The Metabolic Response to Stress: An Overview and Update

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reviews the metabolic, hormonal, and immunologic responses that occur during surgical injury. This is especially timely in light of the recent explosion of knowledge in the areas of immunology and endocrinology. The importance of the components of the immunologic system in controlling many nonimmune functions, coupled with the discovery of many potent endocrine, apocrine, and eccrine substances, has allowed for a better understanding of the response to stress. It is now recognized that there are many links between the endocrine and immunologic systems.

An Overview of the Response to Injury

Major body injury, surgical or accidental, evokes reproducible metabolic, hormonal, and hemodynamic responses. These responses are characterized by altered protein homeostasis, hypermetabolism, altered carbohydrate metabolism, sodium and water retention, and increased lipolysis. The abnormal carbohydrate metabolism includes increased endogenous hepatic glucose production (gluconeogenesis) and reduced glucose clearance (insulin resistance), which results in hyperglycemia. The major body fuel becomes fat; therefore, lipolysis is increased and lipogenesis is retarded. Protein abnormalities are manifested by negative nitrogen balance reflecting accelerated net protein breakdown (catabolism). The magnitude of these changes is essentially proportional to the extent of the injury.

Mediators of the Response

THE NEUROENDOCRINE AXIS

The mechanisms initiating, regulating, and sustaining this response have not all yet been identified. One area of particular interest has been the neuroendocrine axis (fig. 1). It has long been recognized that injured patients have elevations in the counter-regulatory or anti-insulin hormones: cortisol, glucagon, and the catecholamines. Insulin levels are usually elevated but not sufficiently to prevent the universally observed hyperglycemia. In addition, growth hormone (GH), aldosterone, and vasopressin are elevated. The mechanism for these elevations is thought to be at least partially neurally me-
Diated. Afferent impulses stimulate the secretion of hypothalamic releasing factors (e.g., corticotropin-releasing factor [CRF]) and vasoactive intestinal peptide, which in turn stimulate the pituitary to release proopiomelanocortin, prolactin, vasopressin, and GH. Plasma vasopressin concentrations are elevated following a variety of stresses, including surgery, pneumonia, myocardial infarction with or without left ventricular failure, and electroconvulsive therapy. Plasma vasopressin concentrations increase after the start of surgery and remain elevated often for days after surgery. The magnitude and duration of the increases are proportional to the degree of stress. CRF, acting synergistically with vasopressin, stimulates the secretion of proopiomelanocortin from the pituitary gland. Proopiomelanocortin is metabolized to adrenocorticotropic hormone (ACTH) and β-endorphin, thus a linkage between the endogenous opioid and the hypothalamic pituitary-adrenal axis. Another link is the stimulation by CRF of adrenomedullary release of catecholamines and enkephalins. Pituitary prolactin secretion is thought to be at least partially mediated by vasoactive intestinal peptide, although other mediators may also be operative. The role of prolactin in the response to stress is unclear. Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) change little during surgery, but LH and FSH decrease on the first postoperative day. Hume and Egdahl demonstrated that division of the afferent input from an area of injury can reduce the secretion of ACTH. Others have demonstrated that subarachnoid and epidural local anesthetic blockade of the neurogenic stimuli from the area of surgery can attenuate the increases in plasma concentrations of catecholamines, ACTH, aldosterone, cortisol, renin, GH, prolactin, and antidiuretic hormone. High doses of opioids (4 mg/kg of morphine, 100 μg/kg of fentanyl) can also attenuate the increases in the levels of cortisol and catecholamines presumably by suppressing CNS output.

The discovery of neuroendocrine mediators in non-hypothalamic and nonpituitary tissues has raised questions about their actions in these locations. Vasopressin has been found in human pancreas and proopiomelanocortin gene expression has been observed in peripheral mononuclear cells, adrenal, testis, spleen, kidney, ovary, and lung.

Catecholamines

Catecholamines exist in the circulation both as free catecholamines and as the sulphur conjugate that accounts for 60–90% of the total catecholamines. The serum levels of the catecholamines norepinephrine, epinephrine, and dopamine have been observed to increase after a variety of stresses, including anxiety, hypotension, hypothermia, hypercarbia, and accidental injury. In critical illness the proportion of free to total (free plus conjugated) catecholamine remains constant. Epinephrine is secreted by the adrenal medulla in response to sympathetic nervous system activation while norepinephrine spills over into the plasma after release from the sympathetic nerve endings. The sympathetic nervous system, in turn, is controlled by the hypothalamus, the same area of the brain responsible for the excretion of releasing factors (e.g., CRF) that initiate the secretion of other endocrine hormones. Plasma levels of epinephrine and norepinephrine do not necessarily increase concurrently. In a study of major accidental injury, plasma epinephrine concentrations were increased for only a short period (about 48 h) while norepinephrine levels remained elevated for periods of up to 8–10 days. Abdominal and cardiac surgery produces increases in both hormones whereas pelvic surgery increases mainly epinephrine. Importantly, in both abdominal and pelvic surgery the greatest plasma epinephrine concentrations were observed, not during, but immediately following, the completion of surgery. Halter et al. found that during abdominal surgery the initial adrenergic activation occurred during the time of the actual surgery and not between the induction of anesthesia and skin incision. The type of anesthesia has a major influence on the amount of catecholamine secretion during surgery.
Plasma epinephrine concentrations reflect adrenergic activity, whereas plasma norepinephrine concentrations are used as an index of sympathetic nervous system activity. It is important to realize that most of the norepinephrine released by sympathetic ganglia is removed from the synapse by re-uptake into the nerve ending. Thus, only the norepinephrine that spils over into the plasma is assayed. Plasma levels are determined by the relationship between spillover rate and plasma clearance rate. Studies of norepinephrine kinetics after cholecystectomy demonstrated that plasma norepinephrine increased considerably during the postoperative period because of an increase in the appearance (spillover) rate while neither plasma clearance, nor forearm extraction of norepinephrine differed from preoperative values. Christensen et al. noted that despite elevated postoperative plasma norepinephrine levels, there was no change in blood pressure, likely reflecting a decreased sensitivity to norepinephrine.

