Hormonal and Metabolic Response to Operative Stress in the Neonate

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ABSTRACT. It is evident from this review that newborns, even those born prematurely, are capable of mounting an endocrine and metabolic response to operative stress. Unfortunately, many of the areas for which a relatively well-characterized response exists in adults are poorly documented in neonates. As is the case in adults, the response seems to be primarily catabolic in nature because the combined hormonal changes include an increased release of catabolic hormones such as catecholamines, glucagon, and corticosteroids coupled with a suppression of and peripheral resistance to the effects of the primary anabolic hormone, insulin. (Journal of Parenteral and Enteral Nutrition 15:215-238, 1991)

It is apparent that adult patients demonstrate a catabolic response to the stresses induced by operative or accidental trauma. It seems that the degree of this catabolic response may be quantitatively related to the extent of the trauma or the magnitude of associated complications such as infection. The host response to infection, traumatic injury, or major operative stress is characterized by such events as fever, pituitary, and stress hormone elaboration, mineral redistribution, and increased acute phase protein synthesis.\(^1\)

The beneficial effects of this stress response are in providing alternate energy sources to meet metabolic demands as well as to provide essential building blocks for synthetic activities occurring in the postoperative period. It has been suggested that the hyperglycemic response is essential in supplying the increased glucose requirements of injured tissue.\(^2\) In addition, the proteolytic component of the stress response provides the necessary amino acid components for repairative protein synthesis and production of acute phase reactants by the liver. The changes in metabolic patterns induced by the stress response are satisfied in part by increased lipolysis and ketogenesis to provide an alternate source of metabolic fuel for tissues such as the brain and skeletal muscle. Additionally, the observed gluconeogenesis may aid in maintaining the glucose supply for vital organs principally dependent on glucose.\(^3,4\) However, this metabolic response has also been shown to potentiate many adverse conditions in the postoperative period and to further exacerbate the stress response. Examples of this include a hypermetabolic state with attendant increased oxygen consumption, increased energy requirements, increased temperature, elevated cardiac output, and altered or impaired inflammatory or immune responsiveness. Numerous investigators have demonstrated that adult patients exposed to severe degrees of traumatic stress are subjected to greatly increased rates of complications such as cardiac or pulmonary insufficiency, myocardial infarction, impaired hepatic and/or renal function, gastric stress ulcers, and sepsis. Furthermore, evidence exists to suggest that this response may be life threatening if the induced catabolic activity remains excessive or unchecked for a prolonged period. Moyer et al\(^5\) were able to identify with a great degree of certainty the patients who were likely to succumb based on a single analysis of a variety of plasma-borne substrates, obtained up to 9 days prior to death.

It is apparent that modulating or blunting the catabolic response induced by the stress state may have beneficial effects. In studies of postoperative pain management, improved pain control resulted in reduction of postoperative nitrogen loss and in shortened periods of convalescence following operation.\(^6,7\)

It is evident from this review that human newborns, even those born prematurely, are capable of mounting an endocrine and metabolic response to operative stress. Unfortunately, many of the areas for which a relatively well-characterized response exists in adults, are poorly documented in neonates. As is the case in adults, the response seems to be primarily catabolic in nature because the combined hormonal changes include an increased release of catabolic hormones such as catecholamines, glucagon, and corticosteroids coupled with a suppression of and peripheral resistance to the effects of the primary anabolic hormone, insulin.

The catecholamines may be the agents of primary importance in this response and, thus, may modulate the remaining components of the hormonal response to stress as well as the metabolic changes including an inhibition of insulin release, marked hyperglycemia, and a breakdown of the neonate's stores of nutrients (carbohydrate, protein, and fat). These reactions result, ultimately, in the release of glucose, nonesterified fatty acids, ketone bodies, and amino acids. Although these metabolic byproducts are necessary to meet the body's altered energy needs in a time of increased metabolic demands, it is not difficult to imagine that a severe or
prolonged response would be very detrimental to a previously ill neonate with limited reserves of nutrients and already high metabolic demands imposed by rapid growth, organ maturation and adaptation to the postnatal environment. Preliminary investigations by Anand et al outlined in this review indicate that alterations in anesthetic technique with the addition of agents such as halothane and fentanyl may be able to significantly blunt this catabolic response. In addition, it seems that modulation of the immune response may also greatly affect the postoperative catabolic response. It is hopeful that future developments and the acquisition of more detailed knowledge of the response will allow us to modify the stress response in postoperative neonates in order to further decrease their mortality and morbidity.

Postoperative or posttraumatic morbidity and mortality have, in high-risk adult patients, been correlated with, and may be precipitated by, the magnitude and duration of the endocrine and metabolic response to the stressful event. Specifically, complications such as severe weight loss, cardiopulmonary insufficiency, thromboembolic disorders, gastric stress ulcers, impaired immunologic function, prolonged convalescence, and death have been related to aspects of the hormonal and metabolic response to surgical or traumatic stress.5–8

These hormonal and metabolic responses to operative stress in the adult have been the subject of laboratory and clinical investigation for the past century; however, similar responses in newborn infants are not as well documented. The aim of this paper is to review available literature concerning hormonal and metabolic responses to operative stress in human neonates in order to present a concise, complete, and up-to-date compilation of current knowledge for all those caring for infants undergoing surgery. Metabolic complications or aberrations induced by operative stress may upset the delicate metabolic balance of a neonate already involved in the process of adaptation to its postnatal environment. In addition, the normal neonatal reserves of metabolic nutrients, namely carbohydrate, protein, and fat are limited and the energy-consuming processes of rapid growth and maturation are occurring simultaneously with the additional demands produced by an operation. This hypothesis is supported by experimental data which demonstrate a higher morbidity and mortality occurring in neonates than in older children or adults subjected to similar procedures.9,10 For these reasons, knowledge of specific aspects of the neonatal stress response may be of magnified importance in comparison to similar responses in the adult in an otherwise stable environment. Knowledge of this response is imperative for those providing care to these infants.

HISTORICAL BACKGROUND

Justus von Liebig (1848), a German organic chemist, is credited with being the first to recognize the process of metabolism, which he aptly defined as “The sum of chemical changes of materials under the influence of living cells.” This definition remains accurate today.

The interest in metabolic changes following surgical trauma began in 1872, when Joseph Bauer documented increased nitrogen elimination from the body following hemorrhage.12 Subsequently, J. D. Malcolm, in 1893, postulated an increased metabolic rate following abdominal surgery as the explanation for his observation of increased urea excretion following operation.13 Experimental support for these observations was provided by Aub and Wu14 who developed a feline laboratory model for traumatic shock and demonstrated a marked post-shock decline in basal metabolic rate as well as a rise in the nonprotein nitrogen, urea, creatinine, and glucose levels in blood.

Claude Bernard15 was centrally involved in early studies of mammalian metabolism with particular interest in the role of the central nervous system (CNS) in metabolic regulation. He was able to produce glycosuria and a diabetic condition in dogs through CNS manipulation and, in 1855, he postulated a central role for an adrenal gland-derived substance in the control of blood glucose.16 Subsequently, Bernard published his classic treatise on stress-induced physiologic changes, in which he demonstrated an increase in blood glucose associated with a simultaneous depletion of hepatic glycogen stores as a result of hemorrhage and trauma.17 Brown-Sequard18,19 confirmed Bernard’s hypothesis by successfully demonstrating the presence of adrenaline in the secretions of the adrenal gland. Further early observations on postoperative changes included Harold Pringle et al’s20 observations in 1905 that surgical operations were frequently followed by oliguria. G. H. Evans21 in 1911 demonstrated that salt retention was common in the postoperative period.

W. B. Cannon22 further focused attention on the endocrine response to injury when delivering The Shattuck Lecture of 1917. He described a condition of wound shock which produced a marked increase in sympathetic nervous system activity. He described stimulation of the output of adrenaline-like substances and a significant increase in blood sugar as a result of these changes. Cannon later introduced the idea of “homeostasis” to represent the constancy of the cellular environment, and he proposed that operative or traumatic injury posed a threat to the body’s “Homeostatic” mechanism.23,24

Cuthbertson,25 in 1929, characterized a catabolic response to injury consisting of increased losses of nitrogen, sulfur, and phosphorus in the urine. He was the first to propose that skeletal muscle was being catabolized after injury and coined the term “The catabolic response to injury,” which he felt accounted for the changes he observed in the urine.26 He subsequently demonstrated that diets high in protein and energy content were capable of diminishing the posttraumatic nitrogen losses but were unable to completely abolish this response.27

A significant therapeutic advance was made in 1936 with the publication of the classic paper by Hayes and Coller28 which demonstrated that the postoperative use of intravenous fluids was associated with maintenance of normal water exchange.

Hans Selye29 in 1946 described a “general adaptation syndrome” in response to stress and demonstrated that this adaptive process was associated with hypercalcemia, acidosis, and a negative nitrogen balance.

Francis Moore30 is well known for his important con-
Among his most important contributions is the demon-
textbook on this subject remains a classic resource.
tributions to the field of postsurgical metabolism. His
ory of surgery as occurring in four phases: 1) adrenerg-
corticoid phase, 2) the corticoid-withdrawal phase, 3) the
spontaneous-anabolic phase, and 4) the fat-gain phase.

Hayes and Coller demonstrated that postsurgical
cretion was determined primarily by the mag-
metabolism and physiology were greatly facilitated. Thus
Sandberg and his colleagues in 1954 were able to dem-
into the hormonal response to operative stress culmi-
which established the hypothalamus as the center of
control for initiation of the hormonal response to surgical
and nonsurgical stress.

Investigations of normal neonatal metabolism origi-
nated with Albert von Bezold's studies of a stillborn fetus
Camerer and Soldner's investiga-
tion of the hypothalamus which demonstrated the presence of an &ldquo;acidotic condition&rdquo; in new-
born infants. His findings were substantiated in studies
and full term infants are prone to develop acidosis. W. M. Marriott, in the
1919 Harvey lecture, described the many disastrous ef-
effects of dehydration on infants.

Early investigations suggested that the physiological
arrests associated with operative stress in the new-
born infant were the same as in the adult and differed
only in the degree of change. In order to facilitate
the acquisition of knowledge in this area and to optimize
perioperative care of surgical neonates, Peter Rickham
carried out extensive investigations in newborns modeled
after those done in adults by Moore and Ball. His 1957
monograph “The Metabolic Response To Neonatal Sur-
gery” remains a classic work in this area. As a result of
his studies and alterations in perioperative care based on
these, Rickham noted that the mortality for major sur-
gical procedures performed on neonates decreased from
76% in 1949 to about 25% in 1952.

