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REVIEW

HORMONAL CONTROL OF METABOLISM IN TRAUMA AND SEPSIS

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INTRODUCTION

The care of the injured or severely septic patient is often centred around the repair of his injuries or treatment of his infection. However, it has long been recognized that the conditions of injury and sepsis are associated with metabolic changes affecting all parts of the body, and also that these responses change with time in a generally predictable way. The scientific study of the metabolic responses to trauma is often considered to have begun with David Cuthbertson's observation of the marked rise in urinary nitrogen excretion after long-bone fractures (Cuthbertson, 1930). It has received special impetus over the past decade with the recognition of the important role of nutrition in the treatment of these conditions.

However, the hormonal background to these metabolic responses is by no means fully understood. The purpose of this review is to summarize our current understanding of the endocrine control of metabolism in trauma and in sepsis, to point out areas of uncertainty, and to suggest important lines for future investigation. The review will be concerned primarily with endocrine control of 'energy' and protein metabolism. More specialized topics, such as the hormonal control of water and electrolyte balance, have been reviewed elsewhere recently (Barton, 1985).

GENERAL DESCRIPTION OF THE RESPONSES TO INJURY AND SEPSIS

The pattern of responses to physical injury is in some ways easier to describe than that to sepsis, since there is a defined time-sequence from the injury itself until eventual recovery; whereas sepsis can wax and wane in intensity, producing corresponding fluctuations in hormonal and metabolic responses. The response to injury (Fig. 1) may begin before the injury itself, with awareness of approaching danger activating the hypothalamic defence area. This results in the secretion of an array of pituitary hormones including ACTH, GH, PRL and vasopressin, activation of the sympatho-adrenal system and, as a consequence

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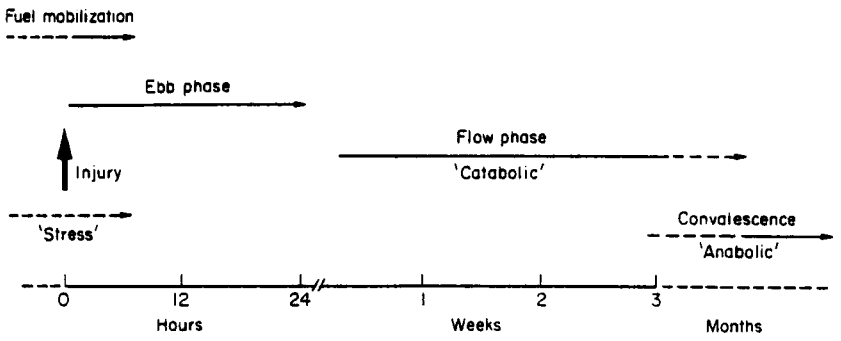

Fig. 1. Phases of the response to injury. The duration of each phase is variable, and representative figures only are given. The first phase, that of fuel mobilization, may begin before injury occurs, initiated by 'stress' or awareness of approaching danger. This is intimately merged, should injury occur, with the 'ebb' or 'shock' phase, which in turn—in survivors—merges into the more prolonged 'flow' phase, often termed the catabolic response. Although wound healing may commence during the flow phase, general anabolism and true recovery do not begin until it has subsided.

of the ACTH release, increased adreno-cortical secretion (Buckingham, 1985). This 'stress' response is reinforced by afferent stimuli arising once the injury has occurred: nociceptive afferents from damaged areas, baro- and volume-receptor inputs responding to hypotension and hypovolaemia, stimuli from osmo-, gluco- and hormone receptors responding to changes in the composition of the blood; and, indeed, the response may commence at this time if injury has occurred without warning.

In metabolic terms, this phase is characterized by a rapid mobilization of the glycogen and triacylglycerol fuel stores in (teleologically speaking) a 'fight or flight' response (Cannon, 1920), although it can be argued that such a massive mobilization can serve little useful purpose and is merely an exaggeration of a response appropriate for more minor degrees of stress and danger. Unlike the classic fight or flight response, however, in which the energy mobilized would be dissipated in increased physical activity, the early phase of the response to severe injury is characterized by a lack of sensitivity to the environment, a noticeable lack of the expected pain sensations, and, according to many writers on the subject of 'traumatic shock', a diminution of metabolic rate (e.g. Cannon, 1923; Cuthbertson, 1942). This concept, based on clinical observation and on animal experiments, is not entirely in accord with the few measurements made in man, although metabolic rate at this stage after injury is certainly not raised to the extent expected from the degree of fuel availability (Little, 1985).

This phase of the response to injury—the mobilization of fuel stores together with apparent restraints on their utilization—has been termed by Cuthbertson (1942) the 'ebb phase', and lasts typically around 12–24 h depending on many factors such as the severity of the injury and the treatment given. In patients who do not receive hospital treatment until 30 h after their injuries, similar changes are still seen (Stoner *et al.*, 1979). Provided that early death from hypovolaemia, or from direct damage to vital organs, is avoided, then the ebb phase merges into a more prolonged period characterized by an increase in metabolic rate and a breakdown of body tissues, the 'catabolic' or Cuthbertson's 'flow'

phase of the response to injury. The duration and intensity of this phase vary according to the severity of the injury (Wilmore, 1977) but in the routine, uncomplicated orthopaedic patient with long-bone fractures, it will be at its peak around 7–10 d after injury, gradually subsiding and merging into the 'anabolic' or 'convalescent' phase over the next 2–4 weeks, depending in part on the speed at which the patient can be mobilized.

The course of the response to sepsis is not so predictable, although the characteristic features of the ebb and flow phases of the response to injury are seen, linked more to the severity than to the time-course of the infection. Thus the critically ill septic patient, particularly the patient in septic shock, will display many of the features of the acute or ebb phase after injury, while the patient with more chronic but less life-threatening infection will display the hypermetabolism and catabolism typical of the flow phase after physical injury.

THE EBB PHASE OF THE RESPONSE TO INJURY

The neuro-endocrine control of metabolism is most clearly understood in this phase of the response to injury. It is dominated by a massive sympatho-adrenal discharge, reinforced by pituitary stimulation of cortisol secretion. Of the many other hypophyseal hormones released at this time, only vasopressin seems at all likely to be involved in the metabolic changes; and whilst the pancreatic hormones insulin and glucagon have a potential role in regulating these metabolic events, their secretion is in turn determined primarily by the sympatho-adrenal response.

The magnitude of the sympatho-adrenal response to severe injury is best seen by comparison with other 'stress' conditions (Table 1). Plasma concentrations of both noradrenaline, an index of sympathetic activity (Cryer, 1980), and adrenaline are well above the levels seen in acute myocardial infarction, although still not comparable with those seen in the extreme stress of cardiac arrest. More importantly, they are well above the threshold levels determined from experimental work as being necessary to produce metabolic changes (Clutter *et al.*, 1980; Galster *et al.*, 1981); a plasma adrenaline concentration above about 0·5 nmol/l will promote lipolysis with elevation of the plasma glycerol and free fatty acid concentrations, above 1·0 nmol/l will raise blood glucose and lactate concentrations through stimulation of hepatic and muscle glycogenolysis, and above 2·2 nmol/l will inhibit insulin secretion, all typical features of the severely injured patient. The response of both adrenaline and noradrenaline is, in fact, logarithmically related to the severity of the injury (Frayn *et al.*, 1985; see Fig. 2), so that very high levels of adrenaline, in particular, are found in the critically injured. It is this very intense response which gives the sympatho-adrenal system a widespread influence on the early metabolic changes.

The hormonal control of the metabolic changes of the ebb phase will now be discussed in more detail, dealing firstly with the fuel mobilization and then with the restraint mechanisms which prevent excessive dissipation of the fuels mobilized.

Neuro-endocrine control of body fuel mobilization

Liver and muscle glycogen

Many of the hormones released in the early response to stress and injury have potential roles in promoting glycogenolysis and lipolysis. Liver glycogen breakdown, for example, may be activated *in vitro* by adrenaline, by glucagon and by high concentrations of

Table 1. Plasma concentrations of catecholamines and of cortisol in various states

Group	Noradrenaline	Adrenaline	Cortisol	48-h mortality (%)	*n*
Controls—indwelling line	0·6±0·3	0·28±0·13	270±100	0	7–10
Blood donation	1·2±0·3	0·23±0·11	—	0	7
Controls—direct venepuncture	2·1±0·7	0·39±0·24	280±30	0	10–12
Acutely injured					
Minor and moderate	3·4±1·3	0·96±0·81	900±250	0	18
Severe	13±21	13±28	770±280	36	22
Septic					
Not in shock	5·3±4·1	1·5±1·1	—	0	6
	3·3±2·3	0·8±1·2	670±300	9	11–12
Septic shock	17±6	6·5±3·5	—	0*	10
Cardiac patients					
Acute infarction	7·5±7·2	1·6±2·2	1120±470	0	49–52
Cardiac arrest	40±42	29±6	850±680	86	47–50

Results are all in nmol/l and are expressed as mean±SD for simplicity, although plasma catecholamines are more closely log-normally distributed.

Blood was taken from controls either via an indwelling cannula or by direct venepuncture. Blood donation samples were taken through the donor line immediately after removal of 500 ml blood.

Injury severity is classified according to the Injury Severity Score (Baker *et al.*, 1974); scores for the Minor and moderate group ranged from 3 to 12, for the Severe group from 14 to 50.

* Mortality in the patients in septic shock was 50% within 4 d, 80% within 6 d.