Epinephrine in physiologic doses results in glycogenolysis, increased hepatic gluconeogenesis with mobilization of gluconeogenic precursors from peripheral tissues, inhibition of insulin release, peripheral insulin resistance, and lipolysis. Epinephrine is a potent stimulator of gluconeogenesis. This is demonstrated by the observation that during starvation there is no diminution in the ability of epinephrine to stimulate gluconeogenesis. This is in contradistinction to glucagon, the gluconeogenic ability of which is less in starved than fed subjects.

**Glucocorticoids and Other Steroids**

Cortisol has many actions, including stimulating gluconeogenesis, increasing proteolysis, and alanine synthesis, and sensitizing adipose tissue to the action of lipolytic hormones (GH and catecholamines) and anti-inflammatory action. In addition, it causes insulin resistance by decreasing the rate at which insulin activates the glucose uptake system, likely because of a postinsulin receptor block. Increased pituitary production of ACTH stimulates increased glucocorticoid production. Glucocorticoids have a negative feedback effect on ACTH production and can also stimulate the adrenomedullary secretion of catecholamines. The administration of 500 mg cortisol sodium succinate at the time of surgical incision attenuated the increase in plasma ACTH. ACTH release is itself stimulated by CRF and by catecholamines, vasopressin, and vasoactive intestinal peptide.

Cortisol is increased in stress and is thought to be a major mediator of the response because adrenalectomized animals and patients with Addison's syndrome fare poorly when stressed. This was well demonstrated by the increased mortality rate observed following the use of etomidate to sedate critically ill patients. It was subsequently discovered that etomidate blocks adrenal steroidogenesis, specifically by inhibiting 11β-hydroxylation and 17α-hydroxylation. Cortisol is thought to be a vital hormone because it diverts glucose utilization from muscles to the brain, facilitates the action of catecholamines, and prevents the overreaction of the immune system to injury. Facilitating catecholamine action and secretion is thought to aid in maintaining cardiovascular stability during surgical stress.

In general, the magnitude and duration of both intraoperative and postoperative ACTH and cortisol concentrations correlate well with the degree of surgical trauma. A recent study demonstrated that patients undergoing neck exploration, a mild degree of trauma, undergoing isoflurane-nitrous oxide anesthesia had elevations in the plasma concentrations of ACTH, cortisol, and epinephrine only upon emergence from anesthesia. The increase in ACTH secretion during surgery is often far greater than that required to produce a maximal adrenocortical response. This was demonstrated by the observation that during surgery the administration of exogenous ACTH resulted in no additional increase in plasma cortisol concentration. The circadian rhythm of cortisol excretion (maximum levels 6 A.M. to 8 A.M. with a subsequent decrease) is altered but not abolished after surgery. The rhythm may, however, be shifted in time by as much as 6 h after major surgery. Studies with labeled cortisol demonstrated that during and after surgery calculated volume of distribution increased about 175% and metabolic clearance rate increased about 130%. During surgery cortisol binding to albumin, but not transcortin, decreased while postoperatively the reverse was true.

Thus, in both situations free cortisol increased more than reflected by measurement of total serum cortisol alone. The increased free cortisol seen following surgery is due to an increase in total plasma cortisol as well as a decrease in cortisol binding capacity. Barton and Passingham found a constant yet nonlinear relationship between free and total plasma cortisol. They concluded that measurement of total serum cortisol was an adequate measurement of cortisol response in surgical and injured patients.

In accidentally injured patients Barton et al. observed that within 2 h of injury patients with moderate injury had plasma cortisol increases in proportion to severity. In those with more severe trauma, plasma cortisol levels declined in relation to ACTH as well as in absolute terms. The authors thought this may be at least partially due to a poor response of the adrenal cortex to ACTH. This situation was associated with poor survival.

The production of other steroid hormones is also altered by injury. Parker and Baxter observed that although cortisol increased postburn injury, the production of the adrenal androgen dehydroepiandrosterone sulfate was decreased. Decreased plasma testosterone levels have
been observed after surgery and myocardial infarction. Woolf et al. observed that critically ill men and women have decreases in plasma concentrations of testosterone and estradiol, respectively. The latter explains the amenorrhea seen during such stressful situations. The exact cause is not clear but may be due to decreased or altered secretion of intrapituitary and suprapituitary substances (e.g., FSH and LH) and/or decreased response of the pituitary to gonadotropin-releasing hormone.

**Glucagon and Insulin**

Glucagon and insulin are both secreted by the pancreas, the former by α-cells and the latter by β-cells. These endocrine secretions enter the portal vein so that the liver is exposed to high concentrations of these hormones. Glucagon increases hepatic cytoplasmic AMP and promotes gluconeogenesis; insulin has the opposite effect—it decreases intracellular cyclic AMP concentration and prevents gluconeogenesis. In addition, glucagon increases glycogenolysis, lipolysis, and hepatic ketogenesis in the liver during starvation and diabetic ketoadidosis. The receptor mechanism that increases cyclic AMP concentrations is not the same as used by adrenergic mediators. Stimulators of glucagon secretion include hypoglycemia, protein ingestion, amino acid infusion, endorphins, exercise, GH, epinephrine, and glucocorticoids. Suppressors of glucagon secretion include the infusion and ingestion of glucose, somatostatin, and insulin. Insulin is an anabolic hormone with a multitude of effects. In addition to its role in increasing glucose transport across the cell membranes of adipose tissue and muscle, it stimulates glycogen production, inhibits lipolysis in adipose tissue, inhibits hepatic ketogenesis, and increases the rate of amino acid transport and protein synthesis in muscle, adipose tissue, and liver. It is the glucagon to insulin ratio that is the major determinant of the degree of gluconeogenesis. During starvation the ratio is increased (increased glucagon and decreased insulin levels) and gluconeogenesis is promoted, whereas the reverse is true in the fed state.

After most types of major surgery there is an increase in plasma glucagon, although some have failed to observe an increase after abdominal hysterectomy. The attainment of peak values is later than with cortisol, occurring 18–48 h after injury or surgery. Like starvation, there is an increased glucagon:insulin ratio. Insulin levels are decreased during surgery due to the suppression of secretion by elevated levels of catecholamines and/or increased urinary losses. This suppression can be abrogated by alpha-adrenergic blockade. The hormonal milieu of low insulin with elevated counter-regulatory hormones is thought to be a stimulus to gluconeogenesis. In septic patients this mechanism may fail and cause hypoglycemia.