Since the publications of Moore and Rickham, a great
number of investigators have been involved in the study
of postsurgical hormonal and metabolic changes in both
adults and neonates. We have attempted to summarize
the current knowledge of these responses in the following
sections.

ENDOCRINE RESPONSE TO SURGERY

Suits and Bottsford outlined a neuroendocrine reflex
which is set in motion by significant stress; components
of this reflex include an afferent arc consisting of those
stimuli that initiate the metabolic responses, and an
efferent arc which leads to volume restoration and energy
substrate production. The sequence is initiated by sur-
gical stress affecting the neuroendocrine reflex directly
through a nervous system signal to the CNS and indi-
rectly through the elaboration of catecholamines, the
major mediators of the hypermetabolic response, and
adrenocorticoids, major augmentors of this response. Components of the afferent arc involved
in such a system are nociceptors, chemoreceptors and
baroreceptors, all of which are capable of sending signals
to the hypothalamus where they become integrated into
the physiologic response seen in the stress state.

The efferent arc is described as originating in the
hypothalamus with efferent limbs traveling through the
brainstem autonomic regions and the pituitary. These
brainstem autonomic areas then send efferent fibers via
the parasympathetic and sympathetic nervous systems
to the periphery affecting neuromuscular junctions in
the circulatory system and receptors at end organs, which
stimulate the release of peripheral hormones. The pitui-
tary response leads to increased adrenocorticotropic
hormone (ACTH), vasopresin (ADH), growth hormone,
and prolactin release.

Neonates have well-developed neural pathways for
pain, in fact, the density of nociceptive nerve endings
in the skin of newborns is at least equivalent to that in
adult skin. These receptors have been noted to be present
throughout fetal cutaneous and mucosal surfaces by the
20th week of gestation. Thus, the initial component of
the proposed afferent arc is present early in fetal devel-

Endorphins

Numerous investigators have examined the role of
levels of endorphins in the postsurgical stress
response of adult patients. These studies have docu-
mented the importance of these opioid substances and
of hypothalamic receptors for these substances in the
initiation of the postsurgical stress response. The hypo-
thalamus is capable of modulating a wide variety of
hormonal secretions through its action on the pituitary
gland. There is growing evidence that they are closely
linked with other factors released simultaneously from
the pituitary such as ACTH. There is also experimental
evidence that beta-endorphin may be capable of gener-
ating a sympathetic nervous system response in the
hypothalamic nuclei resulting in a marked increase in
catecholamine secretion. The endorphins may also play
a role in the control of the release of the pancreatic
hormones, glucagon, and insulin. The precise source of
these endorphins is unknown with the hypothalamus,
pituitary, and adrenal glands all contributing to their
production.

In addition to the above-mentioned roles, it is generally
accepted that these substances (endogenous opioids)
cause some degree of analgesia. Recent studies have
demonstrated that encephalins, catecholamines, and ste-
roid hormones are released simultaneously from the ad-
renal gland in response to stressful stimuli. It is possible that another of the major effects of these opioid substances liberated during the stress response is to act as mediators of immune responsiveness in the stress state. It is known that components of the immune and endocrine systems share a common embryonic origin. In addition, it has been demonstrated that these two systems may share receptors as well as signal molecules. Some experimental studies have demonstrated a role for opiate antagonists in the shock state with resultant reversal of the hemodynamic and biological sequelae of shock, suggesting that endogenous opioid generation may indeed impair the ability of the host to mount an effective immune response. Present experimental evidence using a variety of opioid compounds in in vitro systems of lymphocyte and neutrophil function have demonstrated that either stress-mediated endogenous or exogenous opioids are capable of altering neutrophil and lymphocyte function, thus altering host immune defenses.

The importance of immune responsiveness in primarily mediating posttraumatic stress responses was supported in a recent study by Michie and co-workers, who demonstrated that infusion of the macrophage-derived cytokine, tumor necrosis factor (TNF), was capable of inducing a significant stress response in otherwise healthy humans. These responses were similar to those produced by injection of endotoxin in healthy volunteers. Hormonal alterations such as elevated ACTH and, subsequently, cortisol levels were marked and were attributed to TNF’s ability to directly influence pituitary hormone release as well as elaboration of stress hormones. TNF was also capable of inducing significant formation of the acute phase reactant, C-reactive protein. These authors even postulated an immunoregulatory feedback loop which is active in controlling the magnitude of the TNF-mediated stress response, indicating that elevated circulating levels of TNF were capable of stimulating ACTH release, which results in an increase in circulating glucocorticoids, which may subsequently inhibit further synthesis of TNF by macrophages. Tumor necrosis factor has also been heralded by Beutler and Cerami as a general mediator of inflammatory and catabolic processes, capable of effecting stress responses from the hypothalamus and adrenal cortex. The role of the TNF in mediating the neonatal or adult response to the stresses induced by operation is unknown but it is conceivable that this may be yet another important mediator in the postoperative response observed.

Increased beta endorphin, as well as ACTH levels, have been documented in cord blood at the time of delivery, which clearly produces a significant physiological stress. These substances have been demonstrated to be elevated in neonatal blood following periods of stress as well as in amniotic fluid during periods of fetal distress. Neonates subjected to increased stress at the time of delivery (breech presentation or vacuum extraction) have documented further elevations in cord blood beta endorphin levels, suggesting a maturation of the capacity for stress related to release of this hormone. Altered beta endorphin levels have also been demonstrated in neonatal septic shock and have been considered to play a significant role in this state. There is some evidence to suggest that altered beta endorphin levels may be related to neonatal apnea and even the sudden infant death syndrome.  No data on the effect of operative stress on beta endorphin levels in neonates have been reported.

**Pituitary Hormones**

Upon initiation of the stress response, in addition to stimulation of endorphin release as mentioned above, there is also liberation of anterior and posterior pituitary hormones. This has been demonstrated in both clinical and experimental models with elevations of ACTH, growth hormone, prolactin, and arginine vasopressin being documented. The role of these elevated hormone levels in mediating the metabolic response to surgery is, however, not well established. The literature contains no studies documenting alterations in the levels of these hormones in the postoperative neonate. Boix-Ocha et al recently published a study examining the cortisol response to operative stress in neonates, as well as the response to exogenously administered ACTH. He demonstrated significant increases in cortisol levels following ACTH administration and noted that this response was similar to the increases noted in postoperative neonates. This study provides indirect evidence for the role of pituitary-derived ACTH in the hormonal/metabolic response to operative stress in the neonate.

**Catecholamines**

Studies in adult patients have repeatedly documented substantial rises in serum adrenaline and noradrenaline levels in response to operative or traumatic stress. Investigations of catecholamine responses in neonates are also numerous. Nakai and Yamada in 1978 studied catecholamine secretion in normal neonates and in neonates subjected to the stress of birth asphyxia. They demonstrated significant (approximately two-fold) rises in adrenaline and noradrenaline levels after a normal birth. In addition a further significant increase in noradrenaline (2-fold) was noted following asphyxia; however, no additional significant rise in adrenaline concentration was noted. They attributed these rises to responses by the adrenal medulla and sympathetic nervous system to the combined stresses of labor and asphyxia. They concluded that noradrenaline was the dominant amine secreted by fetal and neonatal chromaffin tissue during stress and postulated that extramedullary chromaffin tissues (sympathetic nervous system) of the fetus play a significant role in this response. Talbert et al. in 1967 studied neonates undergoing bilateral inguinal herniorrhaphy and documented rises, though not statistically significant, in epinephrine levels, presumably secondary to the operative stress. The same statistically insignificant rise was also demonstrated with norepinephrine. The absence of significant increases in these two hormones was attributed to the relatively minor surgical stress of inguinal herniorrhaphy. They also expressed methodological concern regarding the difficulty
of measuring circulating catecholamines systemically. Their concerns centered around using a relatively insensitive assay, and the knowledge that these molecules may be rapidly cleared from the systemic circulation into more localized peripheral tissues where they exert their effects.

Anand et al\(^4\)–\(^6\) have reported extensively on fetal metabolic and hormonal responses to operative stress and anesthetic management. They have published several studies on the catecholamine response to surgery. In 1985, they reported their studies on various metabolic and hormonal parameters in neonates undergoing surgery and correlated these findings with a quantitative measure of the amount of stress encountered in the form of a surgical stress score.\(^4\) They documented a highly significant increase in the plasma adrenaline and noradrenaline concentrations at the end of surgery. They postulated that the catecholamine response was important in the initiation of the hyperglycemic response noted in postoperative neonates. In addition, they suggested that elevated catecholamines in postoperative neonates may also play a role in hepatic gluconeogenesis by providing significant amounts of substrate in the form of plasma lactate and pyruvate from the breakdown of glycogen in peripheral tissue.\(^6\)

A subsequent study again demonstrated significant increases in plasma adrenaline and noradrenaline concentrations by the end of an operation, but, by 6 hours postoperatively, the levels of adrenaline and noradrenaline had returned to preoperative values, in both term and preterm infants.\(^5\) They noted that the pattern of change in noradrenaline levels was similar to that of adult patients, however the increases in adrenaline during surgery contrasted with the data available from adult subjects in whom adrenaline levels may fall or remain unchanged during surgery and rise only during the postoperative period.

These findings were confirmed in a study documenting a significant rise in plasma adrenaline concentrations during patent ductus arteriosus (PDA) ligation; however, this response was abolished by fentanyl anesthesia.\(^6\) Significant increases in plasma noradrenaline concentration following surgery were also noted. Fentanyl had little effect on noradrenaline production in the immediate postoperative period, but a diminution of noradrenaline levels was noted in the fentanyl group at 24 hours postoperatively.

In another study comparing anesthetic techniques with or without halothane the most prominent difference in the hormonal responses between the halothane and nonhalothane groups was the changes in the catecholamine concentrations during operation. Neonates in the group that received unsupplemented nitrous oxide (without halothane) showed changes in adrenaline and noradrenaline concentrations that were two to three times greater than the changes seen in the group receiving halothane.\(^7\) The ability to ablate these stress-related responses by either halothane or fentanyl anesthesia suggests that these reactions are initiated by nociceptive stimuli during surgery.

