48
63. Hargrove DM, Bagby GJ, Lang CH, Spitzer JJ. 1988. Adrenergic blockade does not abolish elevated glucose turnover during bacterial infection. *Am. J. Physiol.* 254:E16–22
64. Hargrove DM, Bagby GJ, Lang CH, Spitzer JJ. 1988. Adrenergic blockade prevents endotoxin-induced increases in glucose metabolism. *Am. J. Physiol.* 255: E629–35
65. Hellerstein MK. 1999. De novo lipogenesis in humans: metabolic and regulatory aspects. *Eur. J. Clin. Nutr.* 53(Suppl. 1):53–65
66. Holste LC, Connolly CC, Moore MC, Neal DW, Cherrington AD. 1997. Physiological changes in circulating glucagon alter hepatic glucose disposition during portal glucose delivery. *Am. J. Physiol.* 273:E488–96
67. Horton RA, Knowles RG, Titheradge MA. 1994. Endotoxin causes reciprocal changes in hepatic nitric oxide synthesis, gluconeogenesis, and flux through phosphoenolpyruvate carboxykinase. *Biochem. Biophys. Acta* 204:659–65
68. Hotamisligil GS. 2003. Inflammatory pathways and insulin action. *Int. J. Obes. Relat. Metab. Disord.* 27(Suppl. 3):53–55
69. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. 1994. Tumor necrosis factor-$\alpha$ inhibits signaling from the insulin receptor. *Proc. Natl. Acad. Sci. USA* 91:4854–58
70. Ishida T, Lewis RM, Hartley CJ, Entman ML, Field JB. 1978. Comparison of hepatic extraction of insulin and glucagon in conscious dogs. *Endocrinology* 112:1098–109
71. Jacobs DO, Maris J, Fried R, Settle RG, Rolandelli RR, et al. 1988. In vivo phosphorus 31 magnetic resonance spectroscopy of rat hind limb skeletal muscle during sepsis. *Arch. Surg.* 123:1425–28
72. Jahoor F, Herdon DN, Wolfe RR. 1986. Role of insulin and glucagon in the response of glucose and alanine kinetics in burn-injured patients. *J. Clin. Invest.* 78:807–14
73. Jahoor F, Peters EJ, Wolfe RR. 1990. The relationship between gluconeogenic substrate supply and glucose production in humans. *Am. J. Physiol.* 258:E288–96
74. Johnson TS, O'Leary M, Justice SK, Maamra M, Zarkesh-Esfahani SH, et al. 2001. Differential expression of suppressors of cytokine signalling genes in response to nutrition and growth hormone in the septic rat. *J. Endocrinol.* 169:409–15
75. Kilberg MS, Stevens BR, Novak DA. 1993. Recent advances in mammalian

amino acid transport. *Annu. Rev. Nutr.* 13: 137–65
76. Kim HJ, Higashimori T, Park SY, Choi H, Dong J, et al. 2004. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. *Diabetes* 53:1060–67
77. King WWK, Boelhouwer RU, Kingsworth AN, Ross JS, Young VR, Malt RA. 1983. Nutritional efficacy and hepatic changes during intragastric, intravenous and prehepatic feeding in rats. *J. Parenter. Enteral Nutr.* 7:443–46
78. Klover PJ, Zimmers TA, Koniaris LG, Mooney RA. 2003. Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. *Diabetes* 52:2784–89
79. Krogh-Madsen R, Moller K, Dela F, Kronborg G, Jauffred S, Pedersen BK. 2004. Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF-alpha, and FFAs to low-dose endotoxemia in humans. *Am. J. Physiol. Endocrinol. Metab.* 286:E766–72
80. Kudsk KA, Whitnal M, Abrams JS, Mougey EH. 1993. Enteral and tumor necrosis factor in normal rats. *J. Trauma* 132:946–52
81. Landau BR. 1999. Quantifying the contribution of gluconeogenesis to glucose production in fasted human subjects using stable isotopes. *Proc. Nutr. Soc.* 58:963–72
82. Lang CH. 1992. Sepsis-induced insulin resistance in rats is mediated by a beta-adrenergic mechanism. *Am. J. Physiol.* 263:E703–11
83. Lang CH. 1993. Beta-adrenergic blockade attenuates insulin resistance induced by tumor necrosis factor. *Am. J. Physiol.* 264:R984–91
84. Lang CH. 2001. Sepsis-induced changes in pancreatic hormone secretion. In *Handbook of Physiology: The Endocrine Pancreas and Regulation of Metabolism*, ed. LS Jefferson, AD Cherrington, pp. 999–1014. New York: Oxford Univ. Press