For further details see original papers. Data collected and combined from: Benedict & Grahame-Smith, 1978; Frayn *et al.*, 1985; Little *et al.*, 1985a, 1985b; Little *et al.*, 1986; White *et al.*, 1986.

vasopressin, and *in vivo* in experimental animals by stimulation of the sympathetic innervation of the liver (Hems & Whitton, 1980). Of these, adrenaline seems to play the major role after injury, since the resultant hyperglycaemia is fairly closely related to plasma adrenaline concentrations (Frayn *et al.*, 1985). Glucagon secretion after injury is largely β-adrenergically mediated (Porte & Robertson, 1973; Lindsey *et al.*, 1975; Rose & Heath, 1986) and so might be involved in this relationship, but several studies have shown that glucagon secretion responds relatively slowly to injury (e.g. Meguid *et al.*, 1972; Giddings *et al.*, 1976; see also Fig. 5, below) compared with its rapid release after experimental stresses (Bloom *et al.*, 1973). Its role in the early fuel mobilization is therefore equivocal. However, the proviso must be made that the above observations are based on peripheral blood glucagon concentrations; some animal studies suggest that hepatic glucagon clearance is increased in sepsis and trauma, and that portal vein concentrations show a much more rapid response (Zenser *et al.*, 1974; K.N. Frayn, K.J. O'Connor & J.G. Rose; unpublished work). The role of vasopressin is also uncertain and clarification of this awaits detailed studies of its concentration in injured patients, which will be dependent on factors such as the extent of hypovolaemia and hypotension, and of how this is related to the metabolic changes. Vasopressin-stimulation of glycogenolysis in hypovolaemic states is a teleologically attractive idea in that mobilization of the water

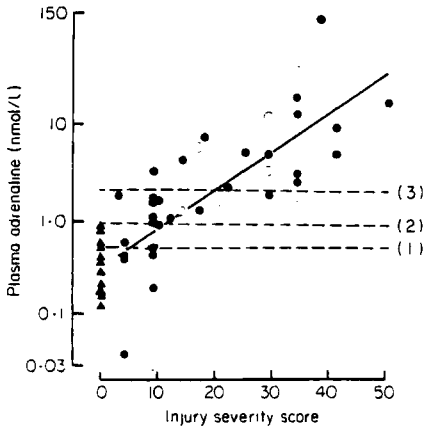

Fig. 2. Plasma adrenaline concentrations shortly after injury. Each point represents a separate patient; samples were taken within 3 h of injury. Severity is rated according to the Injury Severity Score (Baker *et al.*, 1974); scores > 12 are regarded as severe injuries (Stoner *et al.*, 1977), and > 30 usually represent critical injuries. (▲) Samples taken by direct venepuncture from normal control subjects; (○) samples from patients with an elevated plasma ethanol concentration (> 10 mmol/l or 46 mg/dl). Results are those of Frayn *et al.* (1985). Dashed lines show threshold concentrations of adrenaline necessary for various metabolic effects, as determined by infusion into normal subjects (Clutter *et al.*, 1980; Galster *et al.*, 1981): (1) stimulation of lipolysis; (2) elevation of plasma glucose and lactate concentrations, with stimulation of glucose production and inhibition of its clearance; (3) suppression of the plasma insulin concentration. Note that adrenaline concentrations are plotted on a logarithmic scale, and cover more than three orders of magnitude.

stored with the glycogen (three times its own weight) could aid compensation for fluid loss (Hems & Whitton, 1973).

The main hormonal signal for mobilization of muscle glycogen is probably adrenaline (Rennie & Edwards, 1981) and, in view of the concentrations involved, this is likely to occur after injury. The extent of muscle glycogenolysis in the early response to injury is not certain, animal experiments suggesting a small (Stoner, 1958; Frayn *et al.*, 1978) to absent (Hessman & Thorén, 1975) effect. In the rather similar hormonal environment in patients with accidental hypothermia, however, muscle glycogenolysis was shown to be rapid, as judged by net efflux of glucose from the forearm (Stoner *et al.*, 1980), a situation which arises only under conditions of brisk glycogen breakdown (Wicklmayr & Dietze, 1978), since free glucose arises in muscle only from branch-points in the glycogen molecule (about 8% of the glucose units released in glycogen breakdown) and is normally removed by glycolysis. The elevated plasma lactate concentrations in injured patients, thought to arise in part from muscle glycogenolysis (Daniel *et al.*, 1978), bear a weak but significant relationship to plasma adrenaline concentrations (Frayn *et al.*, 1985). Muscle glycogenolysis can only contribute to hyperglycaemia through release of lactate and pyruvate and their conversion to glucose in the liver (ignoring the small contribution of free glucose released from branch points in the glycogen molecule, as discussed above). It is probable that the hyperglycaemia after injury is prolonged by a stimulation of hepatic gluconeogenesis such that it is not suppressed, as it would normally be, by the elevated plasma glucose concentration. This stimulation would be brought about both by increased substrate supply (particularly lactate released in muscle glycogenolysis and in

the metabolism of hypoxic tissues, and glycerol released from adipose tissue lipolysis) and hormonally. Adrenaline, cortisol and glucagon act synergistically to promote and sustain hepatic glucose production (Shamoon *et al.*, 1981) and, as the response proceeds, their joint effects probably come fully into play.

Triacylglycerol

Adipose tissue lipolysis may be stimulated by many factors *in vitro* (Fain, 1980), but the relevance of these *in vivo* after injury is uncertain. Again, from a consideration of the concentrations needed, and reached by, various effectors, it seems probable that adrenaline and possibly activation of the sympathetic innervation of adipose tissue play major roles. The potential role of glucagon must be doubtful in view of its delayed release, as discussed above. The catecholamine-stimulation of lipolysis may be potentiated by cortisol (Goodman, 1970; Fain, 1980) and this interaction seems probable *in vivo* after injury; the effect of cortisol requires induction of protein synthesis, and so this would be seen as a factor maintaining rather than initiating fuel mobilization. Growth hormone has a similar delayed action on adipose tissue and the high levels reached soon after injury or major surgery (Carey *et al.*, 1971; Salter *et al.*, 1972; Frayn *et al.*, 1984b) may well potentiate lipolysis. On the other hand, very similar early metabolic responses to injury are seen in man and rat (reviewed by Heath, 1985), the latter being a species in which GH secretion is suppressed by stress and injury (Barton, 1977).

Maintenance of the ebb phase

Carbohydrate metabolism

Although the fuel mobilization is probably at its peak within an hour or two of injury, the characteristic metabolic features of the ebb phase may be maintained for much longer. The persistence of the hyperglycaemia, for instance, long after liver glycogen stores have been largely depleted, is at least partly due to a continuation of hepatic glucose production by gluconeogenesis; but it also reflects an inhibition of the increase in peripheral glucose utilization which would normally accompany hyperglycaemia. This general picture has been borne out both by glucose tolerance tests in man (Howard, 1955; Allison *et al.*, 1968) and, in more detail, by tracer studies of glucose turnover in animals (e.g. Heath & Corney, 1973). Glucose oxidation, in particular, is inhibited even in absolute terms after severe injury in man, and may be reduced to the level accounted for by the central nervous system alone (Little *et al.*, 1981). Teleologically speaking, it seems that the body is now trying to conserve the fuels mobilized in the initial (presumably unsuccessful) attempt at fight or flight.

A rise in the plasma glucose concentration normally stimulates peripheral glucose utilization both through a 'mass action effect' (metabolic clearance unchanged), and through insulin secretion which increases metabolic clearance in responsive tissues such as muscle and adipose tissue. After severe injury, several mechanisms seem to operate to prevent this occurring.

Perhaps the most studied—and the least understood hormone—in the early response to injury is insulin. Many of the features of the response—mobilization of glycogen and triacylglycerol, impairment of subsequent glucose utilization and oxidation, continued glucose production—might be explained by a suppression of insulin secretion, and since the finding in the 1960s that adrenaline could inhibit pancreatic insulin release (reviewed by Porte & Robertson, 1973), much effort has been directed towards looking for such an

effect in man. Allison *et al.* (1968) clearly showed suppression of the insulin response to an intravenous glucose load during the acute phase of severe burn injury, but in less severely injured patients very high insulin concentrations may be seen, so that in any survey of recently-injured patients an extremely wide range of insulin concentrations is a prominent feature (e.g. Vitek *et al.*, 1979; reviewed by Frayn, 1982). It seems that the plasma insulin concentration after injury reflects the opposing effects of the stimulus of hyperglycaemia and the inhibitory effect of adrenaline, and the relationship between plasma concentrations of adrenaline and insulin bears this out (Fig. 3). In the face of this variability in insulin concentrations, the metabolic responses seem to be relatively uniform, suggesting that even in those whose insulin concentration rises it is ineffective metabolically.

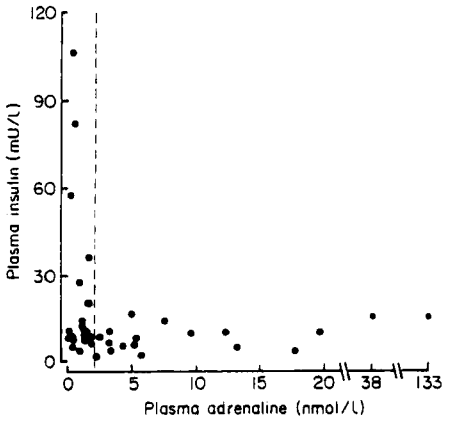

Fig. 3. Relationship between plasma concentrations of insulin and adrenaline in injured patients. Each point represents the result from a single recently-injured patient, as described for Fig. 2. The dashed line shows the concentration of adrenaline (2·2 nmol/l) necessary for suppression of the plasma insulin concentration in experimental studies (Clutter *et al.*, 1980). In patients with plasma adrenaline concentrations above this level, insulin concentrations are uniformly low (< 18 mU/l) despite marked hyperglycaemia (5·9–11·0 mmol/l); in patients with lower adrenaline concentrations, insulin responds very variably to the hyperglycaemia.

The apparent lack of insulin's normal effects is thus brought about in part by the adrenaline response which will both inhibit insulin secretion, as discussed above, and antagonize insulin's stimulation of peripheral glucose utilization (Deibert & DeFronzo, 1980). There is also experimental evidence for an important role of glucocorticoids in these metabolic responses (Barton & Passingham, 1980). Plasma cortisol concentrations soon after injury in man do not respond in such a straightforward severity-related manner as do those of adrenaline (Table 1); they may be lower after severe injuries than after injuries of lesser magnitude, and in either case are far from maximal (Stoner *et al.*, 1979). This sub-maximal response seems to stem both from a lack of the expected pituitary drive and from a lessened responsiveness of the adrenal cortex to ACTH (Barton *et al.*, 1984). The cortisol response in the severely injured improves over the first few hours (Barton *et al.*, 1984), perhaps as the blood supply to the adrenal cortex, which may be reduced in acute hypovolaemia (Walker *et al.*, 1959; Mack & Egdahl, 1970), is restored by fluid replacement. Because of this time-course, and because the actions of cortisol are mediated

mainly through enzyme induction, it seems probable, as discussed already, that the metabolic role of cortisol is concerned more with maintenance than with initiation of the response. Accordingly, blockade of the glucocorticoid response to injury in animals causes the hyperglycaemic response to be transient rather than sustained, and tracer studies have shown that this reflects a failure of the normal peripheral 'insulin resistance' to develop (Barton & Passingham, 1980). In man, in whom the ebb phase is longer lasting, cortisol would be expected to stimulate hepatic gluconeogenesis in addition (Exton, 1972), thus further potentiating the maintenance of hyperglycaemia (Shamoon *et al.*, 1981). Although the metabolic role of cortisol after accidental injury has not been tested directly in man, suppression of its response to surgery with the drug etomidate did not affect—or slightly increased—the hyperglycaemic response (Sear *et al.*, 1983); but since this response is of shorter duration the effects of cortisol might not be so apparent.

