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Student Symposium

Some aspects of the metabolic response to surgical trauma

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The metabolic response to trauma is characterized by hypermetabolism, increased N excretion, accelerated fluxes of substrates (particularly glucose) between organs, and anorexia (Wilmore & Kinney, 1981). The combination of hypermetabolism and anorexia leads to negative energy and N balance. In the case of patients undergoing surgery, this situation is often superimposed on a state of nutritional depletion caused by pre-existing disease. The result is the high incidence of malnutrition among surgical patients which has been reported frequently over the past 30 years (Bistrian *et al.* 1974; Hill, 1977; McWhirter & Pennington, 1994), and which is known to cause a longer stay in hospital, a greater risk of infectious complications and an increase in the post-operative mortality rate. Although this area has been the subject of considerable research in recent years, the relative importance of the acute response to surgical trauma, compared with the chronic disease-induced depletion, in causing malnutrition and hence adverse clinical consequences is still far from clear. Furthermore, it is not clear whether the existence of previous undernutrition affects the magnitude of the acute metabolic response to surgery, and if it does, how this affects the ultimate clinical outcome.

One of the difficulties in carrying out these investigations has been assembling homogeneous groups of patients with the same severity of disease, nutritional depletion, surgical intervention and presence of septic complication. Moreover, metabolic studies have rarely been carried out longitudinally, yet this is crucial to understanding both the immediate effect of surgery and the longer-term consequences. Under these circumstances it can be useful to employ animal models, and there are reports in the literature of studies ranging from the relatively mild effects of single-impact blunt trauma (Fisher *et al.* 1991) to the severe effects of extensive burns (Al-Shamma *et al.* 1979). Our own studies have concentrated on the effects of moderate surgery in the form of hysterectomy in rats.

The present paper will review some of the effects of surgical trauma on food intake, body composition, energy expenditure and fuel utilization in both human and animal studies, with some comments on their interaction with malnutrition.

Food intake after injury

It is generally accepted that injury causes anorexia, but there are surprisingly few studies which document the magnitude of this effect. This may be partly due to the difficulty of measuring food intake reliably. Some studies in which energy intake was measured over periods from 7 to 12 d after gastrointestinal surgery are listed in Table 1. The results show a considerable degree of consistency.

It should be noted that in most of these studies there had been a period of approximately 5 d immediately after the operation during which intake was zero or minimal, before the measurements began. Studies of non-gastrointestinal surgery have shown similarly low food intakes, although the period of post-operative starvation would have been shorter (Manners, 1974; Hessov, 1977; Walesby *et al.* 1979). The studies were all uncontrolled, and indeed it is difficult to identify appropriate control data with which to compare these values, but these results seem to indicate that many patients experience a deficit of at least 50 % in food intake over a 2–3 week post-operative period. The study by Keele *et al.* (1997) also showed that the anorexia lasts for a considerable time after the immediate post-operative period, as intakes continued to rise during the second month after discharge from hospital.

Studies in rats have shown a much greater range of responses (Table 2), although the time frame is much shorter. Burn injuries appear to cause only minor and transient decreases in food intake, in contrast with the prolonged elevation of energy expenditure and negative energy balance reported in these animals (Al-Shamma *et al.* 1979). Blunt trauma to the limbs had no effect on food intake, whereas abdominal surgery depressed food intake for several days. There is some evidence that the magnitude of the decrease is related to the severity of the operation, with hysterectomy (Bosagh Zadeh & Emery, 1997) causing a greater and more prolonged reduction in food intake than simple laparotomy (Emery & Ghusain-Choueiri, 1994).