85. Lang CH, Bagby GJ, Blakesley HL, Spitzer JJ. 1987. Fever is not responsible for the elevated glucose kinetics in sepsis. *Proc. Soc. Exp. Biol. Med.* 185:455–61
86. Lang CH, Bagby GJ, Blakesley HL, Spitzer JJ. 1987. Glucose kinetics and pyruvate dehydrogenase activity in septic rats treated with dichloroacetate. *Circ. Shock* 23:131–41
87. Lang CH, Bagby GJ, Blakesley HL, Spitzer JJ. 1987. Inhibition of eicosanoid production by BW755C does not attenuate sepsis-induced alterations in glucose kinetics. *Circ. Shock* 22:105–13
88. Lang CH, Bagby GJ, Blakesley HL, Spitzer JJ. 1989. Importance of hyperglucagonemia in eliciting the sepsis-induced increase in glucose production. *Circ. Shock* 29:181–91
89. Lang CH, Bagby GJ, Buday AZ, Spitzer JJ. 1987. The contribution of gluconeogenesis to glycogen repletion during glucose infusion in endotoxemia. *Metabolism* 36:180–87
90. Lang CH, Bagby GJ, Spitzer JJ. 1984. Carbohydrate dynamics in the hypermetabolic septic rat. *Metabolism* 33:959–63
91. Lang CH, Bagby GJ, Spitzer JJ. 1985. Glucose kinetics and body temperature after lethal and nonlethal doses of endotoxin. *Am. J. Physiol.* 248:R471–78
92. Lang CH, Blakesley HL, Bagby GJ, Spitzer JJ. 1988. Lipoxygenase and cyclooxygenase blockade by BW755C prevents endotoxin-induced hypotension but not changes in glucose metabolism. *Horm. Metab. Res.* 20:551–54
93. Lang CH, Dobrescu C. 1989. In vivo insulin resistance during nonlethal hypermetabolic sepsis. *Circ. Shock* 28:165–78
94. Lang CH, Dobrescu C. 1989. Interleukin-1 induced increases in glucose utilization are insulin mediated. *Life Sci.* 45:2127–34
95. Lang CH, Dobrescu C. 1989. Sepsis-induced changes in in vivo insulin action in diabetic rats. *Am. J. Physiol.* 257(Pt. 1): E301–8

96. Lang CH, Dobrescu C. 1991. Gram-negative infection increases noninsulin-mediated glucose disposal. *Endocrinology* 128:645–53
97. Lang CH, Dobrescu C, Bagby GJ. 1992. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology* 130:43–52
98. Lang CH, Dobrescu C, Meszaros K. 1990. Insulin-mediated glucose uptake by individual tissues during sepsis. *Metabolism* 39:1096–107
99. Lang CH, Obih JA, Bagby GJ, Bagwell JN, Spitzer JJ. 1991. Endotoxin-induced increases in regional glucose utilization by small intestine: a TNF-independent effect. *Am. J. Physiol.* 260(Pt. 1):G548–55
100. Lecavalier L, Bolli G, Gerich J. 1990. Glucagon-cortisol interactions on glucose turnover and lactate gluconeogenesis in normal humans. *Am. J. Physiol.* 258:E569–75
101. Lipman TO. 1998. Grains or veins: Is enteral nutrition really better than parenteral nutrition? A look at the evidence. *J. Parenter. Enteral Nutr.* 22:167–82
102. Long CL, Kinney JM, Geiger JW. 1976. Nonsuppressability of gluconeogenesis by glucose in septic patients. *Metabolism* 25:193–201
103. Long CL, Spencer JL, Kinney JM, Geiger JW. 1971. Carbohydrate metabolism in man: effect of elective operations and major injury. *J. Appl. Physiol.* 31:110–16
104. Magnusson I, Rothman DL, Gerard DP, Katz LD, Shulman GI. 1995. Contribution of hepatic glycogenolysis to glucose production in humans in response to a physiological increase in plasma glucagon concentration. *Diabetes* 44:185–89
105. McCallum RE, Seale TW, Stith RD. 1983. Influence of endotoxin treatment on dexamethasone induction of hepatic phosphoenolpyruvate carboxykinase. *Infect. Immun.* 39:213–19
106. McGuinness OP. 1994. The impact of infection on gluconeogenesis in the conscious dog. *Shock* 2:336–43
107. McGuinness OP, Burgin K, Moran C, Bracy D, Cherrington AD. 1994. Role of glucagon in the metabolic response to stress hormone infusion in the conscious dog. *Am. J. Physiol.* 266:E438–47