Lipid metabolism

Whilst the utilization of glucose is blocked at a peripheral level, the mechanism for conservation of fat stores in the face of a sustained lipolytic drive operates mainly at the level of release. Despite undoubted stimuli for lipolysis, plasma free fatty acid concentrations in the severely injured are often surprisingly low (Allison *et al.*, 1968; Stoner *et al.*, 1979; Frayn, 1982). A similar phenomenon is seen in hypovolaemia in experimental animals, and is brought about largely by an impairment of adipose tissue perfusion (Stoner & Matthews, 1967; Kovách *et al.*, 1970). This reduces the availability of albumin for transport of the free fatty acids released into the general circulation. The effect is probably accentuated by both local and general hypoxia (the latter operating through a rise in blood lactate concentration) leading to a stimulation of the re-esterification of fatty acids within adipose tissue (through a rise in the cytosolic $NADH/NAD^+$ ratio, and increased production of glycerol 1-phosphate; Miller *et al.*, 1964; Fredholm, 1971). This mechanism is potentiated still further in the patient with a high plasma ethanol concentration, ethanol producing a yet more reduced state in the cytoplasm; free fatty acid concentrations in such patients may be very low (Frayn, 1982). Although ethanol may, in animal experiments, reduce the sympatho-adrenal response to stress (DeTurck & Vogel, 1982), this effect is not seen after injury in man (Frayn *et al.*, 1985), so that the lessening of the free fatty acid response must reflect a metabolic mechanism. The impairment of adipose tissue blood flow after injury is, at least in part, yet another manifestation of the widespread influence of the sympatho-adrenal response (Fig. 4), since it is relieved—and systemic free fatty acid concentrations allowed to rise as expected—by α-adrenergic blockade (Kovách *et al.*, 1970). The demonstration (Rofe & Williamson, 1983) that vasopressin can have a similar constrictive effect in adipose tissue suggests that this may be another contributing factor, although, as discussed earlier, we still lack information on the circulating concentrations reached in man after severe accidental injury.

THE FLOW PHASE OF THE RESPONSE TO INJURY

The period during which the patient is stabilized from a haemodynamic point of view, goes through any necessary immediate surgical procedures, and is transferred to an orthopaedic or surgical ward or to an intensive care area, although potentially interesting metabolically (Frayn, 1982), has been little studied. Most studies of the flow phase begin after these initial disturbances have passed, and the patient is displaying the typical

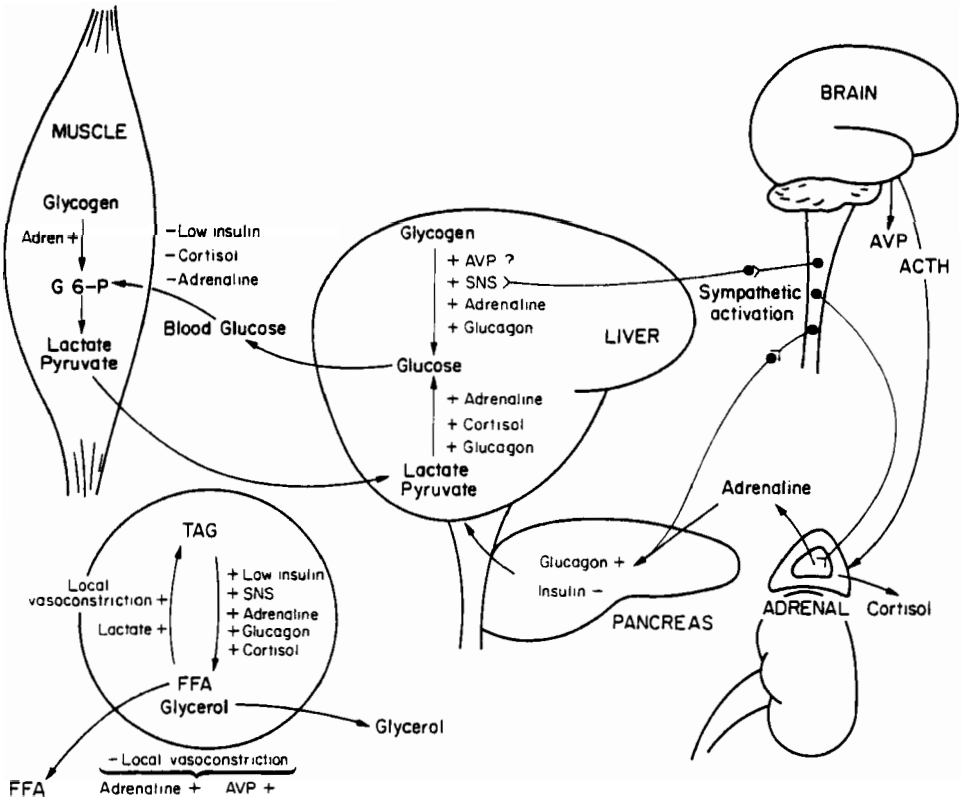

Fig. 4. Central nervous control of metabolism in the ebb phase of the response to injury. Primary events are the activation of the sympathetic nervous system (SNS) and release of adrenaline from the adrenal medulla, with pituitary secretion of vasopressin (AVP) and corticotrophin (ACTH). The metabolic changes can all be viewed as stemming, directly or indirectly, from these central responses. Secondarily, the sympathoadrenal activation acts on the pancreas to stimulate secretion of glucagon and inhibit that of insulin, and ACTH promotes cortisol release from the adrenal cortex (+, stimulation of a process; −, inhibition). These changes result in stimulation of liver and muscle glycogenolysis; release of lactate and pyruvate from muscle, together with the hormonal changes, act to promote hepatic gluconeogenesis. Liver glucose release is thus massively stimulated. Glucose uptake by muscle is not, however, increased as it would normally be in hyperglycaemia because of inhibition by adrenaline and cortisol, and because of the failure of insulin to respond to the hyperglycaemia ('low insulin'). In adipose tissue several factors act to stimulate lipolysis, i.e. the breakdown of triacylglycerol (TAG) to free fatty acids (FFA) and glycerol; impaired insulin secretion ('low insulin') allows this to proceed unchecked. Release of FFA into the general circulation is not, however, as great as expected after severe injury. Local vasoconstriction—brought about by adrenaline and AVP—limits the availability of albumin to transport FFA out of adipose tissue, and local hypoxia, together with any rise in the systemic lactate concentration, act to stimulate reesterification of FFA (through increased provision of glycerol 1-phosphate; see text).

metabolic characteristics of the flow phase: increased metabolic rate in association with elevated core temperature and pulse rate; and increased urinary excretion of nitrogen together with other markers suggestive of (net) muscle protein breakdown, including 3-methylhistidine, zinc, creatine and creatinine (Cuthbertson, 1930, 1980; Threlfall *et al.*, 1981).

The hypermetabolism is initially due primarily to an increased rate of fat oxidation (Frayn *et al.*, 1984a). Although (net) protein breakdown will liberate amino acids for oxidation, the contribution of this pathway to whole-body energy expenditure is rarely more than 20% even in the most severely catabolic patient (Duke *et al.*, 1970). By this time—a few days after injury—it seems reasonable to suppose that little stored carbohydrate remains, so glucose oxidation will only contribute to the increased metabolic rate if exogenous carbohydrate is given. As the patient either resumes voluntary food intake, or receives small amounts of carbohydrate-containing food or infusions, then it appears that glucose oxidation is also accelerated and contributes to the increased metabolic rate (Long *et al.*, 1971; Frayn *et al.*, 1984a). Administration of large amounts of glucose, as in total parenteral nutrition, may, however, lead to a more complicated response in which glucose oxidation is actually reduced in the more severely ill; this is discussed elsewhere (Askanazi *et al.*, 1980a; Stoner *et al.*, 1983; Frayn, 1985).

Non-hormonal mechanisms involved in the response to injury

The hormonal environment which produces these metabolic responses is not, as will be discussed, entirely understood. It is therefore worth considering initially some non-hormonal mechanisms which may be involved.

Metabolism of damaged and reparative tissues

A potentially important factor, particularly in the injured as opposed to the septic patient, is the metabolic contribution of injured tissues. It is abundantly clear, from both clinical (Threlfall *et al.*, 1981) and experimental (Cuthbertson *et al.*, 1939; Frayn *et al.*, 1980; Threlfall *et al.*, 1984) work, and from clinical observation of the general muscle wasting which follows trauma, that the metabolic responses are not produced simply by a local breakdown and resorption of damaged tissue. However, the pattern of metabolism in damaged, and more particularly reparative, tissues may influence the rest of the body (Wilmore & Aulick, 1978). Many of the tissues involved in wound healing are predominantly glycolytic, consuming glucose and returning lactate to the circulation. The wounded area, in addition, receives a privileged, functionally denervated blood supply (Aulick *et al.*, 1977), leading to the view of the wound as a parasite on the host's metabolic resources. The requirement for glucose will necessitate the breakdown of (uninjured) protein to provide amino acids as a gluconeogenic substrate, and gluconeogenesis both from these amino acids and from lactate recycled by the wound will require energy derived from fat oxidation. Thus, both the elevated metabolic rate and the net protein breakdown may be explained in part as meeting the local requirements of wound healing.

This mechanism may make a large contribution to the whole-body responses. Most of the approximate doubling of glucose turnover seen after extensive burns, for instance, can be accounted for by wound glucose consumption (Wilmore & Aulick, 1978). However, it cannot function at a purely metabolic level. How is the wound's need for glucose, for instance, made known to the host? Not simply through depletion of glucose and the resultant counter-regulatory responses, since the injured patient displays hyper- rather than hypo-glycaemia. This mechanism must therefore serve as an explanation more of the reason (in teleological terms) for the flow-phase response, than of how it is mediated. It does, however, illustrate an interesting point about the response. It has been suggested that the wound signals its existence through the lymphokine interleukin-1 (IL-1) (Wilmore, 1986a), a substance whose role will be discussed again later. IL-1 is produced

by stimulated macrophages, perhaps at the site of injury, and (in its role as 'endogenous pyrogen') will act on the hypothalamus to raise temperature set-point. This would fit well with the observation that many of the metabolic changes after injury give an impression of a centrally-coordinated, integrated response (Frayn, 1985), although it does not help in defining the efferent neural or endocrine arm of such a reflex loop.

