Sir David Cuthbertson Medal Lecture

Insulin resistance and glucose-induced thermogenesis in critical illness

Gordon L. Carlson

Department of Surgery, Hope Hospital, Salford M6 8HD, UK

Critical illness is associated with a marked increase in metabolic rate and progressive wasting, despite aggressive nutritional support. The metabolic events which are responsible for these phenomena are unclear, but are characterised by marked impairment of the anabolic effects of insulin on glucose metabolism and excessive activation of the sympathetic nervous system. It has been suggested that critical illness may be associated with impaired carbohydrate oxidation and a marked increase in the loss of heat energy associated with glucose administration (glucose-induced thermogenesis). This situation may result in impaired efficiency of nutrient assimilation. Studies employing combinations of nutrient infusions both at clinically-relevant rates and in association with euglycaemic hyperinsulinaemia have, however, demonstrated that nutrient-induced thermogenesis is unaffected in critical illness in human subjects, and that defective glucose utilization occurs as a consequence of impaired insulin-mediated glucose storage rather than oxidation. Although the cellular and molecular mechanisms underlying these changes are controversial, the recent validation of a human model of insulin resistance in critical illness should provide a means of studying this response in future, and allow the identification of therapeutic targets. This information should increase the efficacy of nutritional support in some of our most seriously-ill patients.

Critical illness: Insulin resistance: Glucose-induced thermogenesis: Nutritional support

Nutrient-induced thermogenesis

It has long been recognised that feeding induces changes in energy expenditure. Although the concept of 'specific dynamic action' has traditionally been ascribed to the work of Professor Max Rubner, the earliest studies demonstrating an increase in O_2 consumption following feeding were reported more than one century beforehand by Lavoisier (Lavoisier & LaPlace, 1784). Indeed, studies investigating the effects of varying combinations of nutrients on heat production had also been performed by other researchers (Smith, 1859; Magnus-Levy, 1894) before the publication of Rubner's (1902) classic monograph. Max Rubner's (1902) work is notable not because of the originality of the data, but rather because of his interpretation of the findings. Following a series of studies in which nutrient mixtures of varying amounts of carbohydrate, fat and protein were administered to dogs, Rubner (1902) concluded that the increased heat production which resulted from food consumption developed as a consequence of the metabolic utilisation of the nutrients and fulfilled a thermoregulatory role.

The concept of 'specific dynamic action' persisted for over 50 years, despite the later demonstration that the actions of food on energy production were, in the strict sense, neither specific nor dynamic. Energy production after feeding was studied by Benedict & Carpenter (1918) and Graham Lusk (1922), who showed that protein induced the largest increase in heat production (up to 30% of the energy administered was dissipated as heat), whereas the values for fat and carbohydrate appeared to be far smaller (6 and 4% respectively). Understanding of the precise mechanisms by which nutrient administration led to an increase in energy expenditure was, however, initially hampered by an inadequate knowledge of the metabolic processes involved in the assimilation of nutrients. It was, for example, initially

---

proposed that the sudden availability of a 'plethora' of food in some way triggered metabolic processes within the cell for which nutrients were a limiting factor, and that these processes generated the energy subsequently dissipated as heat (Lusk, 1912). Subsequent studies failed to demonstrate any relationship between the availability of nutrients and the resulting heat production (Carpenter & Fox, 1930), which led Lusk (1931) to conclude that the 'specific dynamic action' might result from the chemical energy liberated in the reactions of the intermediary metabolism of substrates (Lusk, 1931). Although our understanding of the precise metabolic processes involved has increased considerably over the last 70 years, Lusk's (1931) views have been largely proved to be correct.

Mechanisms underlying nutrient-induced thermogenesis

The major advances in biochemistry of the 1960s brought with them a much more detailed understanding of the relationship between energy metabolism and the underlying biochemical processes. In particular, the ability to identify the energy equivalent of ATP (83·6 kJ (20 kcal)/mol) and to calculate the number of mol ATP involved in the assimilation of nutrients allowed Krebs (1964) and Flatt (1977) to estimate, on theoretical grounds alone, the energy required for the absorption, transport and storage of various nutrients, and hence the amount of heat that would be generated following their administration. The term 'thermic effect of feeding' or 'nutrient-induced thermogenesis' (NIT) was used in this context. To allow direct comparison of the thermic effects of different nutrients, the amount of the increased energy expended after feeding was expressed as a percentage of the total energy administered (Table 1).