108. McGuinness OP, Donmoyer CM, Ejiofor J, McElligott S, Lacy DB. 1998. Hepatic and muscle glucose metabolism during total parenteral nutrition: impact of infection. *Am. J. Physiol.* 275:E763–69
109. McGuinness OP, Ejiofor J, Audoly LP, Schrom N. 1998. Regulation of glucose production by NEFA and gluconeogenic precursors during chronic glucagon infusion. *Am. J. Physiol.* 275:E432–39
110. McGuinness OP, Ejiofor J, Lacy DB, Schrom N. 2000. Hepatic glucose metabolism during intraduodenal glucose infusion: impact of infection. *Am. J. Physiol.* 279:E108–15
111. McGuinness OP, Fujiwara T, Murrell S, Bracy D, Neal D, et al. 1993. Impact of chronic stress hormone infusion on hepatic carbohydrate metabolism in the conscious dog. *Am. J. Physiol.* 265:E314–22
112. McGuinness OP, Jacobs J, Moran C, Lacy DB. 1995. Impact of infection on hepatic disposal of a peripheral glucose infusion in the conscious dog. *Am. J. Physiol.* 269:E199–207
113. McGuinness OP, Lacy DB, Anderson J. 1995. Effect of acute glucagon removal on metabolic response to infection in conscious dog. *Am. J. Physiol.* 268:E92–99
114. McGuinness OP, Lacy DB, Eliasson KE. 1996. Hyperglucagonemia and hepatic glucose metabolism during infection in the conscious dog. *Am. J. Physiol.* 270: E580–86
115. McGuinness OP, Murrell S, Moran C, Bracy D, Cherrington AD. 1994. The effect of acute glucagon removal on the metabolic response to stress hormone infusion in the conscious dog. *Metabolism* 43:1310–17
116. McGuinness OP, Shau V, Benson EM,

Lewis M, Snowden RT, et al. 1997. Role of epinephrine and norepinephrine in the metabolic response to stress hormone infusion in the conscious dog. *Am. J. Physiol.* 273:E674–81

117. McGuinness OP, Snowden RT, Moran C, Neal DW, Fujiwara T, Cherrington AD. 1999. Impact of acute epinephrine removal on hepatic glucose metabolism during stress hormone infusion. *Metabolism* 48:910–14
118. McMahon MM, Rizza RA. 1996. Nutrition support in hospitalized patients with diabetes mellitus. *Mayo Clin. Proc.* 71:587–94
119. Meinz HM, Lacy DB, Ejiofor J, McGuinness OP. 1998. Alterations in hepatic gluconeogenic amino acid uptake and gluconeogenesis in the endotoxin-treated conscious dog. *Shock* 9:296–303
120. Meszaros K, Lang CH, Bagby GJ, Spitzer JJ. 1987. Contribution of different organs to increased glucose consumption after endotoxin administration. *J. Biol. Chem.* 262:10965–70
121. Meszaros K, Lang CH, Bojta J, Spitzer JJ. 1989. Early changes in glucose utilization of individual tissues after endotoxin administration. *Circ. Shock* 29:107–14
122. Moore MC, Hsieh PS, Flakoll PJ, Neal DW, Cherrington AD. 1999. Differential effect of amino acid infusion route on net hepatic glucose uptake in the dog. *Am. J. Physiol.* 276:E295–302
123. Morikawa S, Inubushi T, Takahashi K, Ishii H, Ozawa K. 1998. Gluconeogenesis and phosphoenergetics in rat liver during endotoxemia. *J. Surg. Res.* 74:179–86
124. Myers SR, Biggers DW, Neal DW, Cherrington AD. 1991. Intraportal glucose delivery enhances the effects of hepatic glucose load on net hepatic glucose uptake in vivo. *J. Clin. Invest.* 88:158–67
125. Myers SR, McGuinness OP, Neal DW, Cherrington AD. 1991. Intraportal glucose delivery alters the relationship between net hepatic glucose uptake and the insulin concentration. *J. Clin. Invest.* 87:930–39
126. Neimeyer H, Ureta T, Clark-Turri L. 1975. Adaptive character of liver glucokinase. *Mol. Cell Biochem.* 6:109–26
127. Pagliassotti MJ, Cherrington AD. 1992. Regulation of net hepatic glucose uptake in vivo. *Annu. Rev. Physiol.* 54:847–60
128. Piccone VA, LeVeen HH, Glass P, Berlyne G, Lundin AP. 1980. Prehepatic hyperalimentation. *Surgery* 87:263–70