This situation has been correlated with poor survival. Postoperatively, an increase in insulin is seen and thought to be due to increases in both plasma glucose- and epinephrine-induced β-adrenergic stimulation. However, unlike starvation, the plasma insulin concentrations are often markedly increased above basal, although they are inappropriately low for the prevailing level of glycemia. Increased plasma glucagon concentrations are also seen in sepsis and burns.

Recent studies in burn patients have employed somatostatin, a pancreatic D-cell hormone that suppresses growth hormone, insulin, and glucagon release. When somatostatin was infused into these patients, the rate of glucose production decreased as did the rate of glucose clearance. If insulin is also infused into patients receiving somatostatin, the rate of glucose clearance returns to basal levels, thus normalizing glucose kinetics. It thus appears that glucagon is a major mediator of gluconeogenesis. The lesser role of the catecholamines in the abnormal glucose metabolism of burn patients was demonstrated when propranolol failed to reduce the rates of glucose production or glucose cycling. It is likely that catecholamines and glucagon work synergistically because either infused alone into normal subjects only causes transient elevation in gluconeogenesis, whereas more prolonged gluconeogenesis is seen when they are infused together.

**Growth Hormone**

GH is a polypeptide secreted by the anterior pituitary. It is important in the regulation of growth during the prenatal, neonatal, and childhood periods. Many of its actions are indirect, mediated by somatomedins or insulin-like growth factors (IGF). Somatomedin C/IGF-I and somatomedin A/IGF-I are two of these factors; the former is produced by the liver.

GH also has unique metabolic effects: upon initial exposure (2–3 h) there may be insulin-like effects (likely due to the release of insulin) but after longer exposure, there are counter-regulatory and anabolic effects. GH causes glucose intolerance; the mechanism includes insulin resistance likely due to an insulin post-receptor defect both in hepatic and extrhepatic tissues. GH infusion increases lipolysis as evidenced by increases in glycerol and nonesterified fatty acid concentrations. GH also increases the incorporation of amino acids into protein. The release of GH is stimulated by hypothalamic growth hormone-releasing factor. Somatostatin, a hormone found in the hypothalamus and pancreatic D-cells, inhibits GH secretion.
After injury, burns, and surgery concentrations of GH in the blood are elevated. The increase is roughly proportional to the degree of trauma. Fayn et al. noted that after musculoskeletal injury plasma growth hormone levels were high immediately after injury but rapidly returned to normal. Interestingly, plasma somatomedin activity was depressed for 2–3 days after injury, indicating a dissociation between GH and somatomedin. Instead, somatomedin activity was more closely related to insulin concentrations. This may be explained by the evidence that somatomedin activity may reflect the nutritional state and insulin may play a role in its regulation (hence the name insulin growth factor). Somatomedin (C/IGF-I) concentrations are reduced in malnourished children and hospital patients. In studies of critically ill patients, serum somatomedin C/IGF-I concentration consistently and positively correlated with nitrogen balance measurements. Some investigators have investigated the effects of GH infusion in postoperative and burn patients. Increases in nitrogen retention, nitrogen turnover, metabolic rate, and fat oxidation were noted. Whether GH infusions are useful therapeutically is still under investigation.

Thyroid Hormones

In acute nonthyroidal illness there are profound alterations in thyroid homeostasis. Most frequently, the "sick euthyroid syndrome" is produced. This includes a reduction in serum T₃ levels, low or normal T₄, normal free T₄ and elevated reverse T₃ while TSH is normal. T₃ resin uptake is often increased. In postoperative critically ill patients, Zaloga et al. observed that although the serum TSH response to TRH was normal after surgery, the maximal TRH-induced increase in serum TSH and the integrated serum TSH response to TRH were suppressed in the early postoperative period. Postoperative TSH suppression correlated with elevated dopamine concentrations. There is also evidence that the TSH released may have altered glycosylation and be less potent a stimulator of T₄ release in the blood. The increased conversion of T₄ to rT₃ has been observed in severe systemic diseases, including cerebrovascular disease, hepatic disease, malnutrition, starvation fasting, myocardial infarction, after surgery, during treatment with corticosteroids, and in high catecholamine states, such as burns. Smallridge et al. observed that serum angiotensin converting enzyme levels, which parallels thyroid hormonal levels, were reduced as was T₃ after surgery. Some investigators have noted an increase in illness severity and mortality in patients with a significant decrease in T₃ and T₄ concentrations and elevated T₃ RU and rT₃ values.

Dopamine, when administered intravenously to normal subjects, decreases basal TSH levels, inhibits the TSH response to TRH, and decreases serum T₄ and serum T₃. Similar observations have been made in critically ill patients receiving dopamine infusions. Dopamine likely prolongs and aggravates the low T₄ state seen in critical illness. The most intriguing aspect of thyroid metabolism in the critically ill patient is that despite low T₄ and T₃, many of these patients are hypermetabolic.

Counter-regulatory Hormone Interactions

The interaction of the counter-regulatory hormones (glucagon, catecholamines, and cortisol) in the response to injury has been of great interest. Shamoon et al. explored the short-term effects of a combined infusion into normal subjects of hydrocortisone, glucagon, and epinephrine designed to simulate the plasma levels seen after moderate injury. They observed increases in glucose production (gluconeogenesis) and decreases in glucose clearance. The effect was more pronounced when all three hormones were administered than when they were infused individually or in groups of two. It was thus proposed that these hormones act synergistically. A possible cause of this synergism includes the fact that glucagon increases intracellular cyclic AMP, especially in liver by a non-β-receptor mechanism and also may operate via the phosphoinositol pathway. It could thus amplify the actions of epinephrine. Cortisol has been reported to act synergistically with epinephrine and other β-agonists (an action employed in the treatment of asthma). Mechanisms proposed include cortisol induced inhibition of catechol-o-methyl transferase and blockade of catecholamine re-uptake. More recent studies have proposed that cortisol increases β-receptor m-RNA and, thus, presumably increases the number of β-receptors. In other studies infusion of the three hormones caused significant negative nitrogen and potassium balances, glucose intolerance, hyperinsulinemia, insulin resistance, sodium retention, and peripheral leukocytosis. In only one of the studies was significant sustained hypermetabolism observed. The nitrogen losses appear to be due mainly to the effects of cortisol because nitrogen balance during cortisol infusion was similar to that seen during infusion of all three hormones. The nitrogen losses were also not of the magnitude observed after accidental injury. Gelfand et al. observed no significant alterations in leucine flux or oxidation and only small increases in 3-methylhistidine excretion, indicating little muscle breakdown. Therefore, other mediators must cause the proteolysis and massive nitrogen loss observed in patients. Also, the normal subjects were not febrile and did not have increased acute phase reactant proteins and decreased serum iron. Studies wherein the pyrogenic steroid etiocholanolone was injected into normal subjects resulted in fever, leukocytosis,
and hypofebrinemia without elevations in the counter-regulatory hormones, hyperglycemia, or negative nitrogen balance. Infusion of the counter-regulatory hormones plus etiocholanolone simulated more of the features of the response to injury than when they were administered individually. Thus, both endocrine and inflammatory mediators appear to be active in the response to injury and sepsis.

