Surgical procedures evoke an endocrine response which results in substrate mobilization, a change in metabolism towards catabolism with a negative nitrogen balance and retention of salt and water. The magnitude of this response is proportional to the severity of the operative trauma. Intra-abdominal procedures are associated with a much greater response than body surface surgery (Clarke, 1970; Clarke, Johnston and Sheridan, 1970) and cardiac surgery with cardiopulmonary bypass induces profound hormonal and biochemical changes (Stanley et al., 1979).

There is a vast and often conflicting literature on the hormonal and metabolic response to surgery. The purpose of this short article is not to present a complete review of the subject but rather to provide the necessary background information to enable the results described in more detailed studies to be readily interpreted.

Hormones

The initial response to surgical trauma is an increase in the circulating concentrations of the catabolic hormones such as catecholamines, glucagon and cortisol and a concomitant decrease in plasma concentrations of the anabolic hormones, insulin and testosterone. The plasma concentration of cyclic AMP, the common intracellular second messenger for hormones with β-adrenergic agonist activity, has been shown to increase in proportion to the severity of the surgery (Nistrup Madsen et al., 1976). It is not known precisely which hormones are responsible for this increase in plasma cyclic AMP, but Nistrup Madsen and colleagues (1978) have shown a good correlation between changes in plasma adrenaline and cyclic AMP values.

Catecholamines. There are conflicting opinions on the role of circulating catecholamines as mediators of the metabolic response to surgery. This is a result, at least in part, of the recent introduction of radioenzymatic assay techniques the sensitivity and specificity of which render the older fluorimetric methods obsolete. Plasma catecholamines obtained with the fluorimetric method will not be discussed.

Abdominal surgery produces an increase in plasma noradrenaline and adrenaline values (Halter, Pflug and Porte, 1977), whereas pelvic surgery is associated with an increase in plasma adrenaline alone (Nistrup Madsen et al., 1978; Engquist et al., 1980). It is of interest that in both types of surgery the greatest change in adrenaline values was found after the termination of anaesthesia. Cryer and colleagues (Silverberg et al., 1978; Clutter et al., 1980) have attempted to define the circulating concentrations of catecholamines required to produce metabolic and haemodynamic effects by infusing varying concentrations of these agents into normal subjects. Their results suggest that circulating noradrenaline values during surgery are unlikely to cause any metabolic changes, but this does not exclude the possibility of a localized increase in sympathetic efferent activity. On the other hand, plasma adrenaline concentrations during surgery are similar to those at which changes in heart rate, arterial pressure, blood glycerol, blood lactate and plasma glucose occur.

Another method of assessing the importance of sympathoadrenal stimulation during surgery is to investigate the effects of α- and β-adrenergic blockade. Cooper and others (1980) have recently investigated the effect of β-adrenergic blockade with propranolol during pelvic surgery, and found little effect on the overall metabolic response. This result casts doubt on the relevance of the increases in plasma adrenaline described above. Allison, Tomlin and Chamberlain (1969) examined the

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0007-0912/81/020153-08 $01.00

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effects of phentolamine on glucose tolerance during surgery, but failed to observe any beneficial effects of α-adrenergic blockade.

The opinion of Butler and colleagues (1977) that the ideal method of assessing the individual catecholamine response to surgery has yet to be defined, is undoubtedly still valid.

Cortisol and ACTH. The plasma cortisol concentration shows a rapid increase in response to surgical stimulation and remains greater than basal values for a variable time after operation (Lush et al., 1972; Gordon, Scott and Percy Robb, 1973). The magnitude and duration of this increase correlate well with the severity of the surgical trauma. Increased cortisol production is secondary to a preceding increase in ACTH secretion (Oyama and Takiguchi, 1970a), but the plasma ACTH concentration is far greater than that required to produce a maximal adrenocortical response (Thoren, 1974). In addition, the normal pituitary–adrenocortical feedback mechanism is no longer effective as both hormones remain increased simultaneously. The administration of ACTH during surgery produces no further increase in plasma cortisol, and corticosteroid administration in the period after operation does not abolish the ACTH–cortisol response (Thoren, 1974).