These estimates have proved to be remarkably accurate with respect to the measured thermic effects of protein and fat, but the thermic effect of carbohydrate has been reported to be considerably higher than that predicted on the bioenergetics of glucose storage alone (Ravussin & Bogardus, 1982; Thiebaud et al. 1983). The discrepancy between the predicted (obligatory) and measured costs of glucose storage increases with increasing insulin concentration, and the difference (referred to as facultative thermogenesis) has been variously attributed to activation of the sympathetic nervous system, due to carbohydrate (Acheson et al. 1983; DeFronzo et al. 1984), a direct effect of insulin itself (Christin et al. 1986), increased substrate cycling (Newsholme & Crabtree, 1976) or increased activity of the Na

pump (Ng & Hockaday, 1989). Studies in which nutrients have been given in combination or in isolation have revealed that the thermic effects of nutrient mixtures are equivalent to the mathematical sum of the thermic effects of their constituents (Carlson et al. 1994), suggesting that different nutrients increase energy production by separate mechanisms (Carlson, 1998). Although the sympathetic nervous system has been said to play an important role in NIT, especially in critical illness (see pp. 382–383), many of the studies supporting this role have relied on the demonstration that plasma noradrenaline concentrations are increased after oral glucose administration (Welle et al. 1981), intravenous administration of a large glucose bolus (Robertson & Porte, 1974) or combined infusion of glucose and insulin during a euglycaemic hyperinsulinaemic clamp (Acheson et al. 1984). There are two major difficulties, however, with the suggestion that hyperinsulinaemia induces activation of the sympathetic nervous system. It has been demonstrated that the process of glucose clamping itself (prolonged intravenous cannulation, regular blood sampling, enforced bed rest etc.) itself induces increased plasma concentrations of noradrenaline, even in the absence of glucose and insulin infusions (Moan et al. 1995). It is also by no means clear that plasma levels of noradrenaline reflect activity of the sympathetic nervous system, and they have specifically been shown not to reflect sympathetic nervous system activity in critical illness (Leinhardt et al. 1993). Nevertheless, β-adrenergic blockade has been shown to reduce the NIT associated with carbohydrate administration to the level of obligatory thermogenesis (DeFronzo et al. 1984).

Nutrient-induced thermogenesis in critical illness

Whatever the underlying mechanisms, a consideration of NIT is highly relevant to nutritional support in critical illness. Nutritional support is of major therapeutic importance in the modern management of the critically-ill patient, and to be effective it has to address the increased demands for energy associated with critical illness. Since critical-illness states are associated with major changes in fuel substrate utilisation (Carlson & Little, 1994) and activation of the sympathetic nervous system (Barton, 1987), one might predict that there would be associated major changes in NIT. Such changes would have major therapeutic implications for feeding in the setting of critical illness, as it might be predicted that increased NIT would lead to reduced

Table 1. Theoretical values for nutrient-induced thermogenesis of different foods (Flatt, 1977)

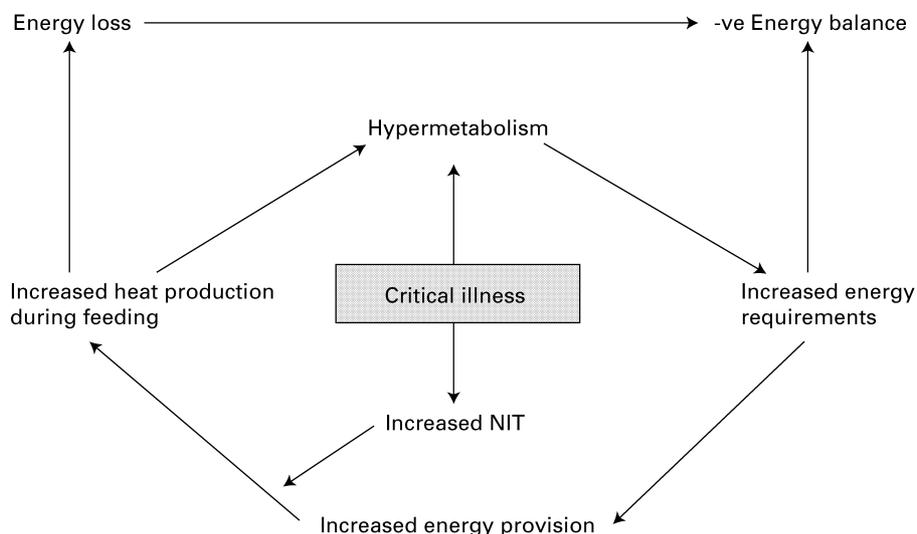| Nutrient	Metabolic fate	Thermic effect (%)
Glucose	Directly oxidized	2
Glucose	Stored as glycogen, then oxidized	7
Fat	Directly oxidized	2
Fat	Stored, then oxidized	4
Protein	Converted to amino acids, then oxidized	25
Protein	Stored as protein, then converted to amino acids and oxidized	25

Fig. 1. Vicious cycle of increased nutrient-induced thermogenesis (NIT) in critical illness. -ve, Negative.

efficiency of nutrient assimilation and, in turn, a need to give more food energy to maintain energy balance. Since this process would itself exacerbate energy loss via the increased NIT, one might hypothesise that the critically-ill patient lay at the centre of a vicious cycle in which attempts to provide additional energy led to increased energy requirements (see Fig. 1).