### THE IMMUNOLOGIC CONNECTION

#### Cytokines

There has been an explosion of knowledge about non-endocrine factors that may play important roles in the response to stress. Much of this knowledge has been gained from the increased understanding of the immunologic system. After etiocholanolone injections it was observed that there was an increase in the plasma activity of interleukin-1 (IL-1). This substance is released by activated human monocytes/macrophages in response to various antigenic stimuli. It is also termed endogenous pyrogen or leukocyte endogenous factor and modulates many of the tissue responses to inflammation. It induces hepatocytes to synthesize and release acute phase reactants (e.g., macroglobulin, complement, immunoglobulins), makes endothelial adhesive for monocytes, promotes fibroblast growth, causes fever, and may be involved in muscle breakdown (Fig. 2). Baracos et al. reported that a biologic extract rich in IL-1 simulated in vitro skeletal muscle proteolysis via protagandin E2 (PGE2) formation. Clowes et al. identified a polypeptide from the serum of septic patients that also caused in vitro muscle proteolysis. Whether IL-1 or a related substance is involved in proteolysis is still unclear. IL-1 also activates the expression of granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and B-cell stimulating factor-2 (BSF-2, also called IL-6) in endothelial cells, helper T-cells, bone marrow stroma cells, and fibroblasts. These factors in turn activate marrow progenitor cells and leukocytosis results. Luger et al. observed that in patients with fatal sepsis there was decreased IL-1 activity, but in those who survived the levels were normal. One explanation is that the elevated plasma concentrations of catecholamines suppress monocytic IL-1 production. Another monokine, hepatocyte stimulating factor (also called BSF-2 and IL-6), has been shown to induce fibrinogen synthesis in hepatocytes. It is also produced by human endothelial cells in response to IL-1 tumor necrosis factor (TNF), and bacterial lipopolysaccharide stimulation.

Another important cytokine that appears to have metabolic effects is cachectin or TNF. This protein is secreted by macrophages in response to exposure to endotoxin and candida albicans. Administration of TNF to animals results in most of the manifestations of septic shock, i.e., hypotension, metabolic acidosis, hemocoencentration, hyperglycemia, hyperkalemia, hemorrhagic lesions of the GI tract, and acute tubular necrosis. Waage et al. noted a correlation between TNF levels, degree of septic shock, and subsequent death in patients with meningococcemia. In addition, TNF causes fever by direct action on the hypothalamus and by inducing IL-1 secretion. The latter substance then mediates many of the changes described. In a recent study Michie et al. induced normal subjects with endotoxin and found that serum levels of TNF peaked after 90-180 min. Associated with this peak were increases in plasma ACTH and epinephrine concentrations, body temperature, and heart rate. Pretreatment with ibuprofen did not affect the increase in TNF levels but did suppress the increase in body temperature and ACTH. It has also been shown that TNF could dramatically decrease the synthesis and activity of lipogenic enzymes in cultured adipocytes, thus the name cachectin. This mirrors the decreased lipogenesis observed with whole body measurements in septic and injured patients. Lymphotoxin, also called TNF-α, is a product of activated T-cells and has biologic activity similar to that of TNF/cachectin.

IL-2 (T-cell growth factor) is another cytokine that may play a role in the metabolic response to stress. This substance is secreted by T-cells in response to stimuli such as IL-1 and causes the generation and proliferation of antigen-specific cytotoxic and helper T-cells required for cell-mediated immunity. Its production is reduced in injured patients, with an inverse correlation between the severity of injury and the degree of IL-2 production.
This decreased IL-2 synthesis is likely due to excessive PGE$_2$ output by inhibitory monocytes.\textsuperscript{168} PGE$_2$ is associated with reduced lymphokine production,\textsuperscript{170} inhibited lymphocyte-mediated cytolysis, and inhibition of lymphocyte mitogenesis.\textsuperscript{169} Partial restoration of IL-2 synthesis can occur by blocking the cyclooxygenase pathway with indomethacin.\textsuperscript{168} In burn patients not only is there decreased IL-2 synthesis but there is also an inability to effect expression of high affinity functional IL-2 receptors.\textsuperscript{170} The duration of reduced IL-2 production may be as long as 60 days postburn and correlates with the severity of the burn.\textsuperscript{168} Also, septic burn patients have lower IL-2 production than nonseptic ones. These alterations in IL-2 homeostasis may thus be one of the mechanisms for postinjury depression of cell-mediated immunity. One of the main interests in IL-2 is its use in cancer immunotherapy.\textsuperscript{171} The complications of such therapy (when used in large doses) is a response similar to that seen after injury and sepsis: weight gain due to fluid retention, noncardiogenic pulmonary edema, hyperpyrexia, nephrotoxicity, and hepatotoxicity.\textsuperscript{172,173} It is still unclear whether this response is due to a pharmacologic effect or a physiologic one and whether it is due to stimulation of other mediators or just an effect of IL-2 itself. In patients receiving IL-2 infusions, the levels of ACTH, cortisol, GH, and $\gamma$-interferon in the blood have been shown to be elevated.\textsuperscript{174-177}

Another mediator of the immunologic stress response is $\gamma$-interferon (IFN), a glycoprotein released by stimulated T-lymphocytes.\textsuperscript{178} It activates macrophages to release IL-1, TNF, G-CSF, M-CSF, and BSF-2,\textsuperscript{149} increases IL-2 receptors on monocytes, and reduces PGE$_2$ release\textsuperscript{180} and urokinase type plasminogen activator release.\textsuperscript{179} It reduces immunologic suppressor activity by inhibiting PGE$_2$ release and by inhibiting viral replication. Elevated serum levels of $\gamma$-IFN have been observed in patients with pelvic inflammatory disease.\textsuperscript{181} Platelet-activating factor, a phospholipid product of activated macrophages, may also be active,\textsuperscript{185} especially in the response to endotoxin.