The metabolic effects of these hormonal changes are multiple. Adrenaline not only stimulates hepatic glucose production and causes a sustained decrease in peripheral glucose utilization, it also stimulates glucagon secretion and suppresses the release of insulin. Arteriovenous catheterization in adult patients has demonstrated that the release of adrenaline during surgery causes an increased production of lactate and pyruvate through glycogenolysis in skeletal muscle.\(^8\)

In addition to the metabolic effects outlined above, the physiologic response to the effects of simultaneous sympathetic nervous discharge with norepinephrine release peripherally, as well as adrenomedullary secretion of both epinephrine and norepinephrine, include: increased minute ventilation, increased cardiac output and heart rate, elevated blood pressure, redistribution of blood flow with splanchnic vasoconstriction, dilatation of the skeletal muscle vasculature, and central nervous system stimulation.

Catecholamines are ultimately also capable of 1) extracellular fluid volume restoration and maintenance and 2) energy substrate production. They may stimulate beta adrenergic receptors in the renal juxtaglomerular apparatus (JGA) causing renin secretion while also decreasing glomerular filtration rate (GFR) in response to decreased extracellular fluid volume (as a result of external losses in the form of hemorrhage or internal redistribution of fluids). Renin may then act on angiotensinogen to convert it to angiotensin I.

**Pancreatic Hormones**

Of the numerous hormones secreted by the endocrine pancreas, glucagon and insulin have received the most attention with regard to postsurgical and posttraumatic metabolic regulation. Numerous studies have demonstrated correlations of levels of these hormones with serum glucose as well as with adrenaline concentrations.

**Insulin**

One of the earliest reports correlating insulin levels with postoperative metabolism came from Ross et al\(^9\) and appeared in the Lancet in 1966. This group demonstrated significant decreases in plasma insulin levels intraoperatively, but noted a significant increase above preoperative levels during the postoperative period. In addition, the patients in these studies were noted to have a reduced tolerance to parenterally administered glucose in the postoperative period, in spite of their elevated insulin levels. These early findings have been confirmed by numerous other investigators.\(^3, 7, 8, 9, 10\)

Finley et al,\(^8\) in contrast, noted a significant drop in arterial serum insulin levels in postoperative adults who had undergone major operative procedures. This decrease was attributed to increased activity of the sympathetic nervous system and was thought to be mediated by an alpha adrenergic mechanism.\(^8\) They proposed that the end result of this presumably norepinephrine-mediated response was regulation of protein metabolism after trauma by changing the ratio of glucagon to insulin, with the resultant increase in hepatic glucose production through increased extraction of glycogenic amino acids.
Neonatal insulin levels and glucose metabolism have been studied experimentally by Mayor et al., who reviewed changes during four stages of the perinatal period (late fetal, presuckling, suckling, and weaning) in a rat model. They documented the important role of insulin along with glucocorticoids in mediating hepatic glycogen deposition. They postulated that insulin aided in this function by activating glycogen synthesis in the late fetal stage of development. They also demonstrated that insulin mediates fetal rat liver lipogenesis, as in the late fetal stage of development. They hypothesized that the relatively blunted effects of fetal insulin on adult, but only very late in gestation. They postulated that these elevated insulin concentrations could potentially antagonize the effects of catecholamines on inducing hepatic glycogenolysis.

Anand and Aynsley-Green have examined the insulin response to operative stress extensively in human neonates and have documented no significant change in the plasma-insulin levels of preterm neonates undergoing ligation of PDA. They did, however, note a significant decrease in the molar insulin/glucose ratio at the end of surgery. This was due to significant increases in blood glucose. The total lack of insulin secretion in response to postsurgical hyperglycemia may be due to either a decreased responsiveness of beta cells in the premature pancreas, which has been documented previously, or a direct inhibition of insulin secretion by the adrenaline which is released during surgery.

In a subsequent study by this group, again no significant alteration in insulin levels was documented by the end of surgery in a group of neonates. They did, however, observe significant elevations in insulin concentrations by 6-, 12-, and 24-hours postoperatively in term neonates, similar to the adult response. Preterm neonates, in contrast, had insulin levels which remained unchanged during the postoperative period. They again postulated that this may be due to a decreased responsiveness of beta cells in the premature pancreas and “may explain the tendency of preterm neonates to develop a greater hyperglycemia than term neonates during and after surgery.” They again suggested that the lack of an insulin response to the hyperglycemia developed during surgery was most likely due to a direct inhibition of insulin secretion by intraoperative adrenaline release.

The total lack of an insulin response in preterm neonates may not only result in unopposed catabolism during the postoperative period, but, through the development of a greater hyperglycemia, may precipitate a rapid increase in plasma osmolality during surgery.

These findings were substantiated in a 1985 study. Support for the inhibitory effect of catecholamines on insulin secretion was provided in 1987 by this group through evaluation of infants undergoing ligation of PDA with or without fentanyl added to a standard anesthetic regimen. They demonstrated that the fentanyl-treated infants had a diminished catecholamine response and an increase in the insulin/glucagon ratio, relative to the nonfentanyl group.

**Glucagon**

Numerous experimental animals as well as adult human studies have demonstrated significant elevations in plasma glucagon concentrations in the postoperative period. Experimentally, the infusion of glucagon leads to an increase in glucose production, which in an experimental model of the metabolic response to stress, was potentiated by adrenaline infusion and sustained for a prolonged period by cortisol. In addition, glucagon acts on skeletal muscle to cause amino acid mobilization, ultimately releasing three carbon amino acids (primarily alanine) which stimulate gluconeogenesis, increase urea production, replenish hepatic cell mass, and lead to the production of acute phase reactant glycoproteins.

Again, little comprehensive data regarding the role of glucagon in the postoperative stress response to neonates exists. Three studies from Anand and his colleagues demonstrated no significant alteration in plasma glucagon levels during or soon after surgery; however, by 24 hours postoperatively, a significant decrease from the preoperative values in term neonates had occurred, in contrast to the above-mentioned adult studies where elevations were noted. They noted strong positive correlations between blood glucose concentrations and plasma glucagon levels at 6 hours postoperatively. The significance of the neonatal glucagon response in contrast to the adult response is unknown. Anand et al pointed out that they studied only a small (n = 7) number of patients and suggested that further confirmatory studies and examinations of the mechanism and implications of this decrease are needed. No clear cut explanation for the marked difference between the adult and neonatal responses exists.

**Adrenocortical Hormones**

Adrenocorticoids, initially considered to be the major mediators of the posttraumatic metabolic response, are currently thought to play a permissive or subsidiary role.

Glucocorticoids are involved in restoration of extracellular fluid volume via a shift of fluid between intracellular and extracellular spaces, through their effect on extracellular osmolality. Glucocorticoids, however, make their greatest contribution by participating in substrate production. Cortisol acts directly on adipose tissue to cause lipolysis and the release of free fatty acids. Additionally, through its mobilization of amino acids from skeletal muscle, its stimulation of glucagon production and its augmentation of catecholamine-induced hepatic glycolysis, cortisol also influences the hyperglycemic state.

The effects of surgery on secretion of adrenal corticosteroid hormones has received much attention. It is well established that glucocorticoid hormones, primarily cortisol, are crucial in the metabolic response to
surgical stress in the adult, modulating the breakdown of proteins and leading to the release of gluconeogenic amino acids from skeletal muscle. In an experimental model Hulton et al.81 were able to attenuate the skeletal muscle proteinolysis initiated by cortisol by blocking the postoperative rise in catecholamines and cortisol with epidural anesthesia. Solomon et al contributed a landmark article concerning steroid biosynthesis and metabolism in the fetus and placenta in 1967.108 Unfortunately, our understanding of the adrenocortical response to operative stress in the neonate has progressed little since these early studies. Anand et al demonstrated that the adrenocortical responses of premature babies were characterized by the diminished secretion of the final products of steroid biosynthesis and an increased secretion of the precursor steroid hormones.86 This was attributed to the immaturity of the steroid biosynthetic process as outlined by Solomon et al.108

**Cortisol**

Circumcision is an operation frequently performed during the neonatal period. Physiologic as well as behavioral effects of circumcision have become the subject of numerous recent studies.109-113 These studies have demonstrated that the neonate is capable of a significant cortisol response to the stress induced by circumcision, as early as in the first 6 hours of life. That these data paralleled the response to exogenous ACTH administration by earlier investigators114 led to the conclusion that the circumcision-induced response is likely secondary to endogenous ACTH production and that an intact hypothalamic-pituitary axis does exist and is capable of generating a stress response in these young infants. The ability to block the cortisol response using the technique of dorsal nerve block suggests that the cortisol response noted with circumcision is mediated at least in part through afferent nerve pathways.115

A more detailed look at adrenocortical responses was outlined in a recent article by Boix-Ocha et al involving a 7-year study of infants and neonates undergoing operative stress or chemical (ACTH administration) stress.117 A number of significant observations were noted: neonates did not demonstrate the normal adult circadian cycle of plasma cortisol levels (this difference was postulated to be secondary to neuroendocrinological immaturity), and the cortisol response to surgical or biochemical (ACTH) stimulation was age dependent, with neonates mounting a quantitatively lesser response than infants. Neonates less than 9 days of age released significantly lesser amounts of cortisol in response to surgical stress. The results were interpreted as follows: "Cortisol liberation is a defense mechanism of the organism in order to mobilize stored energy reserves and form new ones. When faced with a grave situation that requires an urgent response, cellular metabolism is activated. The sparse energy stores of our patients require prompt stimulation. Therefore, as shown in our study, the response is earlier in the neonate than in the infant, according to their reserves." By comparing postsurgical stress to ACTH stimulation, the transmission factor (afferent conduction pathway for pain or the mature neuroendocrine system) was eliminated and the capacity of the adrenal reaction was demonstrated. Both infants and neonates were shown to have an adequate capacity for response. The factor of age or maturation of the transmission system seemed most important. They suggested that the neuroendocrinological maturation of the response seems to become stabilized after 9 to 10 days. Differences noted between infants and neonates included: 1) the chronological appearance of the maximal cortisol peak, which depends on the energy reserves of each group and 2) the intensity of the response, which depends on the adrenal's capacity to respond.

A number of interesting observations have thus been made and a few qualitative and quantitative differences between children and adults have been noted, indicating the need for further study in this area.