Food intake is controlled by a variety of physiological and psychological mechanisms. We have begun to investigate the causes of surgical anorexia by measuring average meal size and meal frequency, and have found that

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Table 1. Average energy intake during 7–12 d periods following gastrointestinal surgery and post-operative starvation

Study	No. of patients	Energy intake (MJ/d)
Isaksson *et al.* (1960)	7	3·4
Solem *et al.* (1963)	17	4·0
Hessov & Wara (1978)	21	4·1
Hackett *et al.* (1979)	12	4·0
Hoover *et al.* (1980)	22	3·4
Keele *et al.* (1997)	43	5·0

the major cause was a decrease in meal size, indicating premature satiety rather than reduced hunger (Bosagh Zadeh & Emery, 1997). This contrasts with findings in tumour-bearing rats, where tumour growth caused a sustained reduction in meal frequency, which may have been caused by a prolonged high rate of postprandial glycogen synthesis in the liver, delaying the initiation of the next meal (Obeid & Emery, 1992). No such changes in hepatic carbohydrate metabolism have been found in the present surgical model (AR Bosagh Zadeh and PW Emery, unpublished results). Meguid *et al.* (1996) have also concluded that anorexia in different pathological situations may be caused by different changes in meal size and meal frequency. In most chronic situations meal frequency was the more severely affected, but injection of an antagonist to the interleukin-1 receptor caused an acute decrease in meal size. There is increasing evidence that cytokines, particularly interleukin-1, interleukin-6 and tumour necrosis factor, are involved in mediating the systemic effects of surgery, including anorexia (McCarthy *et al.* 1985; Lowry, 1992; Shenkin, 1994).

Body composition

When the energy intake of a healthy individual is reduced to below the level of energy expenditure, the body adapts to reduce the amount of urea excreted and thus minimize the amount of lean tissue that is broken down. The response to injury is clearly different, as the main feature that Cuthbertson (1930) noted when he first investigated the metabolic response to injury was an increase in urinary N excretion. Hence, there is concern that prolonged excessive N loss will lead to breakdown of protein from organs and tissues such as the heart and the respiratory muscles, with severe functional consequences.

Not all studies in the literature show clear evidence of excessive loss of protein as compared with fat following surgery. For example, Kinney *et al.* (1968) used indirect calorimetry and urinary N measurements to calculate the proportions of protein and fat lost after elective abdominal surgery and found that protein only accounted for 10–25 % of the energy deficit. Streat & Hill (1987), using sophisticated techniques to measure body composition directly, found that protein accounted for 27 % of the energy content of tissue lost over 14 d following major elective surgery. In contrast, they found that all the tissue lost by patients who had suffered major accidental trauma or had serious sepsis was lean tissue, suggesting that the composition of the tissue lost may depend on the severity and type of the injury. However, the patients in the latter two groups were receiving adequate amounts of parenteral or enteral nutritional support, so it may simply be that it is easier to prevent fat loss than lean tissue loss by nutritional support. It should also be noted that the initial measurements of body composition in these two groups were not made until approximately 6 d after the injury, thus more fat may have been lost at an earlier stage.

Indirect calorimetry has also been performed on rats after femur fracture. Cairnie *et al.* (1957) found only a small (7 %) increase in energy expenditure, which could all be accounted for by increased N excretion, whereas Miksche & Caldwell (1967) found that protein could only account for 24 % of the excess heat production. Carcass analysis of rats 57 d after burn injury showed a tissue deficit to which protein contributed 28 % in energetic terms (Al-Shamma *et al.* 1979). Our own studies have shown that protein only accounted for 23 % of the energy deficit 4 d after hysterectomy, and this was no greater than the corresponding value in pair-fed controls (AR Bosagh Zadeh and PW Emery, unpublished results).

It should also be noted that extra fluid was found to be retained in the body in many of these studies, adding a further difficulty to the prediction of changes in body fat and cell mass from changes in body weight.