Other Mediators

Other substances have been implicated as being active in the metabolic response to stress. Bradykinin is a vasoactive substance that stimulates intracellular prostaglandin production and is released by hypoxia and ischemia. When low doses (2.0 and 4.0 $\mu$g · kg$^{-1}$ · h$^{-1}$) of bradykinin were infused into patients after abdominal surgery, there was a decrease in glucose production and arterial glucose concentrations.\textsuperscript{183} It is postulated that the bradykinin-induced increase in hepatic prostaglandins caused an inhibition of glucagon-induced cyclic AMP formation, thus inhibiting hepatic gluconeogenesis.\textsuperscript{183,184} Preliminary reports indicate that such bradykinin infusions may increase nitrogen retention.\textsuperscript{185}

The Endocrine–Immunologic System Interaction

It has long been recognized that pharmacologic doses of glucocorticoids cause suppression of cellular immunity. Glucocorticoids cause release of neutrophils from the bone marrow, a reduction in circulating monocytes and macrophages and sequestration of T-cells in the bone marrow; lyse immature T-cells; inhibit $\gamma$-IFN, IL-1,\textsuperscript{155} and IL-2 production; block phospholipase A$_2$, which is responsible for prostaglandin and leukotriene production; and block the action of certain proteases involved in inflammation.\textsuperscript{186} There are glucocorticoid receptors on leukocytes. Peripheral leukocytes have also been observed to secrete ACTH when virally infected or exposed to endotoxin.\textsuperscript{187} Recent observations have identified many more links between the endocrine and immunologic systems.

A number of studies have demonstrated the ability of IL-1 to stimulate ACTH\textsuperscript{188,189} and CRF release.\textsuperscript{189} Brown et al. demonstrated that IL-1 and IL-2 enhance the expression of the mRNA to proopiomelanocortin.\textsuperscript{190} Controversy exists regarding whether IL-1 directly stimulates ACTH secretion by pituitary cells or whether IL-1 directs the release of CRF from hypothalamic cells.\textsuperscript{191} (It is possible that this depends on the type of IL-1, $\alpha$ or $\beta$.) It has also been observed that IL-1 and $\gamma$-IFN\textsuperscript{196} stimulate the release of ACTH-like substances (and endorphins) from peripheral leukocytes. Hepatocyte-stimulating factor can also cause ACTH secretion from pituitary cells via a leukotriene mechanism.\textsuperscript{197} Evidence also points to the ability of IL-1 to stimulate insulin and glucagon secretion.\textsuperscript{198} It thus appears that IL-1 may be an important mediator activating the endocrine response to stress. Platelet-activating factor, another activated monocyte product, increases gluconeogenesis.\textsuperscript{194} The endocrine system may also play a role in the regulation of monokine production.

$\gamma$-IFN increases serum cortisol levels when infused into cancer patients for 20 min (60 mU/M$^2$).\textsuperscript{195} This hypercortisolemia persists for at least 24 h and may explain the impaired immune responsiveness observed after $\gamma$-IFN infusion. Whether $\gamma$-IFN has direct corticotropic action or induces ACTH-like activity is unclear because with short infusions ACTH is only minimally elevated.

Another stress-induced substance that can affect immune function appears to be $\beta$-endorphin. Levy et al.\textsuperscript{196} observed a temporal association between $\beta$-endorphin concentrations and depressed immune function after trauma. In vitro $\beta$-endorphin enhances natural killer lymphocyte activity in a dose-related fashion, an effect that is reversed with naloxone. Other natural opioid substances also have immunomodulating effects.\textsuperscript{197-199} Morphine has
profound effects on neutrophil function; it can decrease chemotaxis, increase bactericidal activity for *Staphylococcus aureus*, and increase resting and zymosan-stimulated neutrophil oxygen consumption.\(^{200}\)

Other endocrine substances besides glucocorticoids appear to have immunologic function. β-Adrenoreceptors have been reported to regulate the function of human natural killer lymphocytes,\(^{201}\) and *in vitro* studies with stress hormones (cortisol, epinephrine, norepinephrine, and glucagon) have demonstrated their ability to modulate neutrophil and lymphocyte activity.\(^{202}\) Recently, somatropin has been shown to prime mononuclear phagocytes (macrophages) to augment production of reactive oxygen metabolites, restore the T-cell proliferative response and IL-2 synthesis, augment the activity of cytolytic delayed hypersensitivity and natural killer T-cells, and increase antibody synthesis in response to T-cell-dependent mitogen.\(^{203}\) It thus appears that the endocrine and immunologic systems interact on many levels.

**Immunologic Changes Following Injury**

Following surgery patients have been found to have significant abnormalities of cellular immunity.\(^{204}\) This is manifest as anergy in response to skin testing and has been correlated with increased risk of sepsis and mortality in surgical patients.\(^{205,206}\) *In vitro* tests of lymphocyte and macrophage function, such as mixed lymphocyte culture reaction, response to lymphokines, generation of cytotoxic T-cells, and proliferative reaction to PPD, are normal in such patients.\(^{204}\) Thus, it is the physiologic environment that contributes to the anergic state. Suppressor T-cells are increased. A major cause of this immune suppression appears to be failure to produce IL-2.\(^{207}\) Humoral immunity is also decreased in surgical patients. It has been observed\(^{208}\) that there is a failure to produce specific antibodies (*i.e.*, those to tetanus toxoid) but not failure of total IgG synthesis. Those patients with depressed cellular immunity have the greatest depression in humoral immunity and elevated PGE\(_4\) production. Elevated PGE\(_2\) suppresses IL-1, IL-2, and γ-INF, a situation that may be present for as long as 7–10 days postinjury.\(^{109}\) Indomethacin, an inhibitor of PGE\(_2\) production, results in restoration of blood monocyte response to antigenic stimulation. Also, the addition of lymphokines abrogates the anergic response to antigenic stimulation.\(^{209}\) It thus appears that the lymphokines are involved in multiple (metabolic, immunologic, and hematopoietic) aspects of the response to stress.