**Aldosterone**

Aldosterone functions by acting on the ascending limb of the loop of Henle as well as the distal tubules and collecting ducts of the kidney leading to increased sodium reabsorption, and secondarily, water reabsorption. These actions lead to volume restoration as well as decreased sodium bicarbonate excretion producing a net increase in potassium and hydrogen ion excretion with a resulting alkalosis. Aldosterone also acts on cardiac and vascular smooth muscle producing a pressor effect. In addition, aldosterone is known to augment the action of ADH, the second major (catecholamine-stimulated) pathway for volume restoration.

In adult patients undergoing major surgical procedures, plasma aldosterone concentrations have been found to increase within minutes following surgery and to remain elevated for up to 24 hours postsurgery.116 Enquist et al.117 found that the aldosterone response to surgery could be inhibited by intravenous saline given during the surgical procedure.117 These authors proposed that infusion of saline inhibits the renin release seen during surgery and thus decreases the aldosterone responses.

No data regarding the aldosterone response in postoperative neonates was found in our review of the literature.

**Growth Hormone**

Growth hormone levels are increased in the posttraumatic state. Either by direct action or via somatomedins, growth hormone inhibits the action of insulin, decreasing glucose uptake in muscle and increasing free fatty acid output by stimulating lipolysis in adipose tissue. Growth hormone also increases peripheral uptake to amino acids, but this effect is not realized unless the patient is fed.

Growth hormone release has been observed in adults subjected to operative stress, and the quantity of growth hormone release was proportional to the degree of stress.118

Ward et al.119 in a recent study, demonstrated that administration of growth hormone following gastrointestinal surgery in adult patients resulted in a postoperative protein synthesis rate 209% higher than in controls. The
protein breakdown rate was 170% higher than controls and the net relative increase in synthesis to breakdown increased by 39%. They suggested that the increased net synthesis rate was due to a greater efficiency of protein metabolism, and thus, that growth hormone administration was capable of improving the efficiency of protein metabolism after surgery. In addition to the observation of diminished oxidation of protein, these investigators demonstrated increased fat oxidation in patients receiving growth hormone, which is consistent with other studies which have documented the capacity of growth hormone to increase lipolysis and free fatty acid oxidation.\(^{120}\)

One study recently demonstrated a postoperative rise in the level of growth hormone following open heart surgery in infants.\(^{121}\)

**Renin-Angiotensin System**

The renin-angiotensin axis plays a crucial role in maintaining perfusion following hypovolemia or injury. Renin is released by the juxtaglomerular apparatus of the afferent renal arterioles in response to decreased perfusion pressure, increased sympathetic stimulation, and decreased sodium chloride delivery to the distal renal tubules. Renin acts upon angiotensinogen, produced in the liver, to convert it to angiotensin I. The synthesis and release of angiotensinogen are increased by ACTH, cortisol, estrogens, and angiotensin II. Angiotensin I exerts its major effects after conversion to angiotensin II. There are three important actions of angiotensin II in the metabolic response to trauma: 1) it is a very potent vasoconstrictor and chronotropic as well as inotropic agent, 2) it may act centrally to effect an indirect stimulation of ACTH and ADH secretion and sympathetic neurotransmission, and 3) it may also act directly by functioning as the primary stimulus to the secretion of aldosterone from the zona glomerulosa of the adrenal cortex.

Adult patients have been demonstrated to produce a 3-fold increase in plasma renin activity following an operation.\(^{122}\) These changes in plasma renin activity have been found to be clearly correlated with blood pressure changes during surgery.\(^{123}\) This alteration in renin activity appears to be a transient phenomenon, with return to normal levels shortly after surgery.\(^{124}\)

No studies detailing the plasma renin response to operative stress in newborns were discovered during our search of the literature; however an increase in plasma renin activity has been observed to follow the stress of venipuncture with return to basal levels 60 minutes thereafter. These findings are somewhat difficult to interpret as there were no significant changes in the plasma levels of cortisol, epinephrine, or norepinephrine following venipuncture. As has been outlined in earlier sections, these hormones have been consistently demonstrated to be increased following operative stress in other newborn studies. It remains possible that renin responses may be triggered by a degree of stress lower than the threshold required to induce the release of catecholamines or cortisol, although this seems unlikely. Certainly this area is ripe for further study.

**Antidiuretic Hormone (ADH)**

In addition to increasing renal water absorption, ADH is a potent vasopressor. It also has a direct sympathetically effect on the pancreatic islet cells, causing glucagon release and insulin suppression.

No data regarding the actual measurement of the ADH response in the stressed situation was found in either the adult or pediatric literature. However, recent studies by Coran and Drongowski\(^{126}\) measuring total body water and extracellular fluid volume in postoperative neonates suggest water retention occurs in the early postoperative period in newborns, and ADH has been postulated to be involved in this process.

**Thyroid Hormones**

Finley and others\(^{80, 127, 128}\) have demonstrated that operative trauma results in a fall in serum active tri-iodothyronine and a rise in inactive tri-iodothyronine (reverse T3) levels.

Hasselgren et al\(^{129}\), in an experimental model of sepsis in thyroidectomized rats, demonstrated reduced serum levels of T3 but maintained or increased muscle concentrations of the hormone, suggesting that increased T3 uptake by muscle may be one mechanism explaining the “Low T3 Syndrome” in sepsis. These studies further support a role for thyroid hormone in the metabolic alterations in muscle protein metabolism during sepsis although the exact mechanisms remain to be elucidated. It is possible that such alterations may also be present in the postoperative state.

It is known that shortly after birth there is a surge in TSH levels, followed by a remarkable change in thyroid hormone economy from preferential formation of reverse T3 to T3. A number of critically ill neonates have been recognized to have a low T4/T3 syndrome. No data specifically concerning changes in thyroid hormones in postoperative neonates are available.

In conclusion, the endocrine response of adult patients to surgical trauma is characterized mainly by a substantial increase in the circulating concentration of the catabolic hormones and a decrease in the plasma concentration of the global anabolic hormone, insulin. The magnitude and duration of this response, particularly with respect to changes in the plasma concentrations of cortisol, catecholamines, glucagon, growth hormone, and vasopressin appears to be proportional to the extent of the surgical injury. In addition, changes in the blood concentrations of some of these hormones may be prolonged in patients with postoperative complications. It has been documented that these hormonal changes may have profound effects on metabolic homeostasis, circulatory hemodynamics, immunocompetence, renal homeostasis, and gastrointestinal physiology as well as having behavioral and psychological effects on patients undergoing surgery. The adjustments in fuel metabolism during and after surgery resulting from these hormonal changes will be discussed in the following section.
The neonatal hormonal response to operative stress is much less well characterized. It is predominantly catabolic as well with documented elevations of catecholamines and endorphins. The alterations in glucagon and insulin levels in neonates do not parallel the adult data. Cortisol responsiveness is also diminished in comparison with data from the adult literature and this difference may be maturation dependent. In short, there are many areas of the hormonal response to operative stress which have not been thoroughly investigated in the neonatal age group (Table I).

**METABOLIC RESPONSE TO SURGERY**

Considerable data have been accumulated which characterize the metabolic response of adults to surgery. A great deal less is known about the metabolic effects produced in neonates by major operative procedures. Metabolic studies, even on normal infants, are few, due to limitations caused by insensitive assays, difficulties inherent in conducting prolonged observations, and the limited amount of blood that can be withdrawn ethically. It is apparent that postoperative treatment would be greatly improved if a thorough understanding of the metabolic consequences of operative stress were achieved. The evidence suggests that neonates frequently respond to trauma and stress in a manner different from that of adults or older children.

There is a reasonable body of data demonstrating that adult patients show an increase in oxygen consumption after trauma or operation after a brief "Ebb" period of a depressed metabolic rate immediately following the trauma or operation. \(^{130,131}\) In a study of oxygen consumption in postoperative neonates, Ito and colleagues \(^{132}\) demonstrated that the oxygen consumption (VO\(_2\)) of a full-term, normally-fed neonate increases with advancing age until approximately the second or third week of life. These investigators demonstrated that some postoperative newborns, predominantly those undergoing major abdominal operations, manifest a lower postoperative oxygen consumption than would be expected (Table II). Additionally, no postoperative increase in mixed venous oxygen saturation (mVO\(_2\)) in comparison with normal newborns of the same age was noted. These findings are in striking contrast to the adult data of increased metabolic rate, noted above. Ito and colleagues concluded that postoperative oxygen consumption in neonates is better correlated with caloric intake than with the intensity of the operative stress, in contrast to the findings in adults.

**Carbohydrate Metabolism**

Adult postoperative changes in carbohydrate metabolism can be summarized as a significant hyper-

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**Table I**

**Hormonal response to operative stress in the adult and neonate**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Actions</th>
<th>Adult</th>
<th>Neutone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endorphins</td>
<td>Actions—Modulate ACTH secretion + Hypothalamic sympathetic response → T Catecholamine release — Modulate insulin and glucagon secretion — Immune modulation</td>
<td>No postoperative data</td>
<td>↑ After stress of delivery</td>
</tr>
<tr>
<td>Pituitary hormones</td>
<td>↑ ACTH, Growth Hormone (GH), prolactin, vasopressin (G.H.) → ↑ Lipolysis &amp; FFA production → ↑ Protein synthesis → ↑ Insulin action</td>
<td>No direct data (Pharmacological administration of ACTH → ↑ Cortisol as in Postop. Neonates, therefore suggests ↑ ACTH Postop)</td>
<td>No direct data (Pharmacological administration of ACTH → ↑ Cortisol as in Postop. Neonates, therefore suggests ↑ ACTH Postop)</td>
</tr>
<tr>
<td>Pancreatic hormones</td>
<td>Insulin ↓ Intraoperatively; Conflicting data for postoperative ↑ or ↓</td>
<td>↑ Glucagon → Amino acid mobilization which → Gluconeogenesis and new protein synthesis</td>
<td>↑ Insulin/glucose ratio secondary to relative ↑ glucose</td>
</tr>
<tr>
<td>Adrenocorticoids</td>
<td>Cortisol ↑ → Lipolysis &amp; FFA release → Amino acid mobilization from skeletal muscle → glucagon production</td>
<td>Little data. No change until 24 hr postoperatively and then ↓</td>
<td>Age dependent ↑</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>↑ — Volume Restoration</td>
<td>No available data</td>
<td>No available data</td>
</tr>
<tr>
<td>Renin/angiotensin</td>
<td>3 × ↑ in renin</td>
<td>No available data</td>
<td>No available data</td>
</tr>
<tr>
<td>Antidiuretic hormone</td>
<td>No available data</td>
<td>Indirect evidence of ↑</td>
<td>No available data</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>↓ T(_3) (active) and ↑ rT(_3) (inactive)</td>
<td>No available data</td>
<td>No available data</td>
</tr>
</tbody>
</table>
TABLE II
Metabolic response to operative stress in the adult and neonate