Immobility and starvation

Other aspects of the injured patient's condition, especially immobility and partial starvation, may also impinge upon his metabolic state. The part played by disuse atrophy in the net muscle loss after injury has long been controversial; a negative nitrogen balance of up to 11 g/d has been produced in some studies of volunteers immobilized in plaster casts (Schønheyder *et al.*, 1954), although other work (Cuthbertson, 1929) shows much smaller changes (around 1 g/d). In any case, the metabolic picture is unlike that of injury, since immobility reduces rather than increases metabolic rate (Cuthbertson, 1929). The same argument can be used against a contribution from starvation, in which condition both metabolic rate and protein breakdown are reduced rather than increased (Cahill, 1976). Rather, the hypermetabolism and net loss of body protein after injury should be seen as all the more striking since they are superimposed on an expected reduction in metabolic activity with reduced mobility and nutrition.

The counter-regulatory hormone hypothesis

The difficulty in pinpointing the hormonal mechanisms involved in producing the typical flow phase responses to injury lies not in identifying hormones with the relevant effects, but in fitting the time-course of the response of any one hormone, or group of hormones, with the very characteristic time-sequence of the metabolic changes.

Counter-regulatory hormones—the background

Because of their known, generally catabolic, effects, much attention has been focused on the so-called counter-regulatory hormones, a group of hormones including adrenaline, cortisol, glucagon and growth hormone which respond to hypoglycaemia and play a role in 'glucose counter-regulation' (Cryer, 1981). For these purposes, activation of the sympathetic nervous system (reflected in a rise in the plasma noradrenaline concentration) will be included as part of the counter-regulatory response. Both adrenaline and noradrenaline are well-recognized short-term stimulators of thermogenesis (Wilmore *et al.*, 1974; MacDonald *et al.*, 1985); high concentrations of cortisol have a pronounced muscle wasting effect (Long *et al.*, 1940; Perkoff *et al.*, 1959); and these hormones in concert produce a generally catabolic state, with stimulation of lipolysis, glycogenolysis and gluconeogenesis. In recent work, to be discussed in more detail later, infusion of a combination of catecholamines, glucagon and cortisol has been shown to mimic most of the metabolic features of the flow phase after injury: increased metabolic rate with elevation of glucose turnover, increased gluconeogenesis unresponsive to hyperglycaemia, and negative nitrogen balance (Bessey *et al.*, 1984; Gelfand *et al.*, 1984). The concentrations of these counter-regulatory hormones are elevated after injury, as described earlier for the 'ebb phase', and in the severely burned patient, for instance, may remain at least moderately elevated well into the flow phase of injury (Batstone *et al.*, 1976; Wolfe *et al.*, 1979).

Observations in patients

However, in at least one group of patients who have been studied in some detail, there are major difficulties in accepting that these counter-regulatory hormones play a directly causal role in the metabolic responses. In the typical routinely-managed orthopaedic patient with long-bone fractures (and no evidence of sepsis), the changes of the flow phase follow a characteristic time-course, with urinary nitrogen excretion and negative nitrogen balance maximal at around 1 week after injury (Cuthbertson, 1930; Shenkin *et al.*, 1980; Frayn *et al.*, 1984a, 1984b; Threlfall *et al.*, 1984). The elevation of metabolic rate occurs roughly coincident with, or a little earlier than, the protein catabolic response (Cuthbertson, 1980; Frayn *et al.*, 1984a). The metabolic responses in this group of patients are obviously of lesser magnitude and duration than those seen after, for instance, major burns or in severe sepsis. However, they are prominent enough to be clinically relevant, and have served, since Cuthbertson's early work (Cuthbertson, 1930), as a very useful model of the responses to more severe conditions. The cumulative nitrogen loss over the first three weeks following long-bone fracture(s) is typically around 80 g (Shenkin *et al.*, 1980; Frayn *et al.*, 1984a), representing loss of 2 kg of lean body mass; and this, occurring in conjunction with a 10–20% elevation in metabolic rate at a time when appetite is often suppressed, can lead to rapid loss of body weight, impairment of muscle function, and consequent delay in rehabilitation.

The difficulty in explaining these changes in conventional hormonal terms is illustrated in Fig. 5, which shows the typical time-course of urinary nitrogen excretion in these patients together with the changes in concentration of the counter-regulatory hormones. The concentrations of catecholamines, cortisol, glucagon and GH are, as already discussed, high during the ebb phase of the response to injury. However, the hormonal picture once the patient leaves the Accident and Emergency Department is generally one of a fairly rapid return towards normality; plasma concentrations of the counter-regulatory hormones fall, more or less rapidly, back towards baseline levels, such that, at the time of the peak 'catabolic' response 7–10 d after injury, there may still be a moderate elevation of plasma cortisol, depending on severity (Barton & Passingham, 1981; Frayn *et al.*, 1983), but concentrations of GH, glucagon and catecholamines are likely to be back into the normal range (Batstone *et al.*, 1976; Benedict & Grahame-Smith, 1978; Davies *et al.*, 1984; Frayn *et al.*, 1984b; see also Fig. 5).

Infusion of counter-regulatory hormones to simulate responses to injury

Attempts to simulate the metabolic responses to injury by infusion of catecholamines, cortisol and glucagon in combination (Bessey *et al.*, 1984; Gelfand *et al.*, 1984) show that a small elevation of counter-regulatory hormones persisting at 1 week after injury is unlikely to have much metabolic effect. Metabolic changes of only modest degree (e.g. < 10% elevation of metabolic rate, 4 g/d rise in urinary nitrogen excretion) are produced by raising the concentrations of these hormones to levels more characteristic of the early, ebb phase response for a period of 3 d (Gelfand *et al.*, 1984) (Table 2). It could perhaps be argued that the initial elevation and steady decline of cortisol concentrations seen after injury might induce a delayed rise in nitrogen excretion, but again this is not borne out experimentally; nitrogen loss rises within 2–3 d on commencing cortisol infusion, and returns again to baseline levels on the day after stopping the infusion (Gelfand *et al.*, 1984), in keeping with the demonstration in both man and rat that high concentrations of glucocorticoids, typical more of the ebb than the flow phase, are needed to stimulate muscle protein breakdown (Tomas *et al.*, 1979; Simmons *et al.*, 1984).

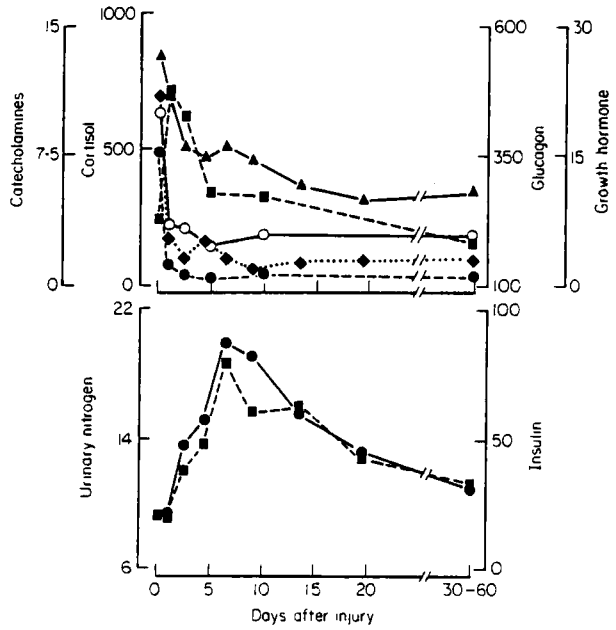

Fig. 5. Counter-regulatory hormone responses to accidental injury, and their relationship to urinary nitrogen excretion, and to plasma insulin concentrations.The patients were similar to those described by Frayn *et al.* (1984a,b), and had suffered musculoskeletal injuries with Injury Severity Scores ranging from 9 to 43. Mean values only are shown for clarity; $n = 4$–15, except for initial glucagon result where $n = 2$.

Top panel: adrenaline (●), noradrenaline (○) and cortisol (▲); glucagon (■); GH (♦). Lower panel: nitrogen (●); insulin (■). Results redrawn from Frayn *et al.* (1984b) except catecholamines and glucagon (see Acknowledgements).

Associated hormonal changes

The early rise in cortisol and other counter-regulatory hormones is accompanied by a depression of plasma somatomedin activity (Coates *et al.*, 1981a, 1981b; Frayn *et al.*, 1984b). This is of potential relevance since, apart from their role in collagen metabolism and hence wound healing and fracture repair, somatomedins may have a general anabolic function including stimulation of muscle protein synthesis (Salmon & DuVall, 1970; Phillips, 1979). However, once again, except in the critically injured in whom somatomedin activity may remain low (Coates *et al.*, 1981a, 1981b), this is an early and transient response, with normal or even elevated somatomedin activity returning within 4–5 d of injury (Frayn *et al.*, 1984b).

Although not normally classed as part of the counter-regulatory hormone response, the secretion and metabolism of thyroid hormones are also affected by injury. Again, there has been considerable interest in this subject because of the potential role of thyroid hormones in the metabolic responses to injury, increased metabolic rate and loss of body protein being prominent features of hyperthyroidism (Hoch, 1974). However, there are varying reports on the precise changes occurring after injury. A general consensus of the reports available (reviewed by Elliott & Alberti, 1983) would suggest that concentrations of T4 change little and in an inconsistent manner, but that there is a consistent and fairly prolonged rise in the rT3/T3 ratio with depressed absolute levels of T3 (e.g. Popp *et al.*,

Table 2. Levels of counter-regulatory hormones necessary to simulate metabolic responses to injury and sepsis: comparison with levels measured in patients

Group	Noradrenaline (nmol/l)	Adrenaline (nmol/l)	Cortisol (nmol/l)	Glucagon (pg/ml)
Patient studies				
Injured (1 week)	2·0 ± 0·9	0·3 ± 0·1	550 ± 180	260 ± 40
Septic	3·3 ± 2·3	0·8 ± 1·2	670 ± 300	150 ± 50
Infusion studies				
Bessey *et al.* (1984)	NM	2·3 ± 0·9	1110 ± 330	510 ± 200
Gelfand *et al.* (1984)	4·1 ± 1·7	2·1 ± 1·0	1160 ± 250	350 ± 150

NM, Not measured. Results are shown as mean ± SD.

'Infusion studies' consisted of infusion of a combination of adrenaline, cortisol and glucagon (with or without noradrenaline) into normal subjects for 3 d; mean plasma concentrations during infusion are shown. The metabolic changes produced (increase in metabolic rate, loss of nitrogen, resistance to insulin-mediated glucose storage) were similar both qualitatively and quantitatively to those observed in the patients (either 1 week after accidental injuries, or suffering from abdominal sepsis). Results in patients are collated from the sources given in Fig. 5 (injured), and from White *et al.* (1986) (septic).