The urinary excretion of cortisol metabolites, 17-oxogenic steroids, is increased for 3–4 days after surgery, and values are further increased and excretion prolonged if surgical complications arise. The urinary 17-oxosteroid excretion, derived mainly from adrenal androgens, hardly changes after surgery (Johnston, 1964), but it is not known whether this reflects altered ACTH control or changes in hormonal utilization.

The administration of large doses of hydrocortisone or ACTH to normal subjects is associated with the occurrence of hyperglycaemia, protein degradation, sodium and water retention and potassium loss; that is, many of the features of the metabolic response to surgery. However, the increased cortisol concentrations during surgery are now considered to have a “permissive” effect rather than a direct causative role. For example, the severe hyperglycaemia of upper abdominal and thoracic surgery can be markedly decreased in the presence of a normal adrenocortical response (Bromage, Shibata and Willoughby, 1971). Adrenalectomized patients maintained on constant doses of glucocorticoids develop a negative nitrogen balance after operation (Johnston, 1964), although the effect of steroid replacement on plasma cortisol values was not stated.

Growth hormone has mixed anabolic and catabolic effects. It promotes amino acid and protein synthesis, has lipolytic properties and at high concentration is diabetogenic (Oyama and Takiguchi, 1970b). An increase in plasma growth hormone concentration has been reported during surgery (Carstensen et al., 1972; Hall et al., 1978), but this response is not maintained into the period after operation even after cardiac surgery (Charters, Odell and Thompson, 1969; Brandt et al., 1976a; Brandt et al., 1978). In non-stressful states, growth hormone secretion is suppressed by the administration of glucose and stimulated by hypoglycaemia (Williams, 1968).

Activation of the hypothalamic–anterior pituitary axis is responsible for the increased plasma growth hormone values found during surgery, and the inability of the hyperglycaemia of surgery to modulate hormone secretion is another example of the failure of normal regulatory feedback mechanisms. It is probable that growth hormone has only a minor role in the metabolic changes occurring in surgery since a normal metabolic response to trauma occurs in hypophysectomized patients maintained on steroid replacement therapy (Thoren, 1974).

Glucagon. An increase in the concentration of plasma glucagon occurs in a wide variety of major surgical procedures (Russell, Walker and Bloom, 1975), although Brandt and colleagues (1976a) failed to observe an increase in circulating glucagon values in six patients undergoing abdominal hysterectomy.

Increased plasma glucagon concentrations are also found with other forms of trauma such as burns (Wilmore et al., 1976) and major injuries (Lindsey et al., 1974). Russell, Walker and Bloom (1975) observed that the hyperglucagonaemia persisted for 4 days after gastric surgery and was exacerbated in those patients who developed complications in the period after surgery. However, Foster and colleagues (1980) showed recently that the plasma glucagon had returned to normal values 48 h after major abdominal surgery.
ENDOCRINE AND METABOLIC CHANGES DURING SURGERY

Many factors have been implicated in the control of glucagon secretion (Alberti and Nattrass, 1977), but it is not known which of these are responsible for glucagon release during surgery or, indeed, the contribution made by the hyperglucagonaemia to the substrate mobilization of surgery. Unger and colleagues (1962) showed that a non-stress induced hyperglycaemia produced a decrease in plasma glucagon, a control mechanism that is not operative in the hyperglucagonaemic (or normoglucagonaemic) patient during surgery when the blood glucose is increased.