This situation was indeed what was found (Askanazi *et al.* 1980) when glucose-based total parenteral nutrition was infused for between 3 and 5 d in two groups of patients. In individuals with simple nutritional depletion intravenous feeding led to a modest (3 %) increment in O_2 consumption, but a large rise in RER as the glucose was converted to lipid and stored. In contrast, patients who were critically ill failed to convert the glucose to lipid, and instead demonstrated marked increases (29 %) in O_2 consumption. These changes were strongly suggestive of increased facultative glucose-induced thermogenesis, and the role of increased sympathetic nervous system activity in this abnormal response was suggested by an accompanying threefold increase in urinary noradrenaline excretion. Similar results were reported by other researchers in relation to glucose infusion and urinary catecholamine excretion in the critically ill (Elwyn *et al.* 1978, Nordenström *et al.* 1981), and seem to be specifically attributable to glucose, since replacing even half the glucose with lipid seems to significantly attenuate the effect (Nordenström *et al.* 1981). These relationships between glucose infusion, O_2 consumption and the activity of the sympathetic nervous system have since been united in an hypothesis to explain both the increased lipid utilisation and reduced glucose utilisation which characterise critical illness, since the increased activity of the sympathetic nervous system enhances lipolysis and the resulting increased free fatty acid availability impairs glucose utilization via the Randle cycle (Randle *et al.* 1963). Since glucose infusion stimulates sympathetic nervous system activity excessively in critical illness, glucose effectively may impair its own utilization via a cycle involving

exaggerated activity of the sympathetic nervous system, increased lipolysis and lipid oxidation, and impaired glucose utilization, leading to a state of insulin resistance (Saeed & Carlson, 1995).

Although corroborating evidence has been produced to suggest that increased NIT occurred in critically-ill patients with burns (Allard *et al.* 1988) and sepsis (Giovannini *et al.* 1988), the results of these and other studies seem to vary widely with the model of illness chosen and the nature, amount and duration of feeding employed. Arnold *et al.* (1989) administered a glucose-based total parenteral nutrition mixture in healthy and septic patients, and demonstrated that although significant increases in resting energy expenditure occurred in both groups, the increases were similar and no differences in NIT could be demonstrated. Similarly, the thermic effects of lipid (Arnold *et al.* 1991), amino acids (Arnold *et al.* 1992) and glucose alone (Carlson *et al.* 1997) have been shown to be broadly similar when subjects with sepsis and healthy subjects have been compared, even though enhanced lipid oxidation was noted in sepsis. Other studies from the same group have even indicated that sepsis is associated with a loss of glucose-induced thermogenesis (White *et al.* 1987). It is unclear why there appears to be a marked discrepancy between these various studies of the effects of critical illness on NIT, although many of the earlier studies administered nutrients at rates that would today be regarded as unphysiological and clinically irrelevant. Nevertheless, more recent studies, which have employed the euglycaemic hyperinsulinaemic clamp technique to administer glucose under conditions which should theoretically favour glucose storage and thus thermogenesis, have also failed to demonstrate disordered glucose-induced thermogenesis in patients with sepsis (Saeed *et al.* 1999). The findings of these recent studies thus suggest that irrespective of the state of the sympathetic nervous system in critical illness, insufficient evidence exists to implicate excessive NIT in the failure of nutritional support to ameliorate the catabolic consequences.
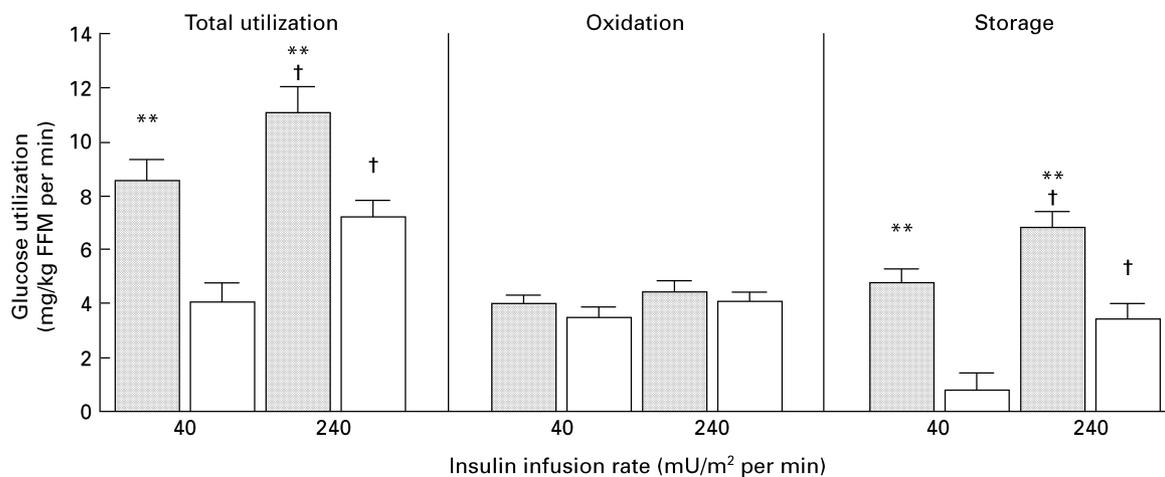
Fig. 2. Total glucose utilization (oxidation + non-oxidative utilization), oxidation and storage in patients with abdominal sepsis (▨; n 24) and healthy controls (▢; n 26) studied during conditions of euglycaemic hyperinsulinaemia at insulin infusion rates of 40 and 240 mU/m^2 per min. Values are means with their standard errors represented by vertical bars. FFM, fat-free mass. Mean values were significantly different from those of patients with abdominal sepsis: **$P < 0.01$. Mean values were significantly different from those at 40 mU/m^2 per min: †$P < 0.05$.