1977; Prescott *et al.*, 1979; Elliott & Alberti, 1983). Since T3 is probably the main component responsible for both regulation of thermogenesis and stimulation of muscle proteolysis, rT3 being relatively inactive (Garrow, 1978; Burman *et al.*, 1979; Danforth, 1985), thyroid hormones would seem to have little role in the metabolic changes after injury.

Unresponsiveness to the anabolic effects of insulin

Plasma insulin concentrations after injury

One exception to the general picture of a fairly rapid return to endocrine normality after injury is the plasma insulin concentration. Plasma insulin concentrations, as discussed earlier, are generally depressed in relation to plasma glucose in the ebb phase after injury. They consistently rise, however, over the first few days following admission of the injured patient (Stoner *et al.*, 1979) and peak at about the time of the maximal catabolic response (Fig. 5); most patients, during the first one or two weeks after injury, will have at least one 'random morning' sample (not fasted) producing a result of over 100 mU/l (Frayn *et al.*, 1984b). The elevation of insulin concentrations is only in part a reflection of the removal of adrenergic restraint on secretion, allowing this to rise to match the prevailing moderate hyperglycaemia. Insulin concentrations over this period are inappropriately high for the plasma glucose concentration (Batstone *et al.*, 1976; Frayn *et al.*, 1984a) and show an exaggerated response to glucose infusion (Black *et al.*, 1982). Why the pancreas responds in this way is not clear. One suggestion (Frayn *et al.*, 1984a) is that this reflects the known potentiation of glucose-stimulated insulin secretion by amino acids (Gerich *et al.*, 1976); plasma concentrations of several amino acids are high at this stage

after injury (Woolf *et al.*, 1979; Askanazi *et al.*, 1980b), including that of arginine, a potent insulin secretagogue (Fajans *et al.*, 1967).

Insulin resistance

Perhaps the more interesting aspect of this elevation of insulin concentrations, however, is that they fail to exert their expected anabolic effects. This does, in fact, provide a unified way of looking at endocrine control of the metabolic changes after injury; these changes all reflect an unresponsiveness of 'net storage' or anabolic processes to the normal effects of insulin. Thus, glucose production is enhanced despite high glucose and insulin concentrations, while insulin mediated glucose storage is markedly reduced (Wolfe *et al.*, 1979; Black *et al.*, 1982). Fat mobilization and oxidation are increased (Askanazi *et al.*, 1980a; Stoner *et al.*, 1983; Frayn *et al.*, 1984a) despite the normal fat storage role of insulin. Most dramatically, protein turnover is resistant to the normal anabolic effect of insulin. This last point is shown clearly by the coincidence in time of the peaks in nitrogen excretion and in the plasma insulin concentration (Fig. 5); the time-courses of these two responses are so similar that a plot of nitrogen excretion against insulin concentration at various times after injury (Fig. 6) shows a striking positive relationship, rather than the negative relationship which might be expected from insulin's normal anabolic role (Rannels *et al.*, 1977).

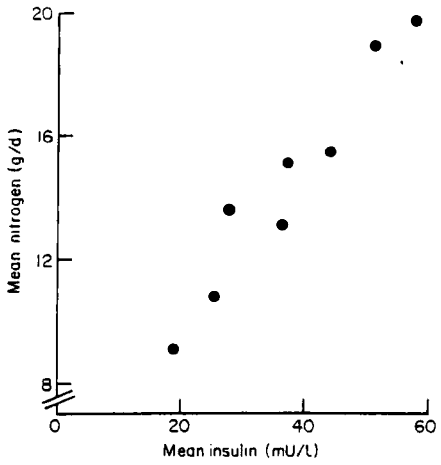

Fig. 6. Relationship between urinary nitrogen excretion and plasma insulin concentration at different stages of the response to injury. The positive relationship is highly significant ($r = 0{\cdot}97$, $P < 0{\cdot}001$). Based on mean values shown in Fig. 5.

Although the general concept of insulin resistance has been promoted for many years in connection with the response to injury (Butterfield, 1955; Howard, 1955; Hinton *et al.*, 1971), it may now be opportune to re-examine this in the light of current understanding of the mechanism of insulin's action: a study of insulin action at the tissue level, from receptor, through possible intermediates, to target pathways now seems to be called for.

Role of interleukin-1

As the difficulty of explaining the metabolic response to trauma in conventional endocrine terms has become apparent, other possible humoral mediators have come into prominence, especially the lymphokine interleukin-1 (IL-1), mentioned earlier as a possible afferent signal from wound to central nervous system. IL-1 has, over the past few years, been recognized as having a number of actions, both central and peripheral, which may be relevant to the responses to injury and sepsis. IL-1 is either a single substance or a group of closely-related substances with actions which were formerly attributed to a number of distinct factors; thus, IL-1 is now thought to combine the actions of: endogenous pyrogen (EP), raising the set-point in the hypothalamic temperature regulating centre; lymphocyte activating factor (LAF), potentiating the lymphocyte proliferative response to mitogens; and leukocytic endogenous mediator (LEM), the white cell-derived mediator responsible for inducing acute-phase reactant production in the liver and changing the plasma concentrations of certain divalent cations (iron and zinc downwards, copper upwards) (Dinarello, 1984; Kampschmidt, 1984). This picture was recently rounded off by the demonstration that purified human IL-1 also has a direct proteolysis-stimulating effect on muscle (Baracos *et al.*, 1983); IL-1 added to rat muscle incubated *in vitro* stimulates protein breakdown, with no effect on protein synthesis. Simultaneously, plasma from injured and septic patients was shown to contain a proteolysis-stimulating factor when tested in a similar system (Clowes *et al.*, 1983); this activity is now known as proteolysis-inducing factor (PIF) (Dinarello *et al.*, 1984; Fleck *et al.*, 1985). PIF, which has a molecular weight of 4·2 kd, is not the same as IL-1, which has a molecular weight of around 15 kd, but it has been argued that it is closely related, and perhaps an active cleavage product of IL-1 (Dinarello *et al.*, 1984).

This work provides a clear unifying hypothesis for many formerly diverse aspects of the responses to sepsis and trauma (Fleck *et al.*, 1985; Beisel, 1986; see Fig. 7). It is not necessarily in conflict with the picture suggested earlier of inhibition of insulin's net anabolic effects. It is interesting to speculate that perhaps IL-1 and insulin might interact at the level of prostaglandin synthesis. PIF exerts its proteolysis-stimulating effect on muscle, as EP does its pyrexial effect on the hypothalamus, through increased synthesis of PGE_2 (Baracos *et al.*, 1983; Goldberg *et al.*, 1984). Many of insulin's actions are now being linked to changes in prostaglandin production, and at least in the case of stimulation of protein synthesis this involves production of $PGF_{2\alpha}$ (Rodemann & Goldberg, 1982; Reeds & Palmer, 1983). Prostaglandins E_2 and $F_{2\alpha}$ are increasingly being recognized as having reciprocal regulatory effects, e.g. on cell growth (Taylor & Polgar, 1977) and more generally (Samuelsson *et al.*, 1978), and it is an attractive idea that in injury and sepsis the more 'catabolic' PGE_2 might predominate over the more 'anabolic' $PGF_{2\alpha}$.

However, as with all theories of the endocrine control of metabolism after injury, there are unanswered questions. The link between PIF and IL-1 remains to be clarified; now that the IL-1 genes from mouse and man have been cloned and sequenced (Lomedico *et al.*, 1984; March *et al.*, 1985) this should hopefully soon be possible by sequence studies. The effect of IL-1 on muscle protein is mediated primarily through a stimulation of protein breakdown (Baracos *et al.*, 1983), whereas the net proteolysis seen in injured and septic patients reflects, at least in moderately severe conditions, mainly a decrease in protein synthesis (Clague *et al.*, 1983; Rennie, 1985). Furthermore, we do not yet know the time-course of IL-1 production after injury, and circumstantial evidence would

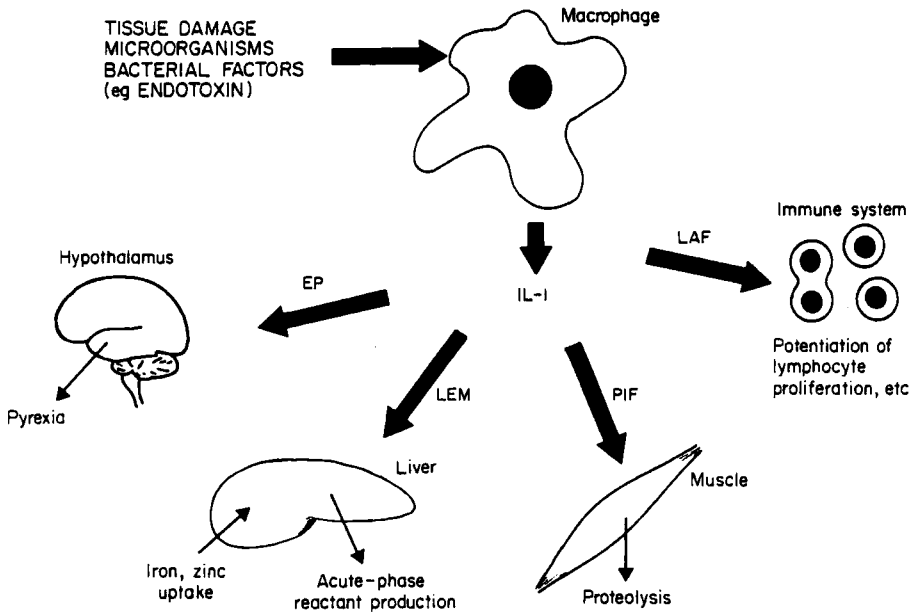

Fig. 7. Suggested integrative role of interleukin-1 (IL-1) in responses to injury and sepsis. For further details see the text. Based on Dinarello (1984), Kampschmidt (1984) and Fleck *et al.* (1985). EP, Endogenous pyrogen; LEM, leukocytic endogenous mediator; PIF, proteolysis-inducing factor; LAF, lymphocyte activating factor.