**Biochemical Changes Following Injury and Sepsis**

**Carbohydrate Metabolism**

The major fuel source in normal human is glucose. It enters the circulation either from endogenous sources (glycogenolysis and gluconeogenesis) or from external sources (*via* the digestive tract or intravenously). It can then be either metabolized to carbon dioxide, water, and energy (ATP) or converted and stored as glycogen or converted into fat (lipogenesis). Insulin facilitates glucose uptake by cells, promotes glycogen synthesis, and opposes gluconeogenesis. Catecholamines and glucagon stimulate glycogenolysis and hepatic gluconeogenesis; cortisol also stimulates the latter. Cortisol, glucagon, and the catecholamines are called counter-regulatory hormones because they oppose the effects of insulin and act synergistically to increase hepatic glucose production.

A prominent feature of the response to injury or sepsis is hyperglycemia. The initial increase in blood glucose after injury is due to the mobilization of liver glycogen. The hyperglycemia persists beyond the exhaustion of the glycogen supply because of a marked increase in hepatic glucose production along with a reduction in glucose clearance. This increase in glucose production is due to hepatic gluconeogenesis with amino acids, lactate, pyruvate, and glycerol as substrates. The lactate and pyruvate are from glycogenolysis and glycolysis in peripheral tissues, especially muscle. The amino acids are from the breakdown of muscle, and the glycerol is from the metabolism of triglycerides (fat). The increase in hepatic glucose production is marked. In normal subjects about 200 g/d of glucose is produced, whereas noninfected burn patients may produce 320 g/day and infected ones, 400 g/day. Black et al.\(^{210}\) using a glucose clamp technique demonstrated that trauma patients have a decreased maximal rate of glucose clearance. The clearance rate of insulin was twice normal and insulin resistance appeared to occur in peripheral tissues, such as skeletal muscle. They ascribed resistance to a postreceptor problem. Some investigators\(^{211}\) have suggested that insulin levels are inadequate to maintain normoglycemia because of the suppression of insulin secretion by high epinephrine concentrations; others have postulated that there is increased insulin turnover resulting in increased insulin clearance.\(^{212}\)

Studies in patients undergoing cholecystectomy demonstrate a small increase in hepatic glucose production with markedly decreased peripheral utilization.\(^{213}\) This was accompanied by increases in hepatic uptake and peripheral production of lactate, glycogen, and alanine. In addition, the linear relationship between arterial glucose and insulin levels existing prior to surgery was no longer present afterwards. A major mediator is epinephrine; infusion into postabsorptive normal subjects results in increased splanchnic release of glucose, *i.e.*, enhanced gluconeogenesis, and reduced peripheral tissue uptake of glucose.\(^{210}\) Similar effects are seen with cortisol infusion. They are seen almost immediately after the start of the epinephrine infusion but are delayed with cortisol infusion.\(^{214}\) Epinephrine inhibits insulin secretion, an action
that likely enhances glucagon's actions. Cortisol does not inhibit insulin release and thus does not result in as severe hyperglycemia. The mechanism for epinephrine's inhibition of insulin secretion appears to be inhibition of insulin exocytosis. This inhibition of insulin release can be reversed with α-adrenergic blockade.215 β-Adrenergic activity is responsible for the increase in hepatic glucose production.216 Infusion of somatostatin, the histamine type 2 receptor antagonist ranitidine, or naloxone failed to alter glucose kinetics in postoperative patients, whereas the prostaglandin antagonists diclofenac and dipyridamole increased insulin levels and decreased the rate of glucose turnover. Thus, prostaglandins may play a role in glucose kinetics.217

The increased gluconeogenesis and insulin resistance result in poor utilization of both endogenous and exogenous carbohydrates in stressed patients. Exogenous glucose administration, which reduces hepatic gluconeogenesis in normal subjects,218 only minimally decreases it in injured and septic patients. The obligate gluconeogenesis in stressed patients can often only be minimally altered by exogenous nutrients.219

FAT METABOLISM

Fat can be either utilized as an energy source or stored. Ingested and endogenous long chain triglycerides are metabolized to free fatty acids and glycerol. The free fatty acids can be metabolized as fuel or reesterified back to triglycerides. In the fed (high insulin) state reesterification predominates and lipolysis is inhibited,220 whereas in the starved state with a high glucagon:insulin ratio, fat is metabolized to free fatty acids (lipolysis) and then oxidized as fuel. This is associated with the production of ketone bodies by the liver mitochondria. Ketone bodies are then transported to other organs for use as fuels. The oxidation of exogenous lipid blocks the lipolysis of endogenous fat. It appears that fat mobilization, with the increase in free fatty acids, impairs muscle glucose uptake and oxidation.221

Glucagon and epinephrine increase the rate and degree of lipolysis; cortisol potentiates their action. This is due to activation of hormonestensitive lipase, the enzyme that controls adipocyte lipolysis. This enzyme is stimulated by β-1-adrenergic agonists and inhibited by α-2 stimulation.222 It is inhibited by insulin (which promotes lipogenesis). Forse et al.222 concluded that the lipolysis seen in sepsis and trauma is due to increased β-1 activity and/or decreased α-2 activity. Infusion of epinephrine-stimulated lipolysis was seen in only four of seven burn patients.223 However, the fact that some were not stimulated is not due to adrenergic receptor desensitization because administration of propranolol markedly decreased lipolysis. This continued responsiveness to catecholamines de-
In traumatized and septic patients it appears that there is reduced lipogenic ability. This becomes especially apparent when such patients are given large glucose loads with the resultant reduced ability to raise their respiratory quotient much above 1.0.\(^{237}\) One cause may be TNF/ cachectin, which can block lipogenesis in isolated adipocytes (it decreases lipoprotein lipase activity and has been implicated as the mediator of cachexia in neoplastic and parasitic diseases.\(^{238}\) IL-1-β may have similar but less potent effects\(^{239}\) as may PGE\(_2\).\(^{240}\)