Glucose utilization and insulin resistance in critical illness

Although the effect of glucose on energy expenditure in critical illness thus remains controversial, it is clear that the metabolic changes which accompany trauma, severe infection and other acute inflammatory states do have a significant impact on glucose metabolism. Although isolated reports of hyperglycaemia in severe infection were published more than one century ago (Fischer, 1862), the concept of alterations in the responsiveness of tissues to insulin as a potential mechanism for the changes in glucose metabolism was first expressed in the 1950s (Evans & Butterfield, 1951; Howard, 1955). Studies have shown that as severity of sepsis increases there is a greater use of lipid as a fuel source under basal conditions, whereas carbohydrate oxidation tends to decline (Stoner et al. 1983). The changes in glucose utilization are, however, complex. Although many studies have suggested that basal glucose oxidation is preserved (Virkamaki et al. 1992; Green et al. 1995) or even increased (Wolfe et al. 1991) in critical illness, other studies have failed to confirm this suggestion (Saeed et al. 1999). Irrespective of changes in basal glucose utlization, it seems likely that impairment of insulin-mediated glucose utilization is of major importance to the observed metabolic effects (Carlson & Little, 1994). Intravenously-administered glucose is either oxidized immediately to provide energy, or stored as either glycogen or lipid. It has been clearly demonstrated that the vast majority of glucose infused under conditions of euglycaemic hyperinsulinaemia is taken up in skeletal muscle (Ferrannini et al. 1985) and, in addition, that the amount of glucose stored as lipid under these conditions is negligible (Bjorntorp & Sjostrom, 1978). This finding implies that defective storage of glucose as glycogen and/or glucose oxidation must contribute to the impairment in insulin-mediated glucose uptake associated with insulin resistance in critical illness. This factor is relevant to an understanding of the precise locus of the defect in insulin's action, since a

defect of glucose transport into the cell might be expected to result in impairment of both oxidation and storage, as glucose cannot be oxidised until it enters the cell.

Despite the finding of impaired basal glucose oxidation, studies conducted using the euglycaemic hyperinsulinaemic clamp and simultaneous indirect calorimetry in severe sepsis (Saeed et al. 1999) have indicated that glucose oxidation during glucose–insulin infusion is normal, but that glucose storage is markedly impaired (Fig. 2). These findings confirm the results of earlier studies in which glucose alone was infused in patients with multiple organ failure and in healthy controls (Green et al. 1995), although in these previous studies the plasma insulin concentration was markedly lower in sepsis, which left open the possibility that glucose storage might have been normal at the same plasma insulin concentration. The demonstration of insulin resistance in this setting suggests that the abnormality of insulin action in critical illness lies distal to the insulin receptor and the glucose transporter, and supports the demonstration that content of insulin receptor proteins and glucose transporter-4 (the principal insulin-sensitive glucose transporter) in skeletal muscle are normal in sepsis (Vary et al. 1995). The findings suggest a specific defect in those metabolic pathways relating to glycogen synthesis, an explanation which is in agreement with the observation that glycogen synthase activity in skeletal muscle is impaired in endotoxaemic animals (Virkamaki & Yki-Jarvinen, 1994), possibly as a consequence of impaired phosphorylation of mitogen-activated protein kinase (Fan et al. 1996). It is unclear, however, whether glycogen synthase activity in man is impaired in critical illness, and studies employing in vivo ^{13}C NMR spectroscopy have suggested that glycogen synthase is not a key regulatory step in determining glycogen storage in human subjects (Shulman et al. 1995).

Mechanisms of insulin resistance in critical illness

Although an acute state of insulin resistance characteristically accompanies the metabolic effects of sepsis and

injury, it is as yet unclear what the exact mechanisms are. In particular, it is unclear whether the molecular pathogenesis of insulin resistance in critical illness is the same as that observed in type 2 diabetes mellitus. It has been suggested frequently that the counter-regulatory hormones (cortisol, growth hormone, glucagon and adrenaline), release of which accompanies injury and infection, are responsible for the associated insulin resistance, but the evidence for this hypothesis is by no means clear (Carlson & Little, 1992, 1994). While infusion of these hormones in healthy volunteers can certainly induce a state of insulin resistance (Bessey *et al*. 1984; Gelfand *et al*. 1984), the plasma concentrations of these hormones at which *in vivo* insulin resistance has been demonstrated in these studies vastly exceed those seen in critical-illness states. In addition, more recent studies have demonstrated that profound insulin resistance occurs after elective abdominal surgery in the presence of trivial and short-lived changes in the plasma concentrations of these hormones (Thorell *et al*. 1994). Studies in which human volunteers have been made insulin resistant by infusion of endotoxin have, however, suggested that the time course of the duration of insulin resistance in this experimental model might be explicable on the basis of the cortisol and/or growth hormone responses to endotoxin (Agwunobi *et al*. 2000). While the role of counter-regulatory hormones in the insulin resistance of critical illness thus remains controversial, attention has recently focused on other potential mediators of insulin resistance in critical illness, such as leptin and the pro-inflammatory cytokines tumour necrosis factor (TNF)-α and interleukin 6.