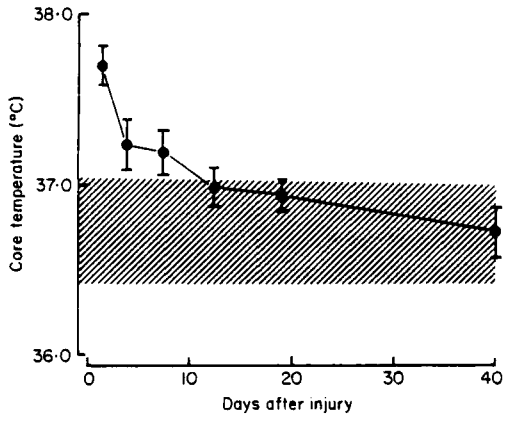

Fig. 8. Core temperature after accidental injury. Results are shown as mean ± SEM; $n = 10$–12. Shaded area shows normal range as one SD either side of mean. Plotted from results given in Frayn *et al.* (1984a).

suggest an early peak response, more like that of the counter-regulatory hormones than of the catabolic response (see Fig. 5). This evidence is based on other proposed actions of IL-1. Core temperature, for instance, which might be expected to reflect EP activity, follows a time-course after accidental injury similar to that of the counter-regulatory hormones, with a steady decline from soon after admission (Fig. 8). Acute-phase reactant production, reflecting LEM activity, is also stimulated from very soon after injury, and after an early peak (2–3 d after surgery, for instance) again returns gradually to baseline (Fleck *et al.*, 1985). Finally, direct attempts to investigate the role of IL-1 in man, stimulating its production by means of etiocholanolone injection (Wilmore, 1986b) have failed to find effects on protein metabolism, although when combined with counter-regulatory hormone infusion (again at high levels) many of the responses to injury were simulated. In view of these difficulties, much work is needed before the suggested integrative role of IL-1 in the metabolic responses to trauma and sepsis can be fully accepted.

CONCLUSIONS

The metabolic changes occurring after injury and in sepsis are still, more than 60 years after their relatively complete description, a cause of significant morbidity and mortality. Although many of their deleterious aspects can be overcome by active nutritional support, this is primarily an empirical means of treatment. The hormonal environment which produces these changes has not been fully elucidated, at least in part because so much of the work in this area has been plagued by the study of small heterogeneous groups of patients at different stages in their response, by a failure to measure the hormones most likely to be relevant, and by an almost universal failure to attempt to relate the endocrine to the metabolic changes observed. This picture is now changing for the better as more interest is centred on the responses to trauma, and we are at last in a position to formulate testable hypotheses about the endocrine control of metabolism in trauma and sepsis. With injury ranking as the major cause of death in the under-40 year age group, and costing the United Kingdom's National Health Service £600 million every year (Irving, 1986), some major advances in understanding its effects, and providing a rational basis for its treatment, are clearly needed.

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REFERENCES

ALLISON, S.P., HINTON, P. & CHAMBERLAIN, M.J. (1968) Intravenous glucose-tolerance, insulin, and free-fatty-acid levels in burned patients. *Lancet*, **ii**, 1113–1116.

ASKANAZI, J., CARPENTIER, Y.A., ELWYN, D.H., NORDENSTRÖM, J., JEEVANANDAM, M., ROSENBAUM, S.H., GUMP, F.E. & KINNEY, J.M. (1980a) Influence of total parenteral nutrition on fuel utilization in injury and sepsis. *Annals of Surgery*, **191**, 40–46.

ASKANAZI, J., CARPENTIER, Y.A., MICHELSEN, C.B., ELWYN, D.H., FURST, P., KANTROWITZ, L.R., GUMP, F.E. & KINNEY, J.M. (1980b) Muscle and plasma amino acids following injury. Influence of intercurrent infection. *Annals of Surgery*, **192**, 78–85.

AULICK, L.H., WILMORE, D.W., MASON, A.D. & PRUITT, B.A. (1977) Influence of the burn wound on peripheral circulation in thermally injured patients. *American Journal of Physiology*, **233**, H520–H526.

BAKER, S.P., O'NEILL, B., HADDON, W. & LONG, W.B. (1974) The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *Journal of Trauma*, **14**, 187–196.

BARACOS, V., RODEMANN, H.P., DINARELLO, C.A. & GOLDBERG, A.L. (1983) Stimulation of muscle protein degradation and prostaglandin E_2 release by leukocytic pyrogen (interleukin-1). *New England Journal of Medicine*, **308**, 553–558.

BARTON, R.N. (1977) Effect of limb ischaemia and scalding on the concentrations of growth hormone and corticosterone in rat plasma. *Journal of Endocrinology*, **73**, 347–353.

BARTON, R.N. (ed) (1985) *Trauma and its Metabolic Problems. British Medical Bulletin, Vol. 41, Part 3.* Churchill Livingstone, London.

BARTON, R.N. & PASSINGHAM, B.J. (1980) Evidence for a role of glucocorticoids in the development of insulin resistance after ischaemic limb injury in the rat. *Journal of Endocrinology*, **86**, 363–370.

BARTON, R.N. & PASSINGHAM, B.J. (1981) Effect of binding to plasma proteins on the interpretation of plasma cortisol concentrations after accidental injury. *Clinical Science*, **61**, 399–405.

BARTON, R.N., STONER, H.B. & WATSON, S.M. (1984) Plasma cortisol and ACTH in the severely injured. *Archives of Emergency Medicine*, **1**, 170.

BATSTONE, G.F., ALBERTI, K.G.M.M., HINKS, L., SMYTHE, P., LAING, J.E., WARD, C.M., ELY, D.W. & BLOOM, S.R. (1976) Metabolic studies in subjects following thermal injury. *Burns*, **2**, 207–225.

BEISEL, W.R. (1986) Sepsis and metabolism. In *The Scientific Basis for the Care of the Critically Ill* (eds R.A. Little & K.N. Frayn), pp. 103–122. Manchester University Press, Manchester.

BENEDICT, C.R. & GRAHAME-SMITH, D.G. (1978) Plasma noradrenaline and adrenaline concentrations and dopamine-β-hydroxylase activity in patients with shock due to septicaemia, trauma and haemorrhage. *Quarterly Journal of Medicine*, NS **47**, 1–20.

BESSEY, P.Q., WATTERS, J.M., AOKI, T.T. & WILMORE, D.W. (1984) Combined hormonal infusion simulates the metabolic response to injury. *Annals of Surgery*, **200**, 264–281.

BLACK, P.R., BROOKS, D.C., BESSEY, P.Q., WOLFE, R.R. & WILMORE, D.W. (1982) Mechanisms of insulin resistance following injury. *Annals of Surgery*, **196**, 420–435.

BLOOM, S.R., DANIEL, P.M., JOHNSTON, D.I., OGAWA, O. & PRATT, O.E. (1973) Release of glucagon, induced by stress. *Quarterly Journal of Experimental Physiology*, **58**, 99–108.

BUCKINGHAM, J.C. (1985) Hypothalamo-pituitary responses to trauma. *British Medical Bulletin*, **41**, 203–211.

BURMAN, K.D., WARTOFSKY, L., DINTERMAN, R.E., KESLER, P. & WANNEMACHER, R.W. (1979) The effect of T3 and reverse T3 administration on muscle protein catabolism during fasting as measured by 3-methylhistidine excretion. *Metabolism*, **28**, 805–813.

BUTTERFIELD, W.J.H. (1955) Hypoglycaemic effect of dimercaprol (BAL) in burned patients and in diabetics with insulin-resistant hyperglycaemia. *Lancet*, **i**, 489–490.

CAHILL, G.F. (1976) Starvation in man. *Clinics in Endocrinology and Metabolism*, **5**, 397–415.

CANNON, W.B. (1920) *Bodily Changes in Pain, Hunger, Fear and Rage. An Account of Recent Researches into the Function of Emotional Excitement.* Appleton, New York.

CANNON, W.B. (1923) *Traumatic Shock.* Appleton, New York.

CAREY, L.C., CLOUTIER, C.T. & LOWERY, B.D. (1971) Growth hormone and adrenal cortical response to shock and trauma in the human. *Annals of Surgery*, **174**, 451–460.

CLAGUE, M.B., KEIR, M.J., WRIGHT, P.D. & JOHNSTON, I.D.A. (1983) The effects of nutrition and trauma on whole-body protein metabolism in man. *Clinical Science*, **65**, 165–175.

CLOWES, G.H.A., GEORGE, B.C., VILLEE, C.A. & SARAVIS, C.A. (1983) Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. *New England Journal of Medicine*, **308**, 545–552.

CLUTTER, W.E., BIER, D.M., SHAH, S.D. & CRYER, P.E. (1980) Epinephrine plasma metabolic clearance rates

and physiologic thresholds for metabolic and hemodynamic actions in man. *Journal of Clinical Investigation*, **66**, 94–101.

COATES, C.L., BURWELL, R.G., CARLIN, S.A., CASON, J.S., LITTLEJOHN, S., SELBY, C. & SWANNELL, A.J. (1981a) Somatomedin activity in plasma from burned patients with observations on plasma cortisol. *Burns*, **7**, 425–433.

COATES, C.L., BURWELL, R.G., CARLIN, S.A., MILLIGAN, G.F., LITTLEJOHN, S., LONDON, P.S., SELBY, C. & SWANNELL, A.J. (1981b) The somatomedin activity in plasma from patients with multiple mechanical injuries: with observations on plasma cortisol. *Injury*, **13**, 100–107.

CRYER, P.E. (1980) Physiology and pathology of the human sympathoadrenal neuroendocrine system. *New England Journal of Medicine*, **303**, 436–444.

CRYER, P.E. (1981) Glucose counterregulation in man. *Diabetes*, **30**, 261–264.

CUTHBERTSON, D.P. (1929) The influence of prolonged muscular rest on metabolism. *Biochemical Journal*, **23**, 1328–1345.

CUTHBERTSON, D.P. (1930) The disturbance of metabolism produced by bony and non-bony injury, with notes on certain abnormal conditions of bone. *Biochemical Journal*, **24**, 1244–1263.

CUTHBERTSON, D.P. (1942) Post-shock metabolic response. *Lancet*, **i**, 433–437.

CUTHBERTSON, D.P. (1980) Alterations in metabolism following injury: part 1. *Injury*, **11**, 175–189.

CUTHBERTSON, D.P., MCGIRR, J.L. & ROBERTSON, J.S.M. (1939) The effect of fracture of bone on the metabolism of the rat. *Quarterly Journal of Experimental Physiology*, **29**, 13–25.

DANFORTH, E. (1985) Hormonal adaptation to over- and underfeeding. In *Substrate and Energy Metabolism in Man* (eds J.S. Garrow & D. Halliday), pp. 155–168. John Libbey, London.

DANIEL, A.M., SHIZGAL, H.M. & MACLEAN, L.D. (1978) The anatomic and metabolic source of lactate in shock. *Surgery, Gynecology and Obstetrics*, **147**, 697–700.