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Adult</th>
<th>Neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic rate and oxygen</td>
<td>Briefly, then ▲</td>
<td>▲ Compared to adults (minimal change compared to age-matched controls)</td>
</tr>
<tr>
<td>consumption</td>
<td>▲ Hyperglycemic response</td>
<td>▲ Glucose 2x immediately postoperatively (less persistent ▲ than in adults)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>▲ Gluconeogenesis and ▲ glucose utilization</td>
<td>—probably secondary to glycogenolysis rather than ▲ gluconeogenesis—neonates may be unable to carry out hepatic gluconeogenesis secondary to lack of key enzyme</td>
</tr>
<tr>
<td>Protein</td>
<td>Negative nitrogen balance—Slight ▲ protein breakdown—dependent on severity of stress; ▲ with increased severity—● Protein synthesis in extrahepatic tissues ▲ Amino acid utilization for gluconeogenesis, acute-phase reactant synthesis and synthesis of components of healing process ● Lipolysis + Ketogenesis (? catecholamine stimulated) — Total ketone bodies, ▲ Glyceral, ▲ Nonesterified fatty acids. Postoperative fat utilization exceeds rate of mobilization of free fatty acids</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>Adipose tissue lipolysis → Mobilization of nonesterified fatty acids and ▲ ketone body formation —Kinney (1970)- 75-90% of postoperative requirements supplied by fat metabolism (10-25% by protein)</td>
<td>● Nitrogen excretion—sustained up to 5 days Negative nitrogen balance 72-96 hr postoperatively ▲ Nitrogen loss in neonates compared to older infants ▲ Muscle protein breakdown, impaired nitrogen utilization, transient ▲ nitrogen excretion ▲ (vs adult) in gluconeogenic amino acids in postoperative plasma</td>
</tr>
</tbody>
</table>

glycemic response both during and after surgery. This effect may be the result of both an increase in glucose production as well as a diminution in peripheral glucose utilization, with a relative decrease in insulin concentrations.

Pioneering work early in this century by Benedict and Talbot, who monitored the respiratory quotients (RQ) of normal newborn babies, demonstrated that as much as 80% of the energy requirements is fulfilled by calories derived from fat. This is interesting in light of the fact that carbohydrates provide the main source of energy in the fetus. However, soon after birth and even before feeding is started, a rapid fall in glycogen reserves has been demonstrated. In addition, the blood glucose concentration is also known to fall in the early postnatal period. An increase of plasma free fatty acids (FFA) and ketone bodies has been documented to occur concurrent with these changes in glucose and glycogen, adding support to the importance of fat-derived calories in the newborn as he/she changes his/her major metabolic foodstuff.

Unfortunately operations on neonates are frequently accompanied by periods of starvation which may be prolonged, especially if the gastrointestinal tract is involved. The advent of hyperalimentation has aided somewhat in altering this pattern. It is known that depot fat accounts for 10-15% of the body weight of the normal human neonate, and, as stated above, this may provide the main source of energy during the period of starvation soon after birth.

**Glucose**

In 1968, intravenous glucose tolerance tests were performed on 14 newborn babies being operated upon for abnormalities of the alimentary tract. The authors observed that six of these 14 infants had a greatly reduced tolerance to glucose administered by intravenous infusion. They noted a constant rate of glucose disappearance which was unrelated to the absolute glucose concentration, in contrast to data in older children and adults whose rate of disappearance varies with the rate of administration. Elphick and Wilkinson postulated as explanations for these observations: 1) babies may be less able than adults to form glycogen from glucose, 2) there may be a temporary increased insulin dependency in the newborn, and 3) the uptake of glucose by the tissues may be reduced by high circulating concentrations of hormones such as adrenaline and growth hormone. These authors also noted depression of the concentration of free fatty acids after the injection of glucose, which suggested that the administered glucose may have had a fat-sparing action even when the Kt values (percent clearance of administered glucose from blood per minute) were low. They concluded that the prolonged use of parenteral glucose solutions might, in some cases, lead to severe hyperglycemia and that there is marked variability between infants in their capacity to handle infused glucose.

Elphick and Wilkinson also demonstrated a postoperative increase in the blood glucose concentration to approximately two times preoperative levels in newborns but noted that the glucose concentration returned to normal within 12 hours. This is in contrast to data from adult surgical patients where blood glucose levels may remain high for several days. These authors noted the similarity of their findings to those of Pinter and
proposed that the elevation in blood glucose noted in the postoperative period may be due to either increased production or decreased utilization of glucose or a combination of the two. In an earlier study of glucose tolerance testing in postoperative infants a diminished glucose utilization had been demonstrated by these investigators. In attempting to explain this relative intolerance, they cited the type of anesthesia as one important contributory factor. The mechanism postulated was a direct effect by endogenous catecholamines resulting in altered glucose metabolism with variations in anesthetic methods effecting the degree of the catecholamine response. This concept has been confirmed in experimental studies with newborn rabbits and puppies. The conclusion from these experiments was that endogenous sources of energy were capable of supplying a sufficient number of calories to satisfy the requirements of normal infants during starvation secondary to congenital anomalies and after the surgical correction of these anomalies but at significant metabolic cost to the patient.

In evaluating starvation, a condition which is frequently linked with operative stress in newborns, Elphick and Wilkinson were unable to document hypoglycemia in normal birth weight infants starved for up to a week. They postulated that the glucose sparing action of free fatty acids was responsible and suggested a relationship between maintenance of a normal blood sugar during starvation and body fat stores.

In a study utilizing stable carbon isotopes, Kalhan et al. examined glucose turnover, systemic glucose production rate, and recycling of glucose carbon as an indicator of gluconeogenesis. Their study included six normal newborn infants ranging in age from 2 hours to 3 days. The human fetus is known to be dependent upon the mother for its glucose needs and no glucose production has been demonstrated in intrauterine life. There is however, the potential for fetal gluconeogenesis. The presence of key gluconeogenic enzymes in fetal liver specimens has been documented.

Kalhan et al. concluded from their stable isotope studies that gluconeogenesis is not expressed in utero. However, during the perinatal period when the fetus’s neonate’s placental or maternal supply of substrate including glucose is abruptly interrupted, the newborn demonstrates a normal capacity for systemic glucose production in order to meet its metabolic needs. Their studies, however, suggest that the source of the available glucose is chiefly from the process of glycogenolysis rather than gluconeogenesis. These authors did demonstrate that gluconeogenesis via the Cori cycle may be possible out as early as 2 hours of life. They also noted that the contribution of recycled carbon to systemic glucose production does not increase during the neonatal period and that glycogenolysis continues to play the key role in maintaining adequate glucose availability for metabolic needs. They postulated that this predominant role of glycogenolysis over gluconeogenesis may be the result of the ready availability of sufficient glycogen stores due to the frequent feeding of neonates. It is not difficult to imagine that this system may be interfered with by the stresses placed on an infant by operation and interruption of dietary intake as well as alteration in gastrointestinal function.

Unfortunately similar stable isotope studies to elucidate stress-induced changes in postoperative glucose homoeostatic mechanisms in neonates are nonexistent. It has been documented through elaborate arteriovenous catheterization studies in adult patients with major injury and sepsis that there is increased splanchnic production of glucose in these states. Concomitant increased uptake of gluconeogenic amino acids (primarily alanine) and increased production of glucose and urea implicate increased gluconeogenesis rather than glycogenolysis as the source of the glucose generated. Exogenous glucose sources were found by these investigators to diminish the observed gluconeogenic response in normal control subjects but not in septic or postoperative patients.

Thus the available evidence in adult patients suggests that increased glucose production from the splanchnic tissues may contribute substantially to the hyperglycemic response to surgical stress. Elphick’s studies showing altered glucose tolerance, however, also suggest a role for decreased glucose utilization in this state. Thus the hyperglycemic response is, in all likelihood, complex and multifactorial. Not only the ability to utilize glucose in peripheral tissues in an impaired state, but also the mechanism of utilization may be altered. In an experimental model of skin healing utilizing carbon-labeled glucose to assess the various pathways of glucose metabolism in wounded tissue resulting in ATP production, and demonstrated a marked increase in glycolytic capacity (Embden-Meyerhof Pathway), as well as increased activity of the pentose shunt and decreased activity of the Krebs cycle. Their wounded skin model was characterized by increased glucose utilization and lactate production. Seventy percent of ATP produced was through the Embden-Meyerhof pathway in wounded tissue, rather than through the Krebs cycle as in normal skin.

Another postulated mechanism for the observed postsurgical hyperglycemia and increase in blood lactate and pyruvate concentrations is the elevated adrenaline level in response to the operative stress, resulting in activation of the Cori cycle. Thus, although the precise mechanism for the hyperglycemic response is not clear, the clinical implications of significant hyperglycemia in a neonate are important. Significant changes in plasma osmolality can result from alterations in glucose levels. It has been documented in newborns that an increase in plasma osmolality of greater than 25 mOsmol/kg over a period of 4 hours can have profound detrimental effects on the renal cortex and cerebral cortex and may even precipitate intracranial hemorrhage in these infants.

Pyruvate, Lactate, Alanine

In addition to the marked postoperative hyperglycemia, a number of investigators have demonstrated increases in blood lactate and pyruvate concentrations in postoperative adult patients. Arteriovenous catheterization studies in adults have demonstrated that adrenaline release during surgery increases lactate and
pyruvate production as a result of glycogen breakdown in peripheral tissues.\textsuperscript{87}

In addition, it is well known that injured tissues surrounding the surgical wound derive their energy mainly from glycolysis and this may contribute to the increased lactate production after surgery.\textsuperscript{2,3}

Other factors involved in the increased lactate levels noted include tissue hypoperfusion and hypoxia during operation.\textsuperscript{2} These changes may be related to anesthesia or may be secondary to hypotension as a result of excessive blood loss or altered circulatory patterns during surgery.\textsuperscript{155} Double isotope turnover studies in normal neonates have demonstrated that many metabolites are removed from the circulation by the liver and are used as substrates for hepatic gluconeogenesis.\textsuperscript{147} It is evident from the preceding discussion, however, that this may not be the case in the stressed neonate.