Elevated serum concentrations of leptin, the protein product of the *ob* gene, have been demonstrated in obesity and type 2 diabetes mellitus, both of which are associated with insulin resistance (Segal *et al*. 1996). In addition, animal studies have shown that inflammatory stimuli elicit synthesis of leptin from adipose tissue (Grunfeld *et al*. 1996) and increase circulating leptin concentration (Moshyedi *et al*. 1998). Since leptin has been shown to inhibit insulin-mediated glucose storage in soleus muscle (Liu *et al*. 1997) and insulin signalling in muscle cell lines (Cohen *et al*. 1996), it emerged as a potential candidate for a mediator of insulin resistance in human injury and infection. Studies of critically-ill patients with sepsis demonstrated modest increases in circulating leptin concentration, and suggested that this response had positive prognostic implications (Bornstein *et al*. 1998*a*). Although elective surgery in man did lead to an increase in circulating leptin concentrations (Stratton *et al*. 1997), the increase was, however, trivial and short-lived. We were unable to demonstrate increased serum leptin concentrations in critically-ill insulin-resistant patients with abdominal sepsis, and leptin concentrations failed to correlate with insulin resistance or hypermetabolism in these patients (Carlson *et al*. 1999). Differences between man and animals with regard to leptin production in stress are also supported by the demonstration that endotoxin administration fails to induce leptin in man (Bornstein *et al*. 1998*b*). Thus, there appear to be important interspecies differences in the role of leptin in stress, although leptin appears to be unlikely to mediate the insulin resistance that follows injury or infection in man.

The role of the cytokines TNFα and interleukin 6 in insulin resistance in critical illness is also unclear, although TNFα has clearly been the source of great interest recently. It has been recognised for many years that infusion of TNFα into rodents can induce many of the abnormalities of glucose metabolism that characterise critical illness (Lang *et al*. 1992), and TNFα appears to inhibit some of the cellular actions of insulin *in vitro* (Begum & Ragolia, 1996). Mice lacking TNF function have been shown to be at least partially protected from the insulin resistance that accompanies overfeeding and obesity (Uysal *et al*. 1997). In human subjects elevated plasma concentrations of TNFα have been demonstrated in insulin-resistant diabetic subjects (Winkler *et al*. 1998), and cancer patients (McCall *et al*. 1992). More importantly, local expression of TNF mRNA in skeletal muscle has been shown to correlate with the severity of insulin resistance in cancer (Noguchi *et al*. 1998). This finding is important, since it places a cytokine (or at least its mRNA) in increased quantities in a target tissue for insulin resistance, and there is increasing evidence that injury can lead to induction of pro-inflammatory cytokines such as TNFα, and interleukins 1 and 6 in uninjured tissues, distant to the site of injury (Molina *et al*. 1997; Catania *et al*. 1999). At the present time, however, TNFα and other pro-inflammatory cytokines have not been shown to be capable of inducing insulin resistance in intact muscle (Furnsinn *et al*. 1997).

Future advances in understanding insulin resistance in critical illness

Human critical illness is characterised by a series of profound physiological alterations which make detailed study and, in particular, interpretation of data extremely difficult. While the use of genetically-modified mouse strains (such as cytokine 'knockout' animals) might provide additional information about the role of specific molecules, there is likely to be considerable duplication and overlap of effects, resulting in both redundancy and pleiotropism which may vary from species to species. For this reason human studies are likely to continue to be valuable, and major elective surgery, which provides both a means of inducing an acute state of insulin resistance and also the opportunity to investigate metabolic processes at the tissue level, will be particularly useful. Key issues to be addressed will be whether injury and/or infection can induce pro-inflammatory cytokine gene expression in muscle, whether blocking these processes alters insulin sensitivity, and whether these changes are mediated by cytokines themselves or via second messengers such as NO (Bedard *et al*. 1997).

Conclusions

Our ability to provide optimal nutritional support for the critically-ill catabolic patient is likely to improve only when we have a clearer understanding of the metabolic processes involved. While early studies suggested that our failure to provide effective nutritional support in critical illness might be associated with reduced efficiency of fuel utilisation in this setting, perhaps associated with increased activity of the sympathetic nervous system, there is in fact little or no

reliable evidence to support this view. What is clear, however, is that the acute state of insulin resistance associated with critical illness can be correlated directly with the severity of illness and determines the speed of recovery. Thus far, it is unclear whether insulin resistance in critical illness can be prevented, but recent advances in our understanding of the molecular basis of insulin sensitivity are likely to produce a series of novel therapeutic targets.

Acknowledgements

References

Acheson KJ, Jequier E & Wahren J (1983) Influence of beta adrenergic blockade on glucose-induced thermogenesis. *Journal of Clinical Investigation* **72**, 981–986.

Acheson KJ, Ravussin E, Wahren J & Jéquier E (1984) Thermic effect of glucose in man. Obligatory and facultative thermogenesis. *Journal of Clinical Investigation* **73**, 1572–1580.