Energy expenditure

It is well established that energy expenditure increases following injury, and that the magnitude of the increase depends on the severity of the injury. However, early estimates of the scale of the increase appear to have been exaggerated, and there has been a downward revision in recent years. Some typical results are shown in Table 3, in which measurements of resting metabolic rate are compared with predicted values based on the Harris–Benedict equation (for males, $BMR = 66{\cdot}5 + 13{\cdot}75W + 5H - 6{\cdot}8A$; for females, $BMR = 66{\cdot}5 + 9{\cdot}6W + 1{\cdot}85H - 4{\cdot}7A$; where BMR is expressed in kcal/d, W is weight (kg), H is height

Table 2. Decrease in food intake in rats following injury

Study	Type of injury	Period of time after injury (d)	Decrease (%)
Al-Shamma *et al.* (1979)	Burn	2–3	< 50
Lee *et al.* (1988)	Burn	2	< 25
Downey *et al.* (1986)	Burn	4	NS
Tischler & Fagan (1983)	Blunt trauma	4	NS
Fisher *et al.* (1991)	Blunt trauma	3	NS
Lee *et al.* (1991)	Hysterectomy	3	20–50
Emery & Ghusain-Choueiri (1994)	Laparotomy	2	20–50
Bosagh Zadeh & Emery (1997)	Hysterectomy	5	20–80

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(cm), A is age (years); Harris & Benedict, 1912). This is the most common way in which the results of such studies are presented. Thus, Quebbeman *et al.* (1982) actually found no significant increase in metabolic rate in heterogeneous groups of patients described as malnourished, catabolic or stressed. Kinney *et al.* (1968) have shown that during uncomplicated post-operative convalescence many patients will have a resting energy expenditure within 10 % of their pre-operative value. Even with severe burns or sepsis the increase appears only to be approximately 15–25 %. On the other hand, Monk *et al.* (1996) found increases up to 55 % in patients who had suffered severe accidental trauma, and they report metabolic rate still elevated by 35 % as late as 25 d after the injury. These authors also point out that the Harris–Benedict equation may overestimate resting metabolic rate if there is fluid retention leading to artefactually high body weight. It should also be remembered that the normal response to decreased food intake is a decrease in metabolic rate, as observed by Gil *et al.* (1985) in their group of 'depleted patients'. Hence, these results may represent a rather greater increment above the metabolic rate appropriate for the plane of nutrition of the patients.

Resting energy expenditure, measured in the post-absorptive state, is not the only component of total energy expenditure. Physical activity will, of course, be severely restricted after injury. On the other hand, there is some evidence that the thermic effect of feeding may be increased. Gil *et al.* (1985) reported that septic and injured patients showed a 25 % increase in O_2 consumption on moving from a 50 g D-glucose/l infusion to total parenteral nutrition, whereas depleted but uninjured patients showed only a 5 % increase.

Calorimetric studies in experimental animals have shown increases in metabolic rate of 7–14 % after femur fracture (Cairnie *et al.* 1957; Miksche & Caldwell, 1967), 15 % after scalding and 40 % after excision of 5 % of the skin (Downey *et al.* 1986).

We have used the comparative carcass technique to measure energy balance, and have found that hysterectomy caused a 33 % increase in energy expenditure compared with pair-fed controls. When the same experiment was repeated with rats which had been malnourished by restricting their intake of protein and energy, there was still a significant increase in energy expenditure but the magnitude was reduced to 22 % (Bosagh Zadeh & Emery, 1998). Malnutrition has previously been shown to suppress other aspects of the metabolic response to injury, e.g. the rise in urinary N (Munro & Cuthbertson, 1943; Abbott & Albertsen, 1963), the acute-phase-protein response (Cruikshank *et al.* 1990), anorexia and the redistribution of protein between tissues (Jennings & Elia, 1996), although the secretion of the cytokine interleukin-6 remains normal (Curtis *et al.* 1993). It has been postulated that the catabolic response is necessary for optimal recovery subsequently, and that any blunting of the response by malnutrition may have adverse clinical consequences, but there is no direct evidence for this at present.

Fuel utilization

A number of quantitative changes in intermediary metabolism have been identified which may account for the increase in metabolic rate following injury. Gluconeogenesis is known to be increased, and the rate of recycling of glucose in a glycolysis–gluconeogenesis cycle was found to be increased by 250 % in burned patients (Wolfe *et al.* 1987). Amino acids released from the breakdown of lean tissue protein are also important precursors for gluconeogenesis, and there is a glucose–alanine cycle analogous to the glucose–lactate cycle. Another so-called futile cycle involves lipolysis and re-esterification of fatty acids, and the activity of this cycle is increased by 450 % in burned patients (Wolfe *et al.* 1987); similar increases have been reported in injured and septic patients (Jeevanandam *et al.* 1990).