129. Pilkis SJ. 1970. Hormonal control of hexokinase activity in animal tissues. *Biochim. Biophys. Acta* 215:461–76
130. Pilkis SJ, el-Maghrabi MR, Claus TH. 1988. Hormonal regulation of hepatic gluconeogenesis and glycolysis. *Annu. Rev. Biochem.* 57:755–83
131. Pilkis SJ, Granner DK. 1992. Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. *Annu. Rev. Physiol.* 54:885–909
132. Pittner RA, Spitzer JA. 1993. Shift from alpha- to beta-type adrenergic receptor-mediated responses in chronically endotoxemic rats. *Am. J. Physiol.* 264:E650–54
133. Reithmann C, Hallstrom S, Pilz G, Kapsner T, Schlag G, Werdan K. 1993. Desensitization of rat cardiomyocyte adenylyl cyclase stimulation by plasma of noradrenaline-treated patients with septic shock. *Circ. Shock* 41:48–59
134. Saeed M, Carlson GL, Little RA, Irving MH. 1999. Selective impairment of glucose storage in human sepsis. *Br. J. Surg.* 86:813–21
135. Saito H, Trocki O, Alexander JW, Kopcha R, Heyd T, Joffe SN. 1987. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. *J. Parenter. Enteral Nutr.* 11:1–7
136. Santos AA, Scheltinga MR, Lynch E, Brown EF, Lawton P, et al. 1993. Elaboration of interleukin 1-receptor antagonist is not attenuated by glucocorticoids after endotoxemia. *Arch. Surg.* 128:138–43

137. Seoane J, Barbera A, Telemaque-Potts S, Newgard CB, Guinovart JJ. 1999. Glucokinase overexpression restores glucose utilization and storage in cultured hepatocytes from male Zucker diabetic fatty rats. *J. Biol. Chem.* 274:31833–38
138. Severin PN, Uhing MR, Beno DW, Kimura RE. 2002. Endotoxin-induced hyperlactatemia results from decreased lactate clearance in hemodynamically stable rats. *Crit. Care Med.* 30:2509–14
139. Shamoon H, Hendler R, Sherwin RS. 1981. Synergistic interactions among antiinsulin hormones in the pathogenesis of stress hyperglycemia in humans. *J. Clin. Endocrinol. Metab.* 52:1235–41
140. Shangraw RE, Jahoor F, Wolfe RR, Lang CH. 1996. Hunterian lecture: insulin resistance in human sepsis-induced insulin resistance. *Crit. Care Med.* 24:75–81
141. Shangraw RE, Jahoor F, Wolfe RR, Lang CH. 1996. Pyruvate dehydrogenase inactivity is not responsible for sepsis-induced insulin resistance. *Crit. Care Med.* 24:566–74
142. Shaw JH, Wolfe RR. 1985. Response to glucose and lipid infusions in sepsis: a kinetic analysis. *Metabolism* 34:442–49
143. Shaw JHF, Klein S, Wolfe RR. 1985. Assessment of alanine, urea and glucose interrelationships in normal subjects and in patients with sepsis with stable isotopes. *Surgery* 97:557–67
144. Sidossis LS, Mittendorfer B, Chinkes D, Walser E, Wolfe RR. 1999. Effect of hyperglycemia-hyperinsulinemia on whole body and regional fatty acid metabolism. *Am. J. Physiol.* 276:E427–34
145. Sidossis LS, Mittendorfer B, Walser E, Chinkes D, Wolfe RR. 1998. Hyperglycemia-induced inhibition of splanchnic fatty acid oxidation increases hepatic triacylglycerol secretion. *Am. J. Physiol.* 275:E798–805
146. Sigurdsson GH. 1995. Is translocation of bacteria and endotoxin from the gastrointestinal tract a source of sepsis in critically ill patients? *Acta Anaes. Scand.* 39:11–19
147. Sindelar DK, Chu CA, Rohlie M, Neal DW, Swift LL, Cherrington AD. 1997. The role of fatty acids in mediating the effects of peripheral insulin on hepatic glucose production in the conscious dog. *Diabetes* 46:187–96
148. Soop M, Duxbury H, Agwunobi AO, Gibson JM, Hopkins SJ, et al. 2002. Euglycemic hyperinsulinemia augments the cytokine and endocrine responses to endotoxin in humans. *Am. J. Physiol.* 282: E1276–85
149. Spitzer JA, Nelson KM, Fish RE. 1985. Time course of changes in gluconeogenesis from various precursors in chronically endotoxemic rats. *Metabolism* 34:842–49