Insulin. Circulating insulin concentrations are decreased during and immediately following surgery in spite of the co-existing hyperglycaemia (Russell, Walker and Bloom, 1975; Brandt et al., 1976a), but return to normal or greater than normal values during the days following surgery (Russell, Walker and Bloom, 1975). The relationship between insulin and glucagon secretion is complex; initially plasma insulin values decrease, whereas plasma glucagon increases, but in the period after operation both hormones increase in concentration. Allison (1971) has suggested that the inhibition of insulin secretion is primarily a result of predominance of α-adrenergic sympathetic activity. The recent finding of significantly lower insulin values in patients who received β-adrenergic blockade during surgery supports this contention (Cooper et al., 1980).

Thyroid hormones. Thyroid function in the perioperative period has received considerable attention. Many factors can influence the assessment of changes in circulating thyroid hormones and these include the choice of anaesthetic agent, the methods of hormone estimation and changes in thyroid binding proteins (Thoren, 1974; Brandt et al., 1976b). Plasma triiodothyronine (T3) values decrease during surgery (Brandt et al., 1976b) and remain low into the period after operation (Burr et al., 1975), while plasma thyroxine (T4) concentration remains unchanged. It is likely that this phenomenon is caused by a change in peripheral deiodination of T4 with an increase in the formation of the inactive reverse triiodothyronine (rT3). The significance of the deficiency of circulating T3 in surgical patients is unknown.

Other hormones. Plasma testosterone decreases during surgery and decreases further during the period after operation (Oyama, Aoki and Kudo, 1972), with values remaining less than normal for 4–9 days (Carstensen et al., 1972). Surgery produces a marked increase in circulating prolactin (Brandt et al., 1976a), even during laparoscopy (Cooper, personal communication). The mechanisms of these hormonal changes and their metabolic consequences have yet to be determined.

It is apparent from the above description that it is not possible, at present, to designate one particular hormone as responsible for a specific metabolic change. It is likely that the metabolic response to surgery is the result of the increased activity of all the catabolic hormones in the presence of a reduction of the key anabolic hormone—insulin.

Protein metabolism

An increase in protein degradation is a major effect of the body’s response to surgical trauma. The urinary excretion of nitrogen is increased for 4–5 days after abdominal surgery and a man of average build may lose 0.5 kg of lean tissue per day after a major abdominal operation (Johnston, 1964). The duration and magnitude of this nitrogen loss is related to the severity of the surgery and the nutritional status of the patient (Fleck, 1980). Well-nourished patients have a greater nitrogen excretion and it has been suggested that severe nitrogen loss in debilitated patients, who normally tend to conserve their protein, is associated with a poor prognosis (Johnston, 1964).

There is an initial decrease in protein synthesis in muscle (O'Keefe, Sender and James, 1974) followed by an increase in protein catabolism (Gross, Holbrook and Irving, 1978). The main effect of protein degradation is the release of certain amino acids; particularly alanine, for transport to the liver for gluconeogenesis. The deamination in the liver of this increased amino acid flux from the periphery leads to the characteristic increase in urea production and excretion. Elia and colleagues (1980) have demonstrated an augmented uptake of infused alanine during surgery which they suggest may reflect an increase in hepatic gluconeogenesis. Thus in the period after operation when liver glycogen stores have been depleted, muscle
protein breakdown ensures the maintenance of the supply of glucose. The hormonal control of muscle proteolysis and gluconeogenesis is complex, but the increased glucagon and cortisol concentrations in the presence of insulin suppression are important factors.

**Carbohydrate metabolism**

The increase in blood glucose concentration found during surgery is roughly proportional to the severity of the surgical trauma. Glucose values greater than 10 mmol litre$^{-1}$ are not uncommon during cardiac surgery and may cause glycosuria (Brandt et al., 1978). The mechanism of the hyperglycaemic response is complex as the normal neurohormonal regulation of blood glucose is no longer effective. Suppression of insulin secretion is an early response to surgical stimulation and this has led to studies of glucose utilization in the perioperative period. Aarimaa and colleagues (1974), using serial i.v. glucose tolerance tests, found that glucose utilization was decreased during surgery, and also in the period after operation when insulin values had returned to normal, suggesting the presence of insulin resistance.