DAVIES, C.L., NEWMAN, R.J., MOLYNEUX, S.G. & GRAHAME-SMITH, D.G. (1984) The relationship between plasma catecholamines and severity of injury in man. *Journal of Trauma*, **24**, 99–105.

DEIBERT, D.C. & DEFRONZO, R.A. (1980) Epinephrine-induced insulin resistance in man. *Journal of Clinical Investigation*, **65**, 717–721.

DETURCK, K.H. & VOGEL, W.H. (1982) Effects of acute ethanol on plasma and brain catecholamine levels in stressed and unstressed rats: evidence for an ethanol-stress interaction. *Journal of Pharmacology and Experimental Therapeutics*, **223**, 348–354.

DINARELLO, C.A. (1984) Interleukin-1. *Reviews of Infectious Diseases*, **6**, 51–95.

DINARELLO, C.A., CLOWES, G.H.A., GORDON, A.H., SARAVIS, C.A. & WOLFF, S.M. (1984) Cleavage of human interleukin 1: isolation of a peptide fragment from plasma of febrile humans and activated monocytes. *Journal of Immunology*, **133**, 1332–1338.

DUKE, J.H., JØRGENSEN, S.B., BROELL, J.R., LONG, C.L. & KINNEY, J.M. (1970) Contribution of protein to caloric expenditure following injury. *Surgery*, **68**, 168–174.

ELLIOTT, M. & ALBERTI, K.G.M.M. (1983) The hormonal and metabolic response to surgery and trauma. In *New Aspects of Clinical Nutrition* (eds G. Kleinberger, E. Deutsch), pp. 247–270. Karger, Basel.

EXTON, J.H. (1972) Gluconeogenesis. *Metabolism*, **21**, 945–990.

FAIN, J.N. (1980) Hormonal regulation of lipid mobilization from adipose tissue. In *Biochemical Actions of Hormones, Vol. 7.* (ed G. Litwack), pp. 119–204. Academic Press, New York.

FAJANS, S.S., FLOYD, J.C., KNOPF, R.F. & CONN, J.W. (1967) Effect of amino acids and proteins on insulin secretion in man. *Recent Progress in Hormone Research*, **23**, 617–662.

FLECK, A., COLLEY, C.M. & MYERS, M.A. (1985) Liver export proteins and trauma. *British Medical Bulletin*, **41**, 265–273.

FRAYN, K.N. (1982) Acute metabolic responses to injury. In *Topical Reviews in Accident Surgery, Vol. 2.* (eds N. Tubbs & P.S. London), pp. 47–66. Wright, Bristol.

FRAYN, K.N. (1985) Substrate turnover after injury. *British Medical Bulletin*, **41**, 232–239.

FRAYN, K.N., LE MARCHAND-BRUSTEL, Y. & FREYCHET, P. (1978) Studies on the mechanism of insulin resistance after injury in the mouse. *Diabetologia*, **14**, 337–341.

FRAYN, K.N., LITTLE, R.A. & THRELFALL, C.J. (1980) Protein metabolism after unilateral femoral fracture in the rat, and comparison with sham operation. *British Journal of Experimental Pathology*, **61**, 474–478.

FRAYN, K.N., STONER, H.B., BARTON, R.N., HEATH, D.F. & GALASKO, C.S.B. (1983) Persistence of high plasma glucose, insulin and cortisol concentrations in elderly patients with proximal femoral fractures. *Age and Ageing*, **12**, 70–76.

FRAYN, K.N., LITTLE, R.A., STONER, H.B. & GALASKO, C.S.B. (1984a) Metabolic control in non-septic patients with musculo-skeletal injuries. *Injury*, **16**, 73–79.

FRAYN, K.N., PRICE, D.A., MAYCOCK, P.F. & CARROLL, S.M. (1984b) Plasma somatomedin activity after injury in man and its relationship to other hormonal and metabolic changes. *Clinical Endocrinology*, **20**, 179–187.

FRAYN, K.N., LITTLE, R.A., MAYCOCK, P.F. & STONER, H.B. (1985) The relationship of plasma catecholamines to acute metabolic and hormonal responses to injury in man. *Circulatory Shock*, **16**, 229–240.

FREDHOLM, B.B. (1971) The effect of lactate in canine subcutaneous adipose tissue in situ. *Acta Physiologica Scandinavica*, **81**, 110–123.

GALSTER, A.D., CLUTTER, W.E., CRYER, P.E., COLLINS, J.A. & BIER, D.M. (1981) Epinephrine plasma thresholds for lipolytic effects in man. Measurements of fatty acid transport with [1-^{13}C]palmitic acid. *Journal of Clinical Investigation*, **67**, 1729–1738.

GARROW, J.S. (1978) *Energy Balance and Obesity in Man 2nd Edn*, pp. 98–101. Elsevier/North Holland, Amsterdam.

GELFAND, R.A., MATTHEWS, D.E., BIER, D.M. & SHERWIN, R.S. (1984) Role of counterregulatory hormones in the catabolic response to stress. *Journal of Clinical Investigation*, **74**, 2238–2248.

GERICH, J.E., CHARLES, M.A. & GRODSKY, G.M. (1976) Regulation of pancreatic insulin and glucagon secretion. *Annual Review of Physiology*, **38**, 353–388.

GIDDINGS, A.E.B., O'CONNOR, K.J., ROWLANDS, B.J., MANGNALL, D. & CLARK, R.G. (1976) The relationship of plasma glucagon to the hyperglycaemia and hyperinsulinaemia of surgical operation. *British Journal of Surgery*, **63**, 612–616.

GOLDBERG, A.L., BARACOS, V., RODEMANN, P., WAXMAN, L. & DINARELLO, C. (1984) Control of protein degradation in muscle by prostaglandins, Ca^{2+}, and leukocytic pyrogen (interleukin 1). *Federation Proceedings*, **43**, 1301–1306.

GOODMAN, H.M. (1970) Permissive effects of hormones on lipolysis. *Endocrinology*, **86**, 1064–1074.

HEATH, D.F. (1985) Subcellular aspects of the response to trauma. *British Medical Bulletin*, **41**, 240–245.

HEATH, D.F. & CORNEY, P.L. (1973) The effects of starvation, environmental temperature and injury on the rate of disposal of glucose by the rat. *Biochemical Journal*, **136**, 519–530.

HEMS, D.A. & WHITTON, P.D. (1973) Stimulation by vasopressin of glycogen breakdown and gluconeogenesis in the perfused rat liver. *Biochemical Journal*, **136**, 705–709.

HEMS, D.A. & WHITTON, P.D. (1980) Control of hepatic glycogenolysis. *Physiological Reviews*, **60**, 1–50.

HESSMAN, Y. & THORÉN, L. (1975) Glycogen storage in rat liver and skeletal muscle in thermal trauma. *Acta Chirurgica Scandinavica*, **141**, 385–392.

HINTON, P., ALLISON, S.P., LITTLEJOHN, S. & LLOYD, J. (1971) Insulin and glucose to reduce catabolic response to injury in burned patients. *Lancet*, **i**, 767–769.

HOCH, F.L. (1974) Metabolic effects of thyroid hormones. In *Handbook of Physiology, Section 7, Vol. 3.* (Section eds R.O. Green & E.B. Astwood), pp. 391–411. American Physiological Society, Washington.

HOWARD, J.M. (1955) Studies of the absorption and metabolism of glucose following injury. *Annals of Surgery*, **141**, 321–326.

IRVING, M.H. (1986) Trauma research in the North West of England—the background. In *The Scientific Basis for the Care of the Critically Ill* (eds R.A. Little & K.N. Frayn), pp. 11–13. Manchester University Press, Manchester.

KAMPSCHMIDT, R.F. (1984) The numerous postulated biological manifestations of interleukin-1. *Journal of Leukocyte Biology*, **36**, 341–355.

KOVÁCH, A.G.B., ROSELL, S., SÁNDOR, P., KOLTAY, E., KOVÁCH, E. & TOMKA, N. (1970) Blood flow, oxygen consumption, and free fatty acid release in subcutaneous adipose tissue during hemorrhagic shock in control and phenoxybenzamine-treated dogs. *Circulation Research*, **26**, 733–741.

LINDSEY, C.A., FALOONA, G.R. & UNGER, R.H. (1975) Plasma glucagon levels during rapid exsanguination with and without adrenergic blockade. *Diabetes*, **24**, 313–316.

LITTLE, R.A. (1985) Heat production after injury. *British Medical Bulletin*, **41**, 226–231.

LITTLE, R.A., STONER, H.B. & FRAYN, K.N. (1981) Substrate oxidation shortly after accidental injury in man. *Clinical Science*, **61**, 789–791.

LITTLE, R.A., FRAYN, K.N., RANDALL, P.E., STONER, H.B. & MAYCOCK, P.F. (1985a) Plasma catecholamine concentrations in acute states of stress and trauma. *Archives of Emergency Medicine*, **2**, 46–47.

LITTLE, R.A., FRAYN, K.N., RANDALL, P.E., STONER, H.B., YATES, D.W., LAING, G.S., KUMAR, S. & BANKS, J.M. (1985b) Plasma catecholamines in patients with acute myocardial infarction and in cardiac arrest. *Quarterly Journal of Medicine*, **NS 54**, 133–140.

LITTLE, R.A., FRAYN, K.N., RANDALL, P.E., STONER, H.B., MORTON, C., YATES, D.W. & LAING, G.S. (1986) Plasma catecholamines in the acute phase of the response to myocardial infarction. *Archives of Emergency Medicine*, **3**, 20–27.

LOMEDICO, P.T., GUBLER, U., HELLMANN, C.P., DUKOVICH, M., GIRI, J.G., PAN, Y-C.E., COLLIER, K., SEMIONOW, R., CHUA, A.O. & MIZEL, S.B. (1984) Cloning and expression of murine interleukin-1 cDNA in *Escherichia coli*. *Nature*, **312**, 458–462.

LONG, C.N.H., KATZIN, B. & FRY, E.G. (1940) The adrenal cortex and carbohydrate metabolism. *Endocrinology*, **26**, 309–344.

LONG, C.L., SPENCER, J.L., KINNEY, J.M. & GEIGY, J.W. (1971) Carbohydrate metabolism in man: effect of elective operations and major injury. *Journal of Applied Physiology*, **31**, 110–116.

MACDONALD, I.A., BENNETT, T. & FELLOWS, I.W. (1985) Catecholamines and the control of metabolism in man. *Clinical Science*, **68**, 613–619.

MACK, E. & EGDAHL, R.H. (1970) Adrenal blood flow and corticosteroid secretion in hemorrhagic shock. *Surgery, Gynecology and Obstetrics*, **131**, 65–71.

