patients with certain types of cancer.[55] Although stress hormones have clearly been shown to affect carbohydrate, lipid and protein metabolism, the factors that cause net protein catabolism have not yet been identified; the catabolic changes in protein metabolism observed in stressed patients cannot be precisely reproduced by stress hormone infusion.[54]

Effects of inflammatory cytokines

Recently, in addition to these classical regulatory and counter-regulatory hormones such as glucagon and catecholamines, inflammatory cytokines have been considered to be independent factors that also affect substrate and protein metabolism.[56,57] The evidence that plasma concentration of tumor necrosis factor (TNF) is shown to be elevated in cancer patients also supports this theory,[58] although this evidence has been still controversial. Therefore, it is reasonable to hypothesize that the changes in substrate metabolism in cancer patients are controlled by TNF. For example, TNF has been shown to cause cachexia,[59] which is similar to the conditions frequently observed in cancer patients. Furthermore, TNF has also been shown to affect substrate and protein metabolism, in which TNF causes an increase in glucose production, glucose utilization, and essential amino acid oxidation, causing net protein catabolism.[57] However, TNF inhibits lipolysis and free fatty acid flux.[56,57] Thus, TNF alone cannot account for all the aspects of metabolic control, and other cytokines may contribute simultaneously to the overall metabolic responses in stressed patients.[60] It has also been demonstrated that TNF causes changes in hormonal milieu,[57,61] causing an increase in plasma glucagon concentration in sublethal doses and increase in glucagon and catecholamine concentration in lethal doses.[61] Thus, alterations in substrate and protein metabolism seem to be controlled by complex mechanisms involving both classical regulatory and counter-regulatory hormones and cytokines.

Although the primary factors that control protein metabolism during critical illness have been identified,[53] a possible mediator and/or humoral factor that causes the net protein catabolism during critical illness has not been identified. However, it has been recently demonstrated that cytokines are the candidates that regulate substrate and protein metabolism.[57] Among the cytokines, TNF is a primary cytokine that plays a central role in the alteration in the overall systemic inflammatory response syndrome of critically ill patients.[57,59,62] TNF also appears to elicit alterations in substrate and protein metabolism because infusion of TNF causes a state that is similar to the condition of the critically ill patients, that is so-called cachexia,[59] (Fig. 3) although it is not clear whether the effects are direct or

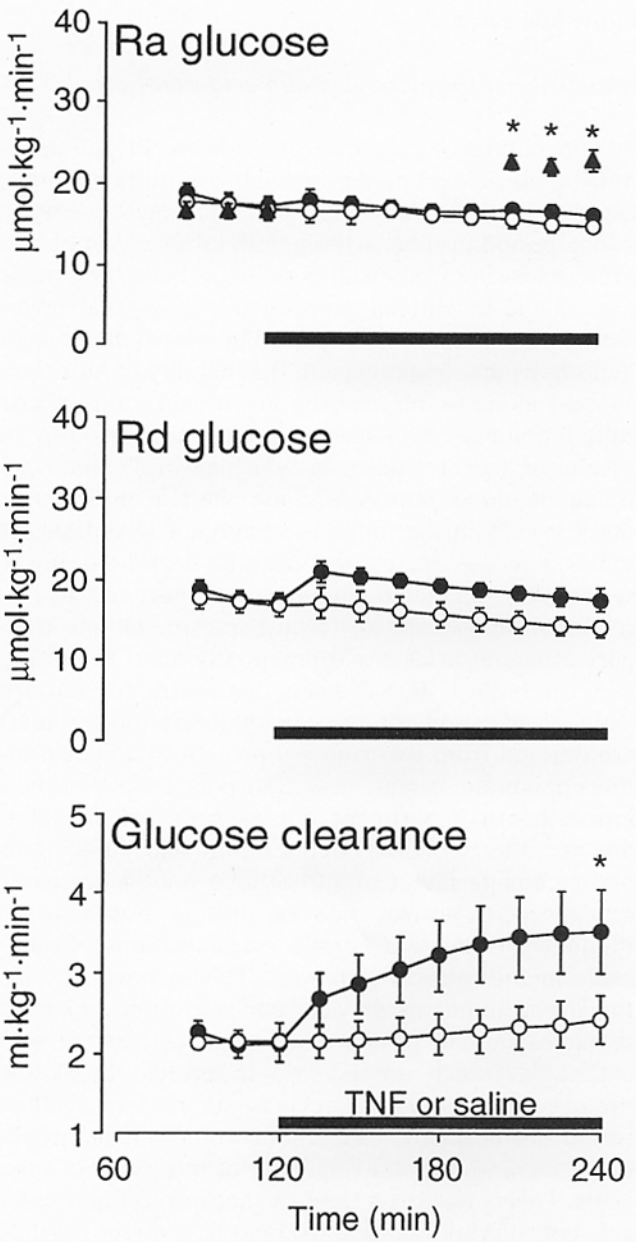

Fig. 3 Effects of TNF on amino acid and protein kinetics during hormonal clamp. TNF infusion causes increases in glucose uptake and leucine oxidation without being mediated by the changes in plasma glucagon and insulin concentration. ○, Placebo; ▲, TNF; ●, TNF with hormonal clamp. While a significant increase in glucose production during TNF infusion is abolished by the hormonal clamp, a significant increase in glucose clearance during TNF infusion is not affected (*$P < 0.05$ vs. Basal). (From Ref. 100 with some modifications)

secondary. Nonetheless, there is no doubt that TNF plays an important role in regulating substrate and protein metabolism. However, the fact that a number of cytokines have been shown to form network[63] *in vivo* has hampered the determination of the precise roles of