Thus the hyperglycaemia of surgery is the result of an increase in glucose production compared with the rate of utilization, although the relative contributions of increased hepatic glycogenolysis and gluconeogenesis are disputed (Cooper et al., 1980; Richards 1980). It is possible that, after operation, the mobilization of free fatty acids (FFA) contributes to the reduction in glucose utilization (the glucose-FFA cycle), but this is unlikely to be of any importance during surgery because there is little change in circulating FFA values (Hall et al., 1978; Kehlet et al., 1979).

**Fat metabolism**

The release of FFA from adipose tissue is the result of two opposing processes, lipolysis and lipogenesis. Lipolysis is stimulated by many hormones, but is most sensitive to β-adrenergic stimulation by catecholamines. Lipogenesis, an anabolic process, is controlled by insulin. There is usually little change in fat metabolism during surgery, although Hall and others (1978) observed a decrease in plasma FFA and glycerol values after the induction of anaesthesia and suggested that this was as a result of a reduction in sympathetic activity caused by apprehension before operation.

Similarly, Cooper and colleagues (1979) and Kehlet and colleagues (1979) found that extradural analgesia for pelvic surgery was associated with a reduction in plasma FFA and glycerol as a result of efferent sympathetic blockade. The administration of heparin during surgery causes a large and immediate increase in plasma FFA because of stimulation of the enzyme, lipoprotein lipase.

There is no clear pattern to the ketone body response to surgery. For example, Brandt and colleagues (1978) reported a small increase in β-hydroxybutyrate values to 250 μmol litre$^{-1}$ after cardiac surgery, whereas Kehlet and colleagues (1979) recorded concentrations of 2 mmol litre$^{-1}$ following hysterectomy. It is possible that the wide variation in ketone body response to surgery is similar to that observed during starvation (Rich and Whitehouse, 1979).

**Salt and water metabolism**

Sodium and water retention and potassium loss are amongst the most constant features of the body’s response to surgery. About two-thirds of the sodium intake after surgery is retained during the 48 h after major surgery (Menzies Gow and Cochrane, 1979). Plasma ADH (Oyama and Kimura, 1970), aldosterone (Engquist et al., 1978) and renin (Robertson and Michaelis, 1972) concentrations are increased during surgery, but the precise mechanism of the alteration in salt and water balance remains unclear. The increase in adrenocortical activity that accompanies surgery may also be a contributory factor.

There are conflicting reports on the effects of extradural analgesia during surgery on sodium and potassium homeostasis. Bevan (1971) reported less sodium retention in the period after surgery with extradural analgesia, although water retention was unchanged. Brandt, Ølgaard and Kehlet (1979) were unable to confirm these changes in sodium balance in spite of the abolition of the increases in plasma cortisol, renin and aldosterone, although the potassium loss after operation was decreased. Similarly, Menzies Gow and Cochrane (1979) found no effect of extradural analgesia on sodium retention after abdominal surgery, but in their study plasma renin values were higher in the extradural group. Differences in the selection of patients, sodium intake, fluid replacement, arterial pressure and other important variables undoubtedly contributed to these findings.
High-dose fentanyl anaesthesia has been shown to abolish the ADH response to cardiac surgery until the onset of cardiopulmonary bypass, but the effect of ADH-inhibition on water balance in the period after operation has not been studied.

Activation of the response
Afferent nerve impulses from the wound area initiate the hormonal and physiological changes which occur in response to surgery. Hume and Egdahl (1959) demonstrated that the adrenocortical response to an injury of the hind-limb in animals can be abolished by peripheral nerve section, transection of the spinal cord above the injury, or section through the medulla oblongata. Wilmore and colleagues (1976) considered that changes in the afferent neuronal input to the hypothalamic area altered central homeostatic mechanisms with consequent changes in pituitary and autonomic nervous system function. Autonomic as well as somatic afferent fibre activity is important in initiating the response, since analgesia per se does not prevent the hormonal changes (Bromage, Shibata and Willoughby, 1971).