The respiratory exchange ratio in injured patients is consistently lower than normal for a given level of intake (Jeevanandam *et al.* 1990), indicating a greater rate of fat oxidation. Thus, fat oxidation provides the energy to drive the gluconeogenic cycles and the lipolysis–re-esterification cycle. Infusion of glucose in amounts which lead to net synthesis of fat in normal volunteers or depleted controls fails to suppress fat oxidation in injured and septic patients, leaving them in negative fat balance (Gil *et al.* 1985; Jeevanandam *et al.* 1990).

Our investigations of the partitioning of fuel utilization in post-operative rats have involved offering a choice between diets of differing fat and carbohydrate contents. The rats showed only a small and transient decrease in carbohydrate intake, but a significant and sustained decrease in fat intake (Fig. 1). We interpret this as a response to the release of fatty

Table 3. Resting energy expenditure in patients (difference (%) between measured and predicted* values)

Study	Patient group	No. of patients	Difference (%)
Quebbeman *et al.* (1982)	Malnourished	8	NS
	Stressed	20	NS
	Catabolic	16	NS
Roulet *et al.* (1983)	Sepsis	11	+15
Gil *et al.* (1985)	Protein–energy depleted	18	−21
	Septic or injured	14	+14
Wolfe *et al.* (1987)	Severe burns	8	+23
Jeevanandam *et al.* (1990)	Injured	5	+9
	Septic	3	+13
Monk *et al.* (1996)	Critically injured	10	+55

* Calculated using Harris–Benedict equation (Harris & Benedict, 1912): for males, BMR = 66·5 + 13·75W + 5H − 6·8A; for females, BMR = 66·5 + 9·6W + 1·85H − 4·7A; where BMR is expressed in kcal/d, W is weight (kg), H is height (cm), A is age (years).

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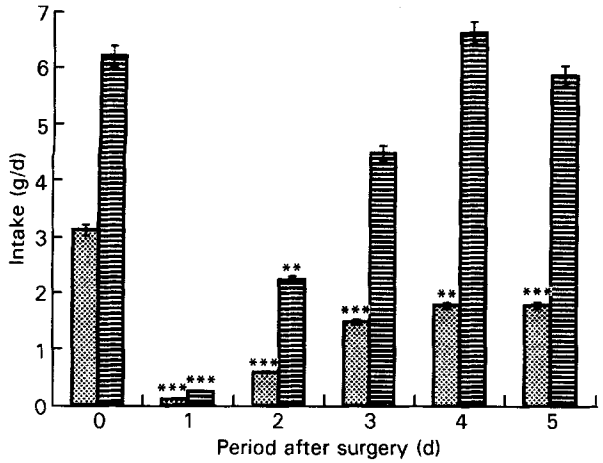

Fig. 1. Intakes of fat (▨) and carbohydrate (▤) in rats offered a choice between a high-fat–low-carbohydrate diet and a low-fat–high-carbohydrate diet before and after surgery. Values are means with their standard errors represented by vertical bars. Day 0 values represent mean intake during the 3 d preceding surgery. Mean values were significantly different from those at day 0: $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$.

acids by the breakdown of triacylglycerol stores in adipose tissue. Thus, increased lipolysis appears to be an obligatory component of the metabolic response to injury, and may act as an initiator of subsequent events. We have found that blocking lipolysis by administering Acipimox (5-methylpyrazine-carboxylic acid 4-oxide, an analogue of nicotinic acid; Farmitalia Carlo Erba, Milan, Italy) causes a small but significant attenuation of the increase in energy expenditure following surgery and, thus, an improvement in energy balance (AR Bosagh Zadeh and PW Emery, unpublished results).

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