The significance of elevated blood alanine concentrations in newborns is much less clear. Although alanine is known to be the key gluconeogenic amino acid in adults, some studies have documented hypoalaninemia in newborn infants receiving glucagon.\textsuperscript{156,157} This effect was postulated to be secondary to an increased splanchnic utilization of alanine for glucagon-stimulated gluconeogenesis. In a subsequent study of the relationships of neonatal plasma levels of alanine, glucagon, and insulin,\textsuperscript{158} however, no correlation was observed between changes in alanine and glucose concentrations, further clouding the role of gluconeogenic substrates and the process of gluconeogenesis in the hyperglycemic response.

In their 1987 study of the effects of fentanyl on postoperative metabolic changes in neonates, Anand et al.\textsuperscript{156} demonstrated increases in blood lactate and pyruvate concentrations during surgery in the nonfentanyl group but noted no similar changes in the fentanyl-treated patients. Twenty-four hours postoperatively blood lactate and pyruvate values had fallen below preoperative levels in the nonfentanyl group of infants. Quantitative blood levels of total gluconeogenic substrates (measured as the sum of the blood concentrations of lactate, pyruvate, alanine, and glycerol) in the nonfentanyl group of babies also increased substantially during surgery but fell by 24 hours postoperatively. These changes in the postoperative period were attributed to the utilization of these substrates for gluconeogenesis with excess glucose production in the nonfentanyl neonates. The differences between the fentanyl and nonfentanyl groups were postulated to be due to a blunting of the stress-induced catecholamine response in the fentanyl group with resultant diminution of catecholamine-induced postoperative changes.

An earlier study from Anand's group provides support for this concept.\textsuperscript{84} Significant increases in blood concentrations of lactate, pyruvate, total ketone bodies (acetoacetate and hydroxybutyrate), and glycerol were noted during surgery in their experimental group, which consisted of both term and preterm neonates. In this study, the levels of blood lactate remained elevated until 12 hours after surgery, whereas all other metabolites measured returned to preoperative levels by 6 hours postoperatively. No significant changes were seen in blood concentrations of the gluconeogenic amino acid alanine during or after surgery. Levels of blood lactate showed a high degree of correlation with plasma adrenaline concentrations at the end of surgery and 6 hours after surgery. There was also a significant correlation between blood glycerol levels and plasma adrenaline and noradrenaline at the end of surgery.

In examining the response of a subgroup of six term and preterm neonates matched for degree of surgical stress and anesthetic technique, some interesting findings were noted. No significant differences in blood glucose, pyruvate, total ketone bodies, or glycerol levels were noted between these two groups of infants either before or after surgery. Preterm neonates did, however, demonstrate a significant rise in blood lactate concentrations during surgery whereas no similar change was noted in the subgroup of term infants.

In summarizing their observations, these investigators suggested that the importance of the changes noted in their study may be in the provision of substrates for hepatic gluconeogenesis in the postoperative period. The significant hyperlactatemia noted during surgery in the premature infants was postulated to be due to deficiency of the key hepatic gluconeogenic enzymes, although separate studies by Kalhan and Marsac do not support this hypothesis.\textsuperscript{148,149}

It is conceivable that the greater degree of hyperlactatemia in preterm neonates may possibly be related to less rich glycogen stores in their skeletal muscles in comparison with term neonates, with resultant increased dependence on gluconeogenesis for substrate provision in the face of an immature gluconeogenic mechanism. However, the rise in blood lactate levels may also be due to tissue hypoxia caused by changes in peripheral circulation during anesthesia and surgery.

From the above discussion, it is apparent that the hyperglycemic response to surgery may result from a combination of increased production and decreased utilization of glucose. Many of the hormonal changes affecting the hyperglycemic response have been described in the previous sections. These hormonal changes are capable of inducing glycogenolysis as well as gluconeogenesis following surgery. These responses are accompanied by a decreased rate of glucose utilization particularly during the surgical procedure itself. Relative contributions of each of these mechanisms may depend on a variety of factors including the degree of surgical trauma as well as particulars of the anesthetic management. In addition nutritional supplementation seems to play a modulating role.

**Protein Metabolism**

Acute malnutrition as a result of insufficient nutrient intake or the increased metabolic demands of illness or trauma leads to increased catabolism of muscle protein and a negative nitrogen balance. These changes, along with rapid utilization of energy substrate stores at a time when nutritional intake is often reduced, will drastically affect the ability to heal wounds, combat infection, and have sufficient muscular strength to breathe adequately,
all resulting in increased morbidity and mortality.\textsuperscript{108}
Even the well-nourished may experience periods of debility after the injury of major surgery, which may relate to the reduction of protein reserves and energy stores.\textsuperscript{109}

Major operative stress in adult patients results in a negative nitrogen balance. A compilation of factors accounts for this result. Among those well-documented factors are increased protein breakdown and decreased protein synthesis in extrahepatic tissues. In addition, there is increased utilization of amino acids for alternate purposes such as gluconeogenesis, synthesis of acute phase reactants by the liver, as well as for synthesis of components of the healing process in injured tissues. Patients experiencing trauma or sepsis have been demonstrated to have rapid onset of muscle wasting, protein depletion, and elevated urea excretion.\textsuperscript{161,162} Therefore, an increased supply of amino acids is made available during sepsis or trauma for energy production by gluconeogenesis and oxidation. These additional amino acids also satisfy the requirements of the liver and other visceral tissues for greatly accelerated synthesis of the proteins essential to immunologic defense, healing of wounds, and maintenance of functions in the vital organs. The adult response to starvation is characterized by sacrifice to visceral protein to furnish amino acids, as are needed, for gluconeogenesis and other purposes, whereas in stressful situations such as trauma or sepsis, muscle protein is degraded and the liver increases its protein content.\textsuperscript{163} Important as this metabolic response may be to survival, prolonged mobilization of amino acids leads to devastating muscle weakness. In some patients muscle weakness is so great that ventilation is insufficient to overcome the respiratory insufficiency associated with the traumatic event. Depletion of protein is also accompanied by deterioration of cellular structure, insufficient production of acute phase reactants, and reduced synthesis of other necessary proteins. Under such conditions, patients are prone to perish from overwhelming infection, culminating in multisystem failure.\textsuperscript{164}

The sick infant is particularly susceptible to the adverse metabolic effects that a major illness or surgical operation may impose. Perioperative protein metabolic and nutritional status must be given special consideration in this population due to smaller body size, rapid growth, highly variable fluid requirements, and the immaturity of certain organ systems. These factors, plus low caloric reserves in the premature infant and sick child, make an adequate caloric and amino acid intake particularly important. Consequently, the infant whose nutritional needs are not met, as a result of functional or organic disorder of the gastrointestinal tract, can very rapidly develop protein-calorie malnutrition and associated complications.\textsuperscript{165}

The most important clinical consequence of a catabolic stress reaction is felt to be increased protein breakdown after surgery.\textsuperscript{166} The consequences, as outlined above, could be particularly deleterious in a postoperative neonate whose nutritional status is already tenuous.

Adult urinary nitrogen excretion is increased following major surgery and may remain elevated for as long as 5 days postoperatively.\textsuperscript{167} Johnston’s study suggests that an adult patient’s nitrogen losses are equivalent to 500 g of lean muscle tissue per day.\textsuperscript{168} An important determinant of the magnitude and duration of the postoperative nitrogen loss appears to be the severity of surgical stress.\textsuperscript{167} There is some evidence in adult patients that the availability of ketone bodies as a metabolic fuel for peripheral tissues may result in a decreased need for amino acid oxidation in extrahepatic tissues (mainly skeletal muscle) and may ultimately result in a decreased nitrogen loss and sparing of muscle protein sources.\textsuperscript{109}

In an elaborate study of muscle protein degradation in nonoperated premature infants, Ballard et al\textsuperscript{166} examined correlations between energy input, nitrogen retention, weight gained and subsequent survival. They demonstrated that approximately 5% of total muscle protein was degraded daily. In addition the total and fractional rates of protein breakdown demonstrated significant reverse correlations with nitrogen retention but had no relationship to total energy input. Not surprisingly, protein degradation was higher than average in infants who were losing weight at the time of the balance study, and lower in infants who demonstrated weight gain. Protein degradation was also higher in infants who died within 2 weeks of the study. It was unclear whether this increased degradation in preterminal infants was related to events which stimulated muscle proteinolysis, such as sepsis, or was due to the underlying nitrogen status of the patients.\textsuperscript{170} Significantly, myofibrillar protein breakdown was not different between infants fed orally and those receiving total parenteral nutrition. These investigators commented that the effects of nitrogen and energy status on muscle protein degradation in premature infants are different from changes reported in adult humans or adult rats. To explain these findings they postulated that the very limited energy reserves of the premature infant may be responsible for the differences observed. They were unable to demonstrate any correlation between energy input in the premature infants and rates of muscle protein breakdown (in contrast to large increases in total muscle protein breakdown seen in rats subjected to total energy restriction, and a slight decrease in muscle protein breakdown in long-term fasting in obese adult humans).\textsuperscript{171,172} They attempted to explain the differences between their results and those of other studies mentioned above on the basis of the size of the fat reserves, since there is evidence that ketonemia produced by fat mobilization is accompanied by a lower rate of muscle protein breakdown; and, since the premature infant clearly has very little adipose tissue, this would explain the difference.\textsuperscript{169} Ballard et al\textsuperscript{166} also demonstrated an increase in muscle protein degradation in premature infants by demonstrating a negative nitrogen balance or minimal retention of nitrogen daily. They postulated that this may be due to increased protein breakdown as a result of a demand for amino acids, which cannot be met simply by a decrease in protein synthesis. They state, however, that the response observed “is surely catastrophic if prolonged for any length of time, thus arguing forcibly that a substantial nitrogen supply to the premature infants should be maintained.” They also noted that the ratio of muscle protein deg-
radiation to total body protein degradation was 7%, in contrast to a value of 30% found in adults. They attributed this difference to the very small pool of muscle protein in premature infants. In addition they speculated on the tissue sites of the remaining 93% of the protein degradation in premature infants and postulated that organs which account for greater relative ratios of neonatal body weight such as brain, liver, or skin may contribute significantly to total body protein degradation. The result of this visceral protein breakdown could be disastrous.