MARCH, C.J., MOSLEY, B., LARSEN, A., CERRETTI, D.P., BRAEDT, G., PRICE, V., GILLIS, S., HENNEY, C.S., KRONHEIM, S.R., GRABSTEIN, K., CONLON, P.J., HOPP, T.P. & COSMAN, D. (1985) Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. *Nature*, **315**, 641–647.

MEGUID, M.M., BRENNAN, M.F., MULLER, W.A. & AOKI, T.T. (1972) Glucagon and trauma. *Lancet*, **ii**, 1145.

MILLER, H.I., ISSEKUTZ, B., PAUL, P. & RODAHL, K. (1964) Effect of lactic acid on plasma free fatty acids in pancreatectomized dogs. *American Journal of Physiology*, **207**, 1226–1230.

PERKOFF, G.T., SILBER, R., TYLER, F.H., CARTWRIGHT, G.E. & WINTROBE, M.M. (1959) Studies in disorders of muscle. XII. Myopathy due to the administration of therapeutic amounts of 17-hydroxycorticosteroids. *American Journal of Medicine*, **26**, 891–898.

PHILLIPS, L.S. (1979) Nutritional regulation of somatomedin activity and growth. In *Somatomedins and Growth. Serono Symposia, Vol. 23*. (eds G. Giordano, J.J. Van Wyk & F. Minuto). Academic Press, London.

POPP, M.B., SRIVASTAVA, L.S., KNOWLES, H.C. & MACMILLAN, B.G. (1977) Anterior pituitary function in thermally injured male children and young adults. *Surgery, Gynecology and Obstetrics*, **145**, 517–524.

PORTE, D. & ROBERTSON, R.P. (1973) Control of insulin secretion by catecholamines, stress, and the sympathetic nervous system. *Federation Proceedings*, **32**, 1792–1796.

PRESCOTT, R.W.G., YEO, P.P.B., WATSON, M.J., JOHNSTON, I.D.A., RATCLIFFE, J.G. & EVERED, D.C. (1979) Total and free thyroid hormone concentrations after elective surgery. *Journal of Clinical Pathology*, **32**, 321–324.

RANNELS, D.E., MCKEE, E.E. & MORGAN, H.E. (1977) Regulation of protein synthesis and degradation in heart and skeletal muscle. In *Biochemical Actions of Hormones, Vol. 4*. (ed G. Litwack), pp. 135–195. Academic Press, New York.

REEDS, P.J. & PALMER, R.M. (1983) The possible involvement of prostaglandin $F_{2\alpha}$ in the stimulation of muscle protein synthesis by insulin. *Biochemical and Biophysical Research Communications*, **116**, 1084–1090.

RENNIE, M.J. (1985) Muscle protein turnover and the wasting due to injury and disease. *British Medical Bulletin*, **41**, 257–264.

RENNIE, M.J. & EDWARDS, R.H.T. (1981) Carbohydrate metabolism of skeletal muscle and its disorders. In *Carbohydrate Metabolism and its Disorders, Vol. 3*. (eds F. Dickens, P.J. Randle & W. Whelan), pp. 1–118. Academic Press, London.

RODEMANN, H.P. & GOLDBERG, A.L. (1982) Arachidonic acid, prostaglandin E_2 and $F_{2\alpha}$ influence rates of protein turnover in skeletal and cardiac muscle. *Journal of Biological Chemistry*, **257**, 1632–1638.

ROFE, A.M. & WILLIAMSON, D.H. (1983) Mechanism for the 'anti-lipolytic' action of vasopressin in the starved rat. *Biochemical Journal*, **212**, 899–902.

ROSE, J.G. & HEATH, D.F. (1986) The effects of stress and injury on the activity of phosphoenolpyruvate carboxykinase in the liver of the rat. *Biochemical Journal*, **233**, 239–244.

SALMON, W.D. & DUVALL, M.R. (1970) *In vitro* stimulation of leucine incorporation into muscle and cartilage protein by a serum fraction with sulfation factor activity: differentiation of effects from those of growth hormone and insulin. *Endocrinology*, **87**, 1168–1180.

SALTER, C.P., FLUCK, D.C. & STIMMLER, L. (1972) Effect of open-heart surgery on growth-hormone levels in man. *Lancet*, **ii**, 853–854.

SAMUELSSON, B., GOLDYNE, M., GRANSTRÖM, E., HAMBERG, M., HAMMARSTRÖM, S. & MALMSTEN, C. (1978) Prostaglandins and thromboxanes. *Annual Review of Biochemistry*, **47**, 997–1029.

SEAR, J.W., ALLEN, M.C., GALES, M., MCQUAY, H.J., KAY, N.H., MCKENZIE, P.J. & MOORE, R.A. (1983) Suppression by etomidate of normal cortisol response to anaesthesia and surgery. *Lancet*, **ii**, 1028.

SCHØNHEYDER, F., HEILSKOV, N.S.C. & OLESEN, K. (1954) Isotopic studies on the mechanism of negative nitrogen balance produced by immobilization. *Scandinavian Journal of Clinical and Laboratory Investigation*, **6**, 178–188.

SHAMOON, H., HENDLER, R. & SHERWIN, R.S. (1981) Synergistic interactions among antiinsulin hormones in the pathogenesis of stress hyperglycemia in humans. *Journal of Clinical Endocrinology and Metabolism*, **52**, 1235–1241.

SHENKIN, A., NEUHÄUSER, M., BERGSTRÖM, J., CHAO, L., VINNARS, E., LARSSON, J., LILJEDAHL, S-O., SCHILDT, B. & FURST, P. (1980) Biochemical changes associated with severe trauma. *American Journal of Clinical Nutrition*, **33**, 2119–2127.

SIMMONS, P.S., MILES, J.M., GERICH, J.E. & HAYMOND, M.W. (1984) Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range. *Journal of Clinical Investigation*, **73**, 412–420.

STONER, H.B. (1958) Studies on the mechanism of shock. The quantitative aspects of glycogen metabolism after limb ischaemia in the rat. *British Journal of Experimental Pathology*, **39**, 635–651.

STONER, H.B. & MATTHEWS, J. (1967) Studies on the mechanism of shock. Fat mobilization after injury. *British Journal of Experimental Pathology*, **48**, 58–65.

STONER, H.B., BARTON, R.N., LITTLE, R.A. & YATES, D.W. (1977) Measuring the severity of injury. *British Medical Journal*, **ii**, 1247–1249.

STONER, H.B., FRAYN, K.N., BARTON, R.N., THRELFALL, C.J. & LITTLE, R.A. (1979) The relationships between plasma substrates and hormones and the severity of injury in 277 recently injured patients. *Clinical Science*, **56**, 563–573.

STONER, H.B., FRAYN, K.N., LITTLE, R.A., THRELFALL, C.J., YATES, D.W., BARTON, R.N. & HEATH, D.F. (1980) Metabolic aspects of hypothermia in the elderly. *Clinical Science*, **59**, 19–27.

STONER, H.B., LITTLE, R.A., FRAYN, K.N., ELEBUTE, A.E., TRESADERN, J. & GROSS, E. (1983) The effect of sepsis on the oxidation of carbohydrate and fat. *British Journal of Surgery*, **70**, 32–35.

TAYLOR, L. & POLGAR, P. (1977) Self regulation of growth by human diploid fibroblasts via prostaglandin production. *FEBS Letters*, **79**, 69–72.

THRELFALL, C.J., STONER, H.B. & GALASKO, C.S.B. (1981) Patterns in the excretion of muscle markers after trauma and orthopedic surgery. *Journal of Trauma*, **21**, 140–147.

THRELFALL, C.J., MAXWELL, A.R. & STONER, H.B. (1984) Post-traumatic creatinuria. *Journal of Trauma*, **24**, 516–523.

TOMAS, F.M., MUNRO, H.N. & YOUNG, V.R. (1979) Effect of glucocorticoid administration on the rate of muscle protein breakdown *in vivo* in rats, as measured by urinary excretion of N^{τ}-methylhistidine. *Biochemical Journal*, **178**, 139–146.

VITEK, V., LANG, D.J. & COWLEY, R.A. (1979) Admission serum insulin and glucose levels in 247 accident victims. *Clinica Chimica Acta*, **95**, 93–104.

WALKER, W.F., SHOEMAKER, W.C., KAALSTAD, A.J. & MOORE, F.D. (1959) Influence of blood volume restoration and tissue trauma on corticosteroid secretion in dogs. *American Journal of Physiology*, **197**, 781–785.

WHITE, R.H., FRAYN, K.N., LITTLE, R.A., THRELFALL, C.J., STONER, H.B. & IRVING, M.H. (1986) Hormonal and metabolic responses to glucose infusion in sepsis studied using the hyperglycemic glucose clamp technique. *Journal of Parenteral and Enteral Nutrition*, in press.

WICKLMAYR, M. & DIETZE, G. (1978) On the mechanism of glucose release from the muscle of juvenile diabetics in acute insulin deficiency. *European Journal of Clinical Investigation*, **8**, 81–86.

WILMORE, D.W. (1977) *The Metabolic Management of the Critically Ill*. Plenum, New York.

WILMORE, D.W. (1986a) The wound as an organ. In *The Scientific Basis for the Care of the Critically Ill* (eds R.A. Little & K.N. Frayn), pp. 45–59. Manchester University Press, Manchester.

WILMORE, D.W. (1986b) Are the metabolic alterations associated with critical illness related to the hormonal environment? *Clinical Nutrition*, **5**, 9–20.

WILMORE, D.W., LONG, J.M., MASON, A.D., SKREEN, R.W. & PRUITT, B.A. (1974) Catecholamines: mediator of the hypermetabolic response to thermal injury. *Annals of Surgery*, **180**, 653–669.

WILMORE, D.W. & AULICK, L.H. (1978) Metabolic changes in burned patients. *Surgical Clinics of North America*, **58**, 1173–1187.

WOLFE, R.R., DURKOT, M.J., ALLSOP, J.R. & BURKE, J.F. (1979) Glucose metabolism in severely burned patients. *Metabolism*, **28**, 1031–1039.

WOOLF, L.I., MOORE, J.P., GROVES, A.C. & DUFF, J.H. (1979) Arterial plasma amino acids during the first week following femoral shaft fracture. *Journal of Trauma*, **19**, 244–247.

ZENSER, T.V., DERUBERTIS, F.R., GEORGE, D.T. & RAYFIELD, E.J. (1974) Infection-induced hyperglucagonemia and altered hepatic response to glucagon in the rat. *American Journal of Physiology*, **227**, 1299–1305.