Agwunobi AO, Reid C, Maycock P, Little RA & Carlson GL (2000) Insulin resistance and substrate utilization in human endotoxaemia. *Journal of Clinical Endocrinology and Metabolism* **85**, 3770–3778.

Allard JP, Jeejeebhoy KN, Whitwell J, Pashutinski L & Peters WJ (1988) Factors influencing energy expenditure in patients with burns. *Journal of Trauma* **28**, 199–202.

Arnold J, Leinhardt D, Carlson G, Gray P, Little RA & Irving MH (1992) Thermogenic and hormonal responses to amino acid infusion in septic humans. *American Journal of Physiology* **263**, E129–E135.

Arnold J, Shipley K, Scott NA, Little RA & Irving MH (1989) Thermic effect of parenteral nutrition in septic and non-septic individuals. *American Journal of Clinical Nutrition* **53**, 853–863.

Arnold J, Shipley KA, Scott NA, Little RA & Irving MH (1991) Lipid infusion increases oxygen consumption similarly in septic and nonseptic patients. *American Journal of Clinical Nutrition* **53**, 143–148.

Askanazi J, Carpentier YA, Elwyn DH, Nordenstrom J, Jeevanandam M, Rosenbaum SH, Gump FE & Kinney JM (1980) Influence of total parenteral nutrition on fuel utilization in injury and sepsis. *Annals of Surgery* **291**, 40–46.

Barton RN (1987) The neuroendocrinology of physical injury. *Clinical Endocrinology and Metabolism* **1**, 355–374.

Bedard S, Marcotte B & Marette A (1997) Cytokines modulate glucose transport in skeletal muscle by inducing the expression of inducible nitric oxide synthase. *Biochemical Journal* **325**, 487–493.

Begum N & Ragolia L (1996) Effect of tumor necrosis factor-alpha on insulin action in cultured rat skeletal muscle cells. *Endocrinology* **137**, 2441–2446.

Benedict FG & Carpenter TM (1918) Food ingestion and energy transformations with special reference to the stimulating effects of nutrients. *Carnegie Institute of Washington* 355–382.

Bessey PQ, Watters JM, Aoki TT & Wilmore DW (1984) Combined hormonal infusion simulates the metabolic response to injury. *Annals of Surgery* **200**, 264–281.

Bjorntorp P & Sjostrom L (1978) Carbohydrate storage in man: speculations and some quantitative considerations. *Metabolism* **27**, 1853–1865.

Bornstein SR, Licinio J, Tauchnitz R, Engelmann L, Negrao AB, Gold P & Chrousos GP (1998*a*) Plasma leptin levels are increased in survivors of acute sepsis: Associated loss of diurnal rhythm in cortisol and leptin secretion. *Journal of Clinical Endocrinology and Metabolism* **83**, 280–283.

Bornstein SR, Preas HL, Chrousos GP & Suffredini AF (1998*b*) Circulating leptin levels during acute experimental endotoxemia and antiinflammatory therapy in humans. *Journal of Infectious Diseases* **178**, 887–890.

Carlson GL (1998) Nutrient induced thermogenesis. In *Baillière's Clinical Endocrinology and Metabolism: Energy Metabolism in Trauma*, pp. 603–615 [RA Little and J Werrneman, editors]. London: Baillière-Tindall.

Carlson GL, Gray P, Arnold J, Little RA & Irving MH (1994) Thermogenic, hormonal and metabolic effects of a TPN mixture. Influence of glucose and amino acids. *American Journal of Physiology* **266**, E845–E851.

Carlson GL, Gray P, Arnold J, Little RA & Irving MH (1997) Thermogenic, hormonal and metabolic effects of intravenous glucose infusion in human sepsis. *British Journal of Surgery* **84**, 1454–1459.

Carlson GL & Little RA (1992) The pathophysiology and pattern of the hormonal response to severe sepsis. In *Endocrine Consequences of Critical Illness*, pp. 57–69 [JM Boles, editor]. Paris: Arnette.

Carlson GL & Little RA (1994) Insulin resistance and tissue fuels. In *Organ Metabolism and Nutrition: Ideas for Critical Care*, pp. 49–69 [JM Kinney, editor]. New York: Raven Press.

Carlson GL, Saeed M, Little RA & Irving MH (1999) Serum leptin concentrations and their relation to metabolic abnormalities in human sepsis. *American Journal of Physiology* **276**, E658–E662.

Carpenter TM & Fox EL (1930) The gaseous exchange of the human subject III. As affected by small quantities of levulose. *Journal of Nutrition* **ii**, 389–408.

Catania RA, Schwacha MG, Cioffi WG, Bland KI & Chaudry IH (1999) Does uninjured skin release proinflammatory cytokines following trauma and hemorrhage? *Archives of Surgery* **134**, 368–374.

Christin L, Nach C-A, Vernet O, Ravussin E, Jéquier E & Acheson K (1986) Insulin – its role in the thermic effect of glucose. *Journal of Clinical Investigation* **77**, 1747–1755.

Cohen B, Novick D & Rubinstein M (1996) Modulation of insulin activities by leptin. *Science* **274**, 1185–1188.