An area of much interest has been the metabolic abnormalities found in patients with cancer. Patients with weight-losing gastrointestinal cancers have a greater ability to oxidize glucose than normal subjects.\(^{241}\) These patients may also have enhanced gluconeogenesis and muscle wasting. The latter is associated with an elevated cortisol and reduced insulin levels, an endocrine milieu that is conducive to catabolism. They may also have elevated rates of lipolysis but have an impairment in the ability to oxidize free fatty acids and infused fat emulsion. The latter is in contradistinction to septic and injured patients who have a marked increased ability to oxidize fat along with elevated lipolysis.\(^{242}\)

**PROTEIN METABOLISM**

Injury (surgical, traumatic, and burn) and sepsis result in accelerated protein breakdown.\(^{243}\) This is manifest by increased urinary nitrogen loss, increased peripheral release of amino acids, and inhibited muscle amino acid uptake observed in sepsis.\(^{244}\) The amino acids originate from both injured tissue and uninjured skeletal muscle and is transported to the liver for conversion to glucose (gluconeogenesis) and protein synthesis. The negative nitrogen balance observed in such patients represents the net result of breakdown and synthesis; with breakdown increased and synthesis either increased or diminished\(^{245}\) (fig. 5). Jahoor et al.\(^{246}\) observed in burned children that the amount of protein breakdown was consistently elevated to the same degree during the acute and convalescent phases, whereas synthesis increased in the latter phase and caused a positive nitrogen balance. Different muscle groups respond differently to injury and sepsis with some undergoing more proteolysis than others.\(^{247}\) Amino acid uptake by the liver is enhanced with resultant increased gluconeogenesis. Also, hepatic protein synthesis of selected proteins (acute phase reactants) increases while others decrease. The acute phase reactants include fibrinogen, complement, C-reactive protein, haptoglobin, α-1 acid glycoprotein, α-1 antitrypsin, α-1 anti-chymotrypsin, ceruloplasmin, ferritin, and serum amyloid A.\(^{248}\) The degree of acute phase response is proportional to the level of tissue injury.\(^{246}\) Those proteins the synthesis of which is decreased include transferrin, albumin, reti-
zymes. Studies in patients after abdominal surgery have indicated that infusion of somatostatin, ranitidine, or naloxone significantly decreased the rate of net protein catabolism while receiving 5% dextrose and during TPN. It is still unclear as to the contribution of the various mediators of stress to proteolysis.

There has been much interest recently in the metabolism of the individual amino acids, especially glutamine. Glutamine is the most abundant amino acid in blood. Its levels in muscle and blood decrease markedly following injury and sepsis, and it is consumed rapidly by replicating cells, such as fibroblasts, lymphocytes, and intestinal endothelial cells. Glutamine and alanine transport two thirds of the circulating amino acid nitrogen and in the postabsorptive and injured state comprise more than 50% of the amino acids released by muscle. In the stressed state the glutamine released by muscle is taken up by the intestinal tract where some is converted to alanine, which is then converted by the liver to glucose. It is likely that a good portion of the alanine converted by hepatic gluconeogenesis is supplied by the intestine. Glutamine is also metabolized to ammonia by the gut. The ammonia is then transported by the portal vein directly to the liver for disposal via the urea cycle. In the stressed state it appears that glutamine can replace glucose as a fuel. Similar observations have been made during glucocorticoid administration. It is possible that the use of glutamine may decrease protein catabolism in the intestine and elsewhere may prevent the gut atrophy seen in starved and parenterally fed individuals.

ENERGY METABOLISM

In most instances stressed patients have an increase in metabolic rate. After elective surgery this increase is about 10–15% with the peak around the third postoperative day. Patients with sepsis may have an even larger increase in energy expenditure (20–40%), whereas those with burns experience the greatest increases (up to 120%, the increase essentially proportional to the extent of the burn). This increase in energy expenditure is likely mediated by the change in metabolic milieu. Catecholamines, when infused into normal subjects, increase metabolic rate. This increase is even greater when cortisol, glucagon, and catecholamines are infused together. IL-1 and TNF both have been reported to increase energy expenditure. The metabolic processes that contribute to this increase in energy expenditure have been the subject of much interest. The increase in energy expenditure seen in the injured state has been ascribed by some to the increase in protein metabolism in these patients, especially the increase in protein synthesis. Yet, this may not always be the case; Lowry et al. noted that after elective surgery there was little change in energy expenditure despite an increase in protein turnover, thus implying little relationship between the two. The other metabolic process that may contribute to the increase in energy expenditure is the substantial increase in carbohydrate and fat futile cycling, a situation that causes a major increase in energy expenditure. The teleologic reason for this increase in futile cycling is that it provides these patients with a flexibility to quickly adapt to changes in energy substrate demands.

Various environmental factors may also affect energy expenditure. Maintaining an elevated ambient temperature (and humidity) has been shown to reduce the energy expenditure of burn patients by reducing evaporative losses and the need to generate increased energy to maintain body temperature.

Anesthetic Implications

The anesthesiologist must deal daily with the consequences of the body’s response to stress. This response manifests itself not only during and after surgery but often also prior to surgery. Before surgery many patients have elevated catecholamine levels due to fear and anxiety. Premedication is designed to allay these anxieties. Some patients may be in a more chronic state of psychologic stress due to prolonged anxiety over their illness, whereas others may have chronic physiologic stress due to the metabolic effects of their underlying pathology. The effect of chronic psychologic stress on both the neuroendocrine axis and the immune system is an area of concern to behavioral scientists. There is some evidence that chronic anxiety may result in suppression of the immune system and an alteration in the response of the neuroendocrine axis. The effects of chronic psychologic and physiologic stress on the outcome of anesthesia and surgery need further investigation.