150. Spitzer JJ, Bagby GJ, Hargrove DM, Lang CH, Meszaros K. 1989. Alterations in the metabolic control of carbohydrates in sepsis. *Prog. Clin. Biol. Res.* 308:545–61
151. Spolarics Z, Bagby GJ, Lang CH, Spitzer JJ. 1991. Up-regulation of glucose metabolism in Kupffer cells following infusion of tumour necrosis factor. *Biochem. J.* 278:515–19
152. Stagnaro-Green A, Barton MK, Linekin PL, Corkery E, deBeer K, Roman SH. 1995. Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia. *Mt. Sinai J. Med.* 62:422–26
153. Stevenson RW, Steiner KE, Connolly CC, Fuchs H, Alberti KG, et al. 1991. Dose-related effects of epinephrine on glucose production in conscious dogs. *Am. J. Physiol.* 260:E363–70
154. Stevenson RW, Steiner KE, Davis MA, Hendrick GK, Williams PE, et al. 1987. Similar dose responsiveness of hepatic glycogenolysis and gluconeogenesis to glucagon in vivo. *Diabetes* 36:382–89
155. Tappy L, Cayeux M, Schneiter P, Schindler C, Temler E, et al. 1995. Effect of lactate on glucose metabolism in healthy subjects and severely injured hyperglycemic patients. *Am. J. Physiol.* 268:E630–35

156. Thompson WA, Coyle S, Van Zee K, Oldenburg H, Trousdale R, et al. 1994. The metabolic effects of platelet-activating factor antagonism in endotoxemic man. *Arch. Surg.* 129:72–79
157. Ueki K, Kondo T, Kahn CR. 2004. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. *Mol. Cell Biol.* 24:5434–46
158. Ueki K, Kondo T, Tseng YH, Kahn CR. 2004. Central role of suppressors of cytokine signaling proteins in hepatic steatosis, insulin resistance, and the metabolic syndrome in the mouse. *Proc. Natl. Acad. Sci. USA* 101:10422–27
159. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. 2002. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J. Clin. Endocrinol. Metab.* 87:978–82
160. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, et al. 2001. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med.* 345:1359–67
161. Vranic M, Engerman R, Doi K, Morita S, Yip CC. 1976. Extrapancreatic glucagon in the dog. *Metabolism* 25:1469–73
162. Wang K, Deutschman CS, Clemens MG, De Maio A. 1995. Reciprocal expression of phosphoenolpyruvate carboxykinase and acute phase genes during acute inflammation. *Shock* 3:204–9
163. White RH, Frayn KN, Little RA, Threlfall CJ, Stoner HB, Irving MH. 1987. Hormonal and metabolic responses to glucose infusion in sepsis studies by the hyperglycemia glucose clamp technique. *J. Parenter. Enteral Nutr.* 11:345–53
164. Wolfe RR. 1999. Sepsis as a modulator of adaptation to low and high carbohydrate and low and high fat intakes. *Eur. J. Clin. Nutr.* 53:S136–42
165. Wolfe RR, Elahi D, Spitzer JJ. 1977. Glucose and lactate kinetics after endotoxin administration in dogs. *Am. J. Physiol.* 232:E180–85
166. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. 1987. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N. Engl. J. Med.* 317:403–8
167. Wolfe RR, Jahoor F, Shaw JH. 1987. Effect of alanine infusion on glucose and urea production in man. *J. Parenter. Enteral Nutr.* 11:109–11
168. Wolfe RR, Shaw JH. 1985. Glucose and FFA kinetics in sepsis: role of glucagon and sympathetic nervous system activity. *Am. J. Physiol.* 248:E236–43
169. Wolfe RR, Shaw JH, Durkot MJ. 1983. Energy metabolism in trauma and sepsis: the role of fat. *Prog. Clin. Biol. Res.* 111:89–109
170. Yki-Jarvinen H. 1993. Action of insulin on glucose metabolism in vivo. *Baillieres Clin. Endocrinol. Metab.* 7:903–27
171. Ziegler TR, Gatzen C, Wilmore DW. 1994. Strategies for attenuating protein-catabolic responses in the critically ill. *Annu. Rev. Med.* 45:459–80

*Annual Review of Nutrition*
*Volume 25, 2005*

# CONTENTS