In the past there has been considerable speculation about the existence of “wound hormones” which may have a role in eliciting the endocrine and metabolic responses to trauma. The release of prostaglandins, serotonin, acetylcholine and various amino acids from the damaged tissues have all been suggested as possible “wound hormones”. The classical experiments of Egdahl (1959) on the isolated dog leg preparation failed to support this concept. However, Wilmore and colleagues (1976) still consider that such substances may have a part to play in burns and severe trauma.

In addition to the increase in afferent neuronal activity from the area of surgery, a variety of other physiological disturbances contribute to the overall hormonal response.

The effects of haemorrhage are well known to the anaesthetist, but partial starvation and dehydration, not uncommon in surgical patients, are probably also important in exacerbating the endocrine changes. Anxiety and fear increase cortisol secretion and cortisol values before operation have been shown to be influenced by premedication and the sleep pattern of the previous night (Oyama, 1973). In the period after operation factors such as infection, prolonged bed rest, hypoxaemia and even alterations in the usual day–night physiological cycles all contribute to the changes in endocrine function.

Modification of the neuroendocrine response to surgery
This may be attempted in two ways. The first method is aimed at the reduction or abolition of the endocrine and metabolic changes that result from surgical stimulation. This may be achieved either by afferent neuronal blockade with local analgesics, for example extradural or spinal analgesia, or by the inhibition of hypothalamic function with large doses of opiates (George et al., 1974). The second approach is to try to minimize the consequences of the altered hormonal environment after this has occurred. This is usually undertaken by the administration, either parenterally or enterally, of appropriate substrates. Other techniques include the infusion of anabolic hormones (particularly insulin) and nursing the patient in a thermoneutral environment.

Extradural analgesia, with or without general anaesthesia, either reduces or abolishes the usual increase in blood glucose and plasma cortisol, growth hormone, adrenaline and cyclic AMP values found during pelvic surgery (Gordon, Scott and Percy Robb, 1973; Kehlet et al; 1979; Engquist et al., 1980). Complete abolition of the cortisol and growth hormone response to pelvic surgery can only be achieved with an extradural block extending from T4 to S5 (Engquist et al., 1977), although this is ineffective in preventing insulin suppression (Brandt et al., 1976a). It is likely that extradural analgesia merely postpones the hyperglycaemic and adrenocortical responses until the period after operation (Lush et al., 1972; Engquist et al., 1980). The desirability of such an extensive blockade for pelvic surgery has been questioned by Cooper and colleagues (1979).

Bromage, Shibata and Willoughby (1971) examined the effect of extradural analgesia on blood glucose and plasma cortisol values during thoracic and upper abdominal surgery. In spite of adequate pain relief, with blockade up to C6 if necessary, there was no reduction in the cortisol response although the hyperglycaemia was virtually abolished. Bromage and colleagues suggested that the inability to inhibit the adrenocortical changes was a result of the
stimulation of vagal afferent fibres during surgery. If this interpretation is correct, then local analgesic techniques will only be of value in abolishing the hormonal response to pelvic and limb surgery.

**High-dose opiate anaesthesia.** While extradural analgesia has many benefits apart from its effect on the metabolic response, and is a clinically acceptable procedure, high-dose opiate regimens are suitable only for carefully selected and supervised patients because of the problems of respiratory depression after surgery.

Morphine 4 mg kg$^{-1}$ (George et al., 1974; Brandt et al., 1978) and fentanyl 75 µg kg$^{-1}$ (Stanley, Philbin and Coggins, 1979) have been shown to inhibit the hormonal and metabolic response to cardiac surgery until the start of cardiopulmonary bypass. Profound endocrine changes occur at this time which are not influenced by the opiate and are probably caused by factors such as hypothermia, non-pulsatile flow and the sudden increase in blood volume with haemodilution. Hall and others (1978) observed that fentanyl 50 µg kg$^{-1}$ prevented the increases in blood glucose, plasma cortisol and plasma growth hormone concentrations found during prolonged pelvic surgery, but the study was not extended into the period after operation.