Another aspect of the response to surgical stress is the major changes in ventilatory and cardiovascular function. Studies of normal volunteers infused with cortisol, glucagon, and epinephrine demonstrate a synergistic effect of the three hormones on minute ventilation and the rate pressure product. These are most evident after surgery when increased heart rate and minute ventilation are commonplace. These are especially stressful to patients with marginal cardiac and pulmonary function who may be unable to tolerate the increased demands. In these cases it may be important to alter the effects of the stress hormones, for example, by using β-adrenergic blockade to reduce heart rate and blood pressure. This often requires large doses to competitively block the increased amounts of circulating catecholamines.

Anesthesiologists must also be cognizant of the effects of anesthetics on the response to stress. As mentioned previously, epidural anesthesia can markedly suppress the
increase in many of the stress hormones. The majority of these studies have been performed in patients undergoing either lower abdominal (hysterectomy) or lower extremity surgery.\textsuperscript{10-42} It is interesting to note that some responses, specifically glucagon and insulin, were not affected. Epidural anesthesia is not able to attenuate the response to upper abdominal surgery completely.\textsuperscript{269,270} This is likely due to the inability of the epidural anesthetic to block all the afferent neural output arising from the upper abdomen. Subarachnoid anesthesia has effects similar to those of epidural anesthesia.\textsuperscript{271,272} Inhalational agents, in general, are unable to suppress any of the response to stress.\textsuperscript{273,274} However, studies using high doses of opioids, e.g., 4 mg/kg of morphine and 100 \mu g/kg of fentanyl, have demonstrated marked suppression in the hormonal (cortisol, catecholamines, GH, aldosterone, \(\beta\)-endorphin, and vasopressin) response to surgery.\textsuperscript{44,45,57} In operations involving cardiopulmonary bypass, the suppression is mainly seen only prior to cardiopulmonary bypass.\textsuperscript{275} The inability to totally suppress the increases in hormones may be due to a variety of factors. These include the inability of epidural anesthesia to totally block all afferent input as measured by sensory evoked potentials\textsuperscript{276,277} and possibly the local (injury site) release of mediators (e.g., IL-1). The use of anesthetics to alter the responses to surgery has previously been reviewed.\textsuperscript{5}

Another aspect of clinical management wherein it is important to have an understanding of the response to stress is the nutritional support of the injured and/or septic patient. The underlying disordered metabolism makes it a difficult task to design a support regimen. Nutritional support can be considered as providing exogenous substrate to a system that has disordered endogenous substrate utilization because injured and septic patients do not respond to nutrients in a manner like that of postabsorptive or starved subjects. Administering glucose to a starved subject causes decreased gluconeogenesis and lipolysis, whereas in stressed patients exogenous glucose fails to suppress gluconeogenesis or lipolysis to the same degree.\textsuperscript{278} Therefore, in stressed, hypermetabolic, and hypercatabolic patients with disordered glucose tolerance, the administration of carbohydrates must be approached carefully. Although it is necessary to provide some glucose calories to achieve some degree of protein sparing (by stimulating increased secretion of the anabolic hormone insulin) and reduce gluconeogenesis, providing excessive glucose loads should be avoided.\textsuperscript{279} Excess glucose is metabolized to carbon dioxide and converted to glycogen but is not as readily converted to fat due to a block in net lipogenesis.\textsuperscript{237} The administration of large glucose loads in such patients may result in additional increases in energy expenditure associated with additional increases in norepinephrine.\textsuperscript{237} This increase in metabolic rate (oxygen consumption) along with increased CO\textsubscript{2} production requires increased minute ventilation. It is thus recommended to limit glucose intake in such patients to less than 6 mg \textsuperscript{\mu}g/kg min\textsuperscript{-1}.\textsuperscript{280,281} This inability to utilize glucose has engendered interest in using other carbohydrates; fructose, xylitol, and glycerol have been or are now being studied.\textsuperscript{282}

Critically ill stressed (trauma, sepsis) patients often derive as much as 80\% of their energy requirements from fat. Fat emulsions containing polysaturated long chain triglycerides are utilized for iv administration. In most patients these are readily cleared and oxidized. However, there is a small minority of patients with severe sepsis who are unable to adequately clear and oxidize fat.\textsuperscript{283} In stressed patients fat is used to provide as much as 50\% of nonprotein calories. Studies have compared nutritional formulations containing only carbohydrate (glucose) as their sole nonprotein source to those containing approximately equal amounts of glucose and fat and found that they are equally nitrogen-sparing.\textsuperscript{284}

The provision of protein to stressed patients is an important aspect of nutritional support. It is necessary to provide adequate nonprotein calories, i.e., lipid and carbohydrates, so that the infused amino acids can be used as substrate for protein synthesis rather than as an energy substrate. The catabolic state found in burns, trauma, and septic patients markedly impairs the efficient utilization of exogenous nitrogen. Therefore, the aim of providing such patients with exogenous nitrogen and nutritional support is to attenuate the nitrogen losses. This has sparked much interest in the optimum nonprotein caloric to nitrogen intake ratio, the amount of protein required, and the type of protein required. There has been much controversy over the use of branched chain enriched amino acid solutions to improve overall nitrogen balance. Some studies have demonstrated better nitrogen retention with the branched chain enriched solutions than with conventional solutions\textsuperscript{285,286} while others have not.\textsuperscript{287,288,289} In one study branched chain enriched solutions did not improve outcome.\textsuperscript{288} There is continued interest in further modifying the composition of amino acid solutions to improve nitrogen retention.

Summary

Recent investigation has demonstrated that the response to stress is mediated by complex interactions between the nervous, endocrine, immune, and hematopoietic systems. Not only is the neuroendocrine system operative but monokines and lymphokines, such as IL-1, IL-6, and TNF, also play important roles. The discovery of these mediators, along with that of macrophage-derived substances that operate at the local wound level, such as platelet-derived, basic fibroblast, transforming, and epidermal growth factors,\textsuperscript{289} coupled with advances in mo-
lecular biology portends much for the future. The ability to alter the endocrine response with techniques such as epidermal anesthesia, the ability to specifically block certain aspects of the response (e.g., with adrenergic and prostaglandin antagonists), and the ability to synthesize potential beneficial mediators with recombinant DNA techniques (e.g., GH) may allow for modulating the response to decrease debility and complications.

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THE METABOLIC RESPONSE TO STRESS


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