Colle and Paulsen, in a 1959 study of postoperative infants, demonstrated urinary nitrogen losses of 200 to 300 mg/kg/24 h in contrast to 80 mg/kg/24 h in normal infants. These losses were, however, transient and not sustained.

Duffy and Pencharz studied the effects of postoperative amino acid intake on urinary nitrogen losses and whole body protein synthesis in 18 neonates. They concluded that a nitrogen intake of about 450 mg/kg/d should meet the needs of a neonate in the immediate postoperative period. This is higher than the data of Zlotkin suggests. These investigators (Duffy and Pencharz) also documented an improved nitrogen balance (the relationship between nitrogen intake and nitrogen retention) in association with an increased nitrogen intake. This improved balance was attributed to a reduction in the fraction of amino nitrogen flux coming from the breakdown of endogenous protein. They were unable to demonstrate any increase in skeletal muscle breakdown postoperatively in the infants studied by measuring urinary creatinine and 3-methyl histidine excretion. Finally, this group was able to show postoperative nitrogen accretion, even during the 3 days immediately postsurgery, but noted that nitrogen utilization may be partially impaired postoperatively. On the basis of these studies, they recommended a nitrogen intake of 450 mg/kg/d with a nonprotein energy intake of 85 to 90 kcal/kg/d.

Rickham in the late 1950’s demonstrated a postoperative increase in nitrogen excretion in neonates, but added that, as in adults, this increase is no greater than that found when the patient is starved. Rickham also noted that a crude protein infusion in the form of plasma resulted in rapid utilization of the infused protein. Therefore, he felt that postoperative plasma infusions served the double purpose of maintaining a normal plasma volume and of restoring the plasma protein concentration.

Winthrop et al demonstrated, in a prospective evaluation of pediatric trauma patients, significant increases in basal metabolic rate (BMR), whole-body protein turnover, protein synthesis, and urinary nitrogen excretion. These patients were found to have a negative nitrogen balance due to the fact that protein breakdown increased relatively more than protein synthesis. The increase in protein breakdown/turover, synthesis, and nitrogen excretion was found to have greatly exceeded the increase noted in BMR (93%, 82%, and 56% vs 14% increase in BMR) in these young (less than 10 years old) posttrauma patients. They were unable to demonstrate a correlation between BMR and whole-body protein turnover, suggesting that changes in energy expenditure and protein metabolism following injury may be mediated by different mechanisms. They concluded that the metabolic response of pediatric patients to multiple trauma differs from that of adults and noted that pediatric trauma patients need not only increased caloric intake but, more importantly, a significant increase in protein intake in an attempt to optimize the balance between protein synthesis and breakdown. Thus, the differences from adults include a much smaller change in total energy expenditure in children and the lack of correlation between an increased metabolic rate and whole-body protein turnover.

Minor or moderate surgical stress is capable of significantly decreasing plasma concentrations of total amino acids. Primarily responsible for this decrease is the reduction in the plasma concentrations of gluconeogenic amino acids, especially alanine. As mentioned earlier, demonstrated, through catheterization studies of muscle vascular beds, that peripheral release of gluconeogenic amino acids accompanies abdominal operations. Therefore, postoperative production of gluconeogenic amino acids may be a result of skeletal muscle catabolism. Gluconeogenesis then can take place as these amino acids are selectively taken up in the splanchnic, hepatic and renal tissues. In contrast to the decreased systemic levels of gluconeogenic amino acids noted above, there is evidence for elevations of branched chained amino acid (BCAAs) concentrations in blood and within skeletal muscle. This is in contrast to the decreased levels documented in patients with liver disease.

Therefore, stress-induced muscle protein catabolism results in the release of gluconeogenic amino acids which are rapidly cleared from the blood to be metabolized by the liver and splanchnic tissues, as well as release of BCAAs into the circulation. These BCAAs are not normally metabolized in the liver but rather, initially, in muscle and other peripheral tissues, where anabolism is diminished in the stressed state, resulting in minimal utilization of these BCAAs.

In addition to being indicators of increased proteolytic activity or altered protein metabolism there may be a functional role for the alterations in amino acid patterns. For example, it has been suggested that arginine may have an immunoregulatory effect as well as an effect on promoting nitrogen retention and wound healing. Arginine may be important because of its effects in augmenting immune responsiveness and in diminishing protein catabolism. Arginine is also known to stimulate secretion of pituitary and pancreatic hormones.

Any of these roles may be important in the postoperative stressed state.

Studies by Clowes et al have demonstrated a nearly identical relationship between the amino acid composition of hydrolyzed muscle protein and the molar proportion of amino acids released into the bloodstream during sepsis or following trauma, implicating the breakdown of muscle protein as the source of these amino acids. A significant breakthrough in the understanding of this
proteolytic response was made when Clowes et al.\textsuperscript{197} demonstrated a circulatory peptide capable of inducing muscle proteolysis in sepsis and trauma. This group suggested that the proteolysis-inducing factor they isolated from plasma was not one of the hormones usually secreted in stressful situations; they postulated that it may be a product released from leukocytes or macrophages in association with the activation of complement in the presence of infection or tissue damage associated with trauma or operation. This was substantiated by the observation that septic patients' plasma could induce proteolytic changes when incubated with normal skeletal muscle. They reiterated that the increased supply of amino acids is made available in sepsis or trauma not only for energy production or oxidation, but, more importantly, to satisfy the requirements of the liver and other visceral tissues for a greatly accelerated synthesis of the proteins essential for immunological defense, healing of wounds, and maintenance of function in vital organs.

Finley et al. examined the effect of major operative trauma on skeletal muscle metabolism in adult patients receiving a constant preoperative infusion of nutrients.\textsuperscript{\textsuperscript{80}} They noted significant postoperative decreases in the plasma concentrations of the following amino acids: taurine, threonine, serine, glycine, alanine, citrulline, amino-N-butyrate, methionine, histidine, arginine, glutamine, glutamate, and branched-chain amino acids including valine and isoleucine. At the same time there was a postoperative increase in amino acid release from a forearm muscle bed which was made up in large part by an increase in the glycogenic amino acids, serine, threonine, glycine and alanine, by a marked increased in the release of branched-chain amino acids, and by an efflux of taurine, methionine, phenylalanine, lysine, and arginine. They suggested that the visceral production of glucose is quantitatively matched by the net uptake of glucose precursors across the splanchic bed.\textsuperscript{196} They noted that infused nutrients suppressed visceral gluconeogenesis in these patients. Their results showed that new glucose production was lower than what was observed in a fasting man suffering from trauma.\textsuperscript{199} This group (Finley) speculated that the increased release of proline, methionine, arginine and phenylalanine from muscle may be related to higher requirements by healing wounds and an increased demand for the precursors of catecholamines.

Hulton et al.,\textsuperscript{81} in 1985, demonstrated, in an animal model, that hormonal blockade of the catabolic responses to surgery by phentolamine and propranolol inhibited net skeletal muscle protein catabolism without altering whole-body nitrogen loss. This may prove clinically useful in that hormonal blockade may attenuate the post-traumatic catabolic response, preventing accelerated skeletal muscle breakdown and body protein loss. Total body nitrogen loss in this study was, however, unaffected indicating that skeletal muscle was spared at the expense of other sources of amino nitrogen. The investigators speculated that these other amino acids were derived from the viscera. It is possible that hormonal blockade could prevent the obligatory loss of skeletal muscle protein in critically ill patients. Simultaneous nutritional support might then provide the amino acids necessary for acute phase protein synthesis, gluconeogenesis, and wound repair.

Warner et al.,\textsuperscript{200} in an experimental animal model, demonstrated that infusion of catabolic hormones (glucagon, epinephrine, and corticosterone) resulted in increased amino acid uptake in the liver; however, these catabolic hormones had no effect on amino acid uptake in skeletal muscle. Total plasma amino acids were reduced in the hormone-infused animals. They concluded that stress-induced elevations of catabolic hormones are, at least in part, responsible for the augmented liver amino acid uptake but that these catabolic hormones are not responsible for the reduced muscle amino acid uptake characteristic of sepsis or severe trauma.\textsuperscript{201}

Moyer et al. studying critically ill adult patients who were septic or posttraumatic, examined concentrations of various plasma substances in an effort to identify plasma profiles reflective of patients' prognosis. They were able to identify numerous amino acid fractional concentrations and patterns which had specific predictive value.

Studies of postoperative nitrogen balance in term neonates originate with Rickham in 1957. Since that time, several investigators have substantiated a strongly negative nitrogen balance in response to surgical stress and have demonstrated that this may persist for 72 to 96 hours.\textsuperscript{41,174,202-204} These studies have demonstrated that the severity of the surgical stress is correlated with the degree of nitrogen loss. In addition, it has been noted that nitrogen loss postoperatively is greater in the neonatal age group than in older infants subjected to similar degrees of surgical stress.\textsuperscript{205,206} In a recent study of neonates undergoing either major or minor operative procedures, a direct relationship was noted between the degree of stress and the quantity of nitrogen loss.\textsuperscript{207}

Zlotkin\textsuperscript{177} in 1984, published a study assessing postoperative nitrogen balance in term neonates who had received parenteral nutrition containing 300 to 600 mg/kg/24 h of nitrogen. These authors demonstrated nitrogen retention in these infants and correlated this with increasing nitrogen intake. They calculated that a nitrogen intake of 280 mg/kg/24 h would be required to duplicate the nitrogen accretion rate of breast-fed infants. This study may be criticized on a methodological basis due to the fact that these neonates had undergone variable degrees of surgical stress and thus represented a nonhomogeneous group. In addition, the studies were carried out at 7 to 9 days postoperatively, which is a time when the major hormonal and metabolic alterations induced by operative stress have returned to baseline. A subsequent study of 18 preterm neonates undergoing a variety of surgical procedures examined early (0–72 h postoperatively) changes in nitrogen retention, protein synthesis, and protein turnover.\textsuperscript{176} The authors demonstrated a strong correlation between nitrogen intake and net nitrogen retention and concluded that the improved nitrogen utilization in the infants receiving the greatest quantity of parenterally administered amino acids was due to a reduced breakdown of endogenous proteins.