These attempts to inhibit the endocrine response to surgery, either by local analgesic techniques or by high-dose opiate anaesthesia, demonstrate further the complexity of the inter-relationships between hormonal activity and substrate mobilization. It is noteworthy that, in all studies in which the cortisol response to surgery was abolished, no ill-effects were observed in these patients. This suggests that vigorous steroid supplementation for patients on long-term steroid therapy is unnecessary.

**Substrate administration.** Recent developments in enteral and parenteral feeding techniques permit vigorous nutritional support, replacing or even exceeding the calorie and nitrogen requirements of the catabolic patient. An appropriate calorie and nitrogen intake can reduce protein loss and possibly improve the prospects of survival in severely catabolic patients. It is important to note that the infusion of some parenteral nutrition solutions stimulates hormone secretion and this may exacerbate the endocrine changes after surgery. For example, the administration of amino acid solutions produces an augmented glucagon secretion following major abdominal surgery (Foster et al., 1980).

**Hormone supplementation**

**Insulin.** The recognition of the occurrence in the surgical patient of insulin suppression followed by resistance prompted the use of insulin infusions to decrease catabolism. Hinton and colleagues (1971) reported that the combination of glucose, insulin and potassium was effective in reducing the excessive protein breakdown in patients with burns, but failed to distinguish between a specific action of insulin and the result of giving extra calories. Woolfson, Heatley and Allison (1979) recently resolved this conflict by demonstrating a protein-sparing effect of insulin in catabolic patients, although they were unable to shed any light on the precise mechanism of action of insulin.

**Growth hormone.** Wilmore and colleagues (1974) observed that the daily i.m. administration of 10 iu of growth hormone improved the nitrogen balance in patients with severe burns maintained on an adequate calorie and nitrogen intake. Growth hormone supplementation produced a marked increase in insulin secretion which was probably responsible for the beneficial effects observed.

**Anabolic steroids.** The administration of methandienone in the period after operation caused a reduction in nitrogen excretion not only after herniorrhaphy, but also following gastric surgery (Johnston and Chenneour, 1963).

**Environmental temperature.** Cuthbertson and colleagues (1972) reported a reduction in protein catabolism in patients with fractures of the major long bones of the lower limb maintained at an environmental temperature of 28–30 °C. Unfortunately, Spivey and Johnston (1972) were unable to demonstrate any beneficial effects on nitrogen loss of nursing patients after abdominal surgery at 30 °C, possibly because of the less severe injury. It is likely that the main application of this technique will be in the management of burns patients (Wilmore et al., 1976), although the precise mechanism by which the protein catabolism is ameliorated has not been elucidated.

**Influence of anaesthesia.** The endocrine response to anaesthetic agents per se has been
comprehensively reviewed (Oyama, 1973). With the exception of diethyl ether, the influence of modern inhalation and i.v. agents on hormone secretion and metabolism is small compared with that of surgical stimulation provided that hypoxaemia, acidosis and hypothermia are avoided. Indeed, halothane may even be beneficial as it has been shown to reduce adrenaline secretion in vitro and in vivo (Roizen et al., 1974; Halter, Pflug and Porte, 1977).

CONCLUSION

The neuroendocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain the function of vital organs. However, in modern anaesthetic and surgical practice where severe physiological disturbances are prevented or rapidly treated, and suitable substrates made readily available, any benefits of this response are no longer apparent. The aim for the future must be the safe prevention of surgically-induced, adverse hormonal and metabolic changes. We consider that it is no longer necessary to defend the charge of attempting to reduce such changes by various anaesthetic techniques, but rather to ask why these effects should be left unaltered.

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