DeFronzo R, Thorin D, Felber J, Simonson D, Thiebaud D, Jequier E & Golay A (1984) Effect of beta and alpha adrenergic blockade on glucose-induced thermogenesis in man. *Journal of Clinical Investigation* **73**, 633–639.

Elwyn DH, Kinney JM, Jeevanandam M, Gump FE & Broell JR (1978) Influence of increasing carbohydrate intake on glucose kinetics in injured patients. *Annals of Surgery* **190**, 117–126.

Evans EI & Butterfield WJH (1951) The stress response in the severely burned. *Annals of Surgery* **134**, 588–613.

Fan J, Li YH, Wojnar MM & Lang CH (1996) Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1 and MAP kinase in skeletal muscle. *Shock* **6**, 164–170.

Ferrannini E, Smith JD, Cobelli C, Toffolo G, Pilo A & DeFronzo RA (1985) Effect of insulin on the distribution and disposition of glucose in man. *Journal of Clinical Investigation* **76**, 357–364.

Fischer P (1862) Du diabete consecutif aux traumatismes (Diabetes following traumas). *Archives Generale de Medecine* **20**, 413–443.

Flatt JP (1977) The biochemistry of energy expenditure. In *Recent Advances in Obesity Research*, pp. 211–228 [GA Bray, editor]. Washington, DC: Newman.

Furnsinn C, Neschen S, Wagner O, Roden M, Bisschop M & Waldhausl W (1997) Acute and chronic exposure to tumor necrosis factor-alpha fails to affect insulin-stimulated glucose metabolism of isolated rat soleus muscle. *Endocrinology* **138**, 2674–2679.

Gelfand RA, Matthews DE, Bier DM & Sherwin RS (1984) Role of counterregulatory hormones in the catabolic response to stress. *Journal of Clinical Investigation* **74**, 2238–2248.

Giovannini I, Chiarla C, Boldrini G, Castiglioni G & Castagneto M (1988) Calorimetric response to amino acid infusion in sepsis and critical illness. *Critical Care Medicine* **16**, 667–670.

Green CJ, Campbell IT, O'Sullivan E, Underhill S, McLaren DPM, Hipkin LJ, MacDonald IA & Russell J (1995) Septic patients in multiple organ failure can oxidize infused glucose but non-oxidative disposal (storage) is impaired. *Clinical Science* **89**, 601–609.

Grunfeld C, Zhao C, Fuller J, Pollock A, Moser A, Friedman J & Feingold K (1996) Endotoxin and cytokines induce expression of leptin the *ob* gene product in hamsters. *Journal of Clinical Investigation* **97**, 2152–2157.

Howard JM (1955) Studies of the absorption and metabolism of glucose following injury. *Annals of Surgery* **141**, 321.

Krebs HA (1964) The metabolic fate of amino acids. In *Mammalian Protein Metabolism*, pp. 125–176 [HN Munro and JB Allison, editors]. New York and London: Academic Press.

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.

Lavoisier AL & LaPlace P (1784) Memoire sur la chaleur (Memoir on heat). *Histoires Academie Royale Science* **355**–408.

Leinhardt DJ, Arnold J, Shipley KA, Mughal MM, Little RA & Irving MH (1993) Plasma NE concentrations do not accurately reflect sympathetic nervous system activity in human sepsis. *American Journal of Physiology* **265**, E284–E288.

Liu YL, Emilsson V & Cawthorne MA (1997) Leptin inhibits glycogen synthesis in the isolated soleus muscle of obese *ob/ob* mice. *FEBS Letters* **411**, 351–355.

Lusk G (1912) Animal calorimetry. The influence of the ingestion of amino acids upon metabolism. *Journal of Biological Chemistry* **XIII**, 155–183.

Lusk G (1922) The specific dynamic action of various food factors. *Medicine* **1**, 311–354.

Lusk G (1931) The specific dynamic action. *Journal of Nutrition* **iii**, 519–530.

McCall JL, Tuckey JA & Parry BR (1992) Serum tumor necrosis factor alpha and insulin resistance in gastrointestinal cancer. *British Journal of Surgery* **79**, 1361–1363.

Magnus-Levy A (1894) Über die Grosse des respiratorischen Gaswechsels unter dem einfluss der nahrungsaufnahme (On the extent of respiratory gaseous exchange in relation to food intake). *Pflugers Archiv* **46**, 1–126.

Moan A, Hoieggen A, Nordby G, Birkeland K, Eide I & Kjeldsen SE (1995) The glucose clamp procedure activates the sympathetic nervous system even in the absence of hyper-insulinemia. *Journal of Clinical Endocrinology and Metabolism* **80**, 3151–3154.

Molina PE, Malek S, Lang CH, Qian L, Naukam R & Abumrad NN (1997) Early organ-specific hemorrhage-induced increases in tissue cytokine content: Associated neurohormonal and opioid alterations. *Neuroimmunomodulation* **4**, 28–36.

Moshyedi AK, Josephs MD, Abdalla EK, Mackay SL, Edwards CK III, Copeland EM III & Moldawer LL (1998) Increased leptin expression in mice with bacterial peritonitis is partially regulated by tumor necrosis factor alpha. *Infection and Immunity* **66**, 1800–1802.