In a recent study, different levels of amino acid intake...
were evaluated with regard to nitrogen retention, ratios of whole body amino acid nitrogen flux, and protein synthesis and breakdown ratios in 18 infants during the 72 hours immediately following surgery.\(^{176}\) One group of infants received 2.3 \pm 0.4 g of amino acid/kg/d and the other 3.9 \pm 0.5 g/kg/d. They demonstrated no differences in amino acid flux or in synthesis and breakdown of protein. However, the group receiving the higher amino acid intake had significantly greater net protein synthesis ratios. This improved nitrogen utilization in this group was again achieved principally by a reduction in endogenous protein breakdown. There were no differences between the two groups in urinary creatinine or 3-methylhistidine excretion. Since these two parameters reflect skeletal muscle protein turnover, the differences between groups in nitrogen retention and protein turnover appear to be mediated through visceral protein sparing.

Another marker of endogenous protein breakdown which has received widespread attention is the molar 3-methylhistidine:creatinine ratio (3MH:Cr).\(^{207}\) The rationale for use of the 3 MH:Cr ratio is the belief that 3-methylhistidine originates from the breakdown of skeletal muscle actin and myosin. A significant series of assumptions accompany use of this ratio. First, this molecule is excreted quantitatively in the urine following its liberation from myofibrils. Second, the contribution of nonskeletal muscle (skin and gastrointestinal muscle) to the total 3 MH pool is negligible. Additionally, this amino acid is not metabolized further and is not used for de novo protein synthesis following its liberation into the circulation. Numerous studies have demonstrated that the urinary 3MH:Cr ratios correlate closely with the net nitrogen balance in preterm and term neonates.\(^{168, 208-210}\)

In addition, preterm neonates stressed by severe clinical illness and manifesting a negative nitrogen balance and weight loss at the time of study have also demonstrated a markedly raised 3MH:Cr ratio.\(^{211}\) Additional studies in postoperative term neonates have demonstrated a significant increase in the 3MH:Cr ratio and in nitrogen loss in the first 72 hours after surgery.\(^{210}\) This finding was later confirmed by the same investigators in preterm neonates undergoing surgery.\(^{86}\) Reduction of the surgical stress responses in preterm and term neonates by using different anaesthetic techniques such as halothane supplementation or fentanyl was found to inhibit these changes in the urinary 3MH:Cr ratio.\(^{86, 212}\)

The most important clinical consequence of the catabolic stress reaction has been said to be the increased protein breakdown after surgery.\(^{211}\) During the first few days after birth human infants lose weight before resuming the rapid weight gain associated with intrauterine development.\(^{166}\) Although much of the weight loss is water, some of it reflects the breakdown of carbohydrate and lipid stores and the relatively high rate of total body and muscle protein degradation which may further contribute to the catabolic state in these infants.\(^{173, 213}\) The previous study\(^{166}\) failed to demonstrate any correlation between energy input in the premature infant and the rate of muscle protein breakdown, in contrast to the findings of Zlotkin\(^{177}\) and Duffy and Pencharz.\(^{176}\) Ballard et al felt this may be due in part to the size of the fat reserves, since there is evidence that ketonemia produced by fat mobilization is accompanied by a lower rate of muscle protein breakdown.\(^{166}\) However, they pointed out that the preterm human neonate has relatively little adipose tissue and may be expected to demonstrate increased muscle protein catabolism when energy intake is minimal. They concluded by stating “Nevertheless we consider it is not possible at the present time to reconcile all of the findings on energy restriction in such a way that an expected response on muscle protein breakdown can be stated.”

Pinter\(^{27}\) in 1973 examined the ratio of nonessential to essential amino acids in 17 infants undergoing surgery. He demonstrated a fall in the ratio during surgery with a gradual postoperative rise. Alpha-amino nitrogen demonstrated a slight, insignificant rise during surgery and then remained at a constant level. Postoperatively, a pronounced fall in alpha-amino nitrogen was observed. Due to the rise in the combined concentrations of the essential amino acids leucine, valine, and methionine, the nonessential:essential amino acid plasma ratio decreases. In addition, the changes in the alpha-amino nitrogen level indicate a marked redistribution of the circulating free amino acids. The rise in blood urea nitrogen (BUN) observed in the early postoperative period is probably due to several factors, such as enhanced protein breakdown, hemoconcentration, and oliguria, which are well-known consequences of surgery.

In a later study of 29 infants undergoing a moderate degree of surgical stress for correction of various congenital anomalies, Pinter\(^{215}\) was unable to demonstrate a statistically significant change in the ratio of nonessential:essential amino acids. Also, no significant change in the alpha-amino-nitrogen level was noted. They did suggest, however, that the plasma-free amino acid pool did change dramatically both during and after surgery.

Therefore, from the adult studies outlined it can be concluded that the negative nitrogen balance seen following moderate surgical stress is mainly due to a decrease in the rate of protein synthesis, while the rate of protein breakdown is unaltered or slightly increased. However, protein metabolism in patients exposed to severe degrees of surgery, trauma, or sepsis is characterized by a massive breakdown of tissue proteins, with protein synthesis rates being unaltered, decreased, or in some cases, slightly increased.

It is in this latter group of critically ill patients that the therapeutic manipulation of protein metabolism may provide the greatest clinical benefit in terms of reduction of morbidity and mortality. The neonatal surgical data indicate a higher degree of muscle protein degradation than seen in adults, resulting in a strongly negative nitrogen balance in the postoperative period. It seems that the provision of adequate amounts of amino acids, either enterally or parenterally, is capable of, at least partially, abating this degradation of endogenous protein.

**FAT METABOLISM**

The postoperative state in adult patients produces a catabolic response which in addition to the already men-
tioned changes in carbohydrates and protein metabolism also results in the mobilization of nonesterified fatty acids (NEFA's) from adipose tissues as well as increased formation of ketone bodies. These changes may be of prime importance in providing an endogenous energy source in the posttraumatic state.

Two decades ago Allison et al documented increased plasma concentrations of nonesterified fatty acids associated with a decreased glucose tolerance in a group of patients suffering burn injuries. Subsequent studies by this same group in postoperative patients also demonstrated an increase in plasma nonesterified fatty acids. This increase was noted both preoperatively and intraoperatively. The preoperative increase was attributed to the catabolic stimulus provided by the emotional stress of anticipating an operation. An increase of nonesterified fatty acids following trauma was confirmed in 1974; and the extent of the response was correlated with the severity of trauma.

The importance of the contribution of fat to energy supply in a stressed state was illustrated by Kinney et al in a 1970 study in which they demonstrated, by indirect calorimetry, that as much as 75 to 90% of postoperative energy requirements were supplied by fat metabolism and the remainder was provided by protein. It may be necessary for these nonesterified fatty acids to undergo conversion by the liver to ketone bodies prior to their utilization as an energy source.

Lipolysis of stored triglycerides and the control of adipocyte lipolysis are important in mobilization of lipid in the injured patient. Lipolysis in the adipocyte is carried out by the enzyme hormone sensitive lipase (HSL). This enzyme complex (HSL) is affected by a number of other circulating hormones, including the catecholamines.

Forse et al in an in vitro study, noted that in trauma the beta-adrenergic responsiveness of adipocytes and the catecholamine receptors on these cells were significantly decreased. This may be interpreted as desensitization of the beta receptors with down regulation and indicates increased in vivo lipolysis early after injury. After 4 days, these changes had returned to normal.

Wolfe et al in a study of patients suffering from severe burn injury, in which he utilized stable isotope tracers, demonstrated changes in the substrate cycle involving the simultaneous breakdown and synthesis of stored triglycerides (triglyceride-fatty acid cycle). The rates of triglyceride-fatty acid and glycolytic-gluconeogenic cycling were elevated in these patients by 450 and 250%, respectively. These investigators concluded that increased substrate cycling contributes to the increased thermogenesis and energy expenditure seen in severe burns and that increased triglyceride-fatty acid cycling is due to beta-adrenergic stimulation. Therefore, the increased metabolic rate observed may be secondary to increased substrate cycling and not solely caused by increased rates of protein synthesis.

Because the stress response associated with surgery causes an elevation of plasma nonesterified fatty acids and decreased insulin secretion, one would expect an increased production of ketone bodies in response to operative stress. However, several studies have shown that the levels range from no change to a mild elevation to a substantial increase. It has been demonstrated that patients who remain normoketonic after major surgery are likely to manifest an increased nitrogen loss in comparison with patients who are hyperketonemic postoperatively. Studies in trauma patients suggest that the lack of ketogenesis is due to postinjury vasopressin release, the degree of which is directly proportional to the severity of injury. Therefore, vasopressin may exacerbate protein catabolism and muscle wasting by suppressing ketogenesis in patients subjected to severe trauma, major surgical stress, or sepsis.

In the human baby, depot fat accounts for 10 to 15% of body weight. From metabolic balance data, Hughes et al calculated that only about 8% of body protein was catabolized when a 3-kg neonate was starved for 12 days, yet 39% of the baby's fat was used up. Because of this low metabolic conversion of protein, the ability to reduce peripheral glucose utilization would be of advantage to the starving neonate. Whether or not high free fatty acid (FFA) turnover can result in reduced peripheral glucose uptake remains to be confirmed. Glycerol released from adipose tissue during lipolysis could be a source for supplementation or maintenance of blood glucose levels.

In their experimental study of perinatal rats, Mayor and Cuezva noted that, in the suckling period, the oxidation of fatty acids, ketone body utilization, and active gluconeogenesis supply the bulk of energy and carbon components required to support the rapid growth rate during this period. This metabolic process begins with an increase in the insulin/glucagon ratio that occurs with the change to a carbohydrate-rich diet, which then initiates the induction of lipogenesis at weaning.

Anand et al demonstrated an increase in blood levels of total ketone bodies and glycerol during surgery in neonates. They believed this increase was a reflection of catecholamine-stimulated lipolysis and ketogenesis. They noted a strong correlation between serum levels of glycerol and adrenaline and noradrenaline at the end of an operation. In addition to their use as an energy source, they postulated that the ketone bodies in peripheral tissues, through the formation of citrate and the inhibition of phosphofructokinase, may also further inhibit the peripheral utilization of glucose and contribute to the postoperative hyperglycemia seen in neonates.

In a study of the effectiveness of improved anesthetic management through the use of halothane, this group demonstrated that concentrations of ketone bodies increased during surgery in the group not receiving halothane but were unchanged in the group receiving halothane, with a significant difference at the end of the operation. Plasma concentrations of nonesterified fatty acids (NEFAs) were significantly higher in the group not receiving halothane than in the other group at the end of, and 6 hours after, operation. These responses indicate a greater degree of lipolysis, probably mediated by the release of catecholamines in the nonhalothane group and facilitated by the decrease in the ratio of insulin to glucagon