Newsholme EA & Crabtree B (1976) Substrate cycles in metabolic regulation and in heat generation. *Biochemical Society Symposia* **41**, 61–109.

Ng LL & Hockaday TD (1989) The effect of environmental temperature on prandial changes in leucocyte sodium transport. *British Journal of Nutrition* **62**, 639–645.

Noguchi Y, Yoshikawa T, Marat D, Doi C, Makino T, Fukuzawa K, Tsuburaya A, Satoh S, Ito T & Mitsuse S (1998) Insulin resistance in cancer patients is associated with enhanced tumor necrosis factor alpha expression in skeletal muscle. *Biochemical and Biophysical Research Communications* **253**, 887–892.

Nordenström JM, Jeevanandam M, Elwyn DH, Carpentier YA, Askanazi J, Arnold R & Kinney JM (1981) Increasing glucose intake during total parenteral nutrition increases norepinephrine in trauma and sepsis. *Clinical Physiology* **1**, 525–534.

Randle PJ, Garland PB, Hales CN & Newsholme EA (1963) The glucose fatty acid cycle, its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* **i**, 787–788.

Ravussin E & Bogardus C (1982) Thermogenic response to insulin and glucose infusions in man: a model to evaluate the different components of the thermic effect of carbohydrate. *Life Science* **31**, 2011–2018.

Robertson RP & Porte D Jr (1974) Plasma catecholamine responses to intravenous glucose in normal man. *Journal of Clinical Endocrinology and Metabolism* **39**, 403–405.

Rubner M (1902) *Die Gesetze die Energieverbrauchs bei der Ernahrung* (The laws of energy consumption with nutrition). Leipzig and Vienna: Rubner.

Saeed M & Carlson GL (1995) Substrate utilisation after injury. *International Journal of Orthopaedic Trauma* **5**, 152–157.

Saeed M, Carlson GL, Little RA & Irving MH (1999) Selective impairment of glucose storage in human sepsis. *British Journal of Surgery* **86**, 813–821.

Segal KR, Landt M & Klein S (1996) Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. *Diabetes* **45**, 988–991.

Shulman RG, Bloch G & Rothman DL (1995) In vivo regulation of muscle glycogen synthase and the control of glycogen synthesis. *Proceedings of the National Academy of Sciences USA* **92**, 8535–8542.

Smith E (1859) Experiments on respiration-second communication. On the action of foods upon the respiration during the primary processes of digestion. *Philosophical Transactions of the Royal Society* **149**, 715–742.

Stoner HB, Little RA, Frayn KN, Elebute EA, Tresadern J & Gross E (1983) The effect of sepsis upon the oxidation of carbohydrate and fat. *British Journal of Surgery* **70**, 32–35.

Stratton RJ, Dewit O, Crowe E, Jennings G, Villar RN & Elia M (1997) Plasma leptin, energy intake and hunger following total hip replacement surgery. *Clinical Science* **93**, 113–117.

Thiebaud D, Schutz Y, Acheson K, Jacot E, DeFronzo R, Felber J-P & Jequier E (1983) Energy cost of glucose storage in human subjects during glucose-insulin infusions. *American Journal of Physiology* **244**, E216–E221.

Thorell A, Efendic S, Gutniak M, Haggmark T & Ljungqvist O (1994) Insulin resistance after abdominal surgery. *British Journal of Surgery* **81**, 59–63.

Uysal KT, Wiesbrock SM, Marino MW & Hotamisligil GS (1997) Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* **389**, 610–4.

Vary TC, Drnevich D, Jurasinski C & Brennan WA (1995) Mechanisms regulating skeletal muscle glucose metabolism in sepsis. *Shock* **3**, 403–410.

Virkamaki A, Puhakainen I, Koivisto VA, Vuorinen-Markkola H & Yki-Jarvinen H (1992) Mechanisms of hepatic and peripheral insulin resistance during acute infections in humans. *Journal of Clinical Endocrinology and Metabolism* **74**, 673–679.

Virkamaki A & Yki-Jarvinen H (1994) Mechanisms of insulin resistance during acute endotoxaemia. *Endocrinology* **134**, 2072–2078.

Welle S, Lilavivat U & Campbell RG (1981) Thermic effect of feeding in man: increased plasma norepinephrine levels following glucose but not protein or fat consumption. *Metabolism* **30**, 953–958.

White RH, Frayn KN, Little RA, Threlfall CJ, Stoner HB & Irving MH (1987) Hormonal and metabolic responses to glucose infusion in sepsis studied by the hyperglycaemic glucose clamp technique. *Journal of Parenteral and Enteral Nutrition* **11**, 345–353.

Winkler G, Salamon F, Salamon D, Speer G, Simon K & Cseh K (1998) Elevated serum tumour necrosis factor alpha levels can contribute to the insulin resistance in Type II (non-insulin-dependent) diabetes and in obesity. *Diabetologia* **41**, 860–861.

Wolfe RR, Jahoor F, Herndon D & Miyoshi H (1991) Isotopic evaluation of the metabolism of pyruvate and related substrates in normal adult volunteers and severely burned children: effect of dichloroacetate and glucose infusion. *Surgery* **110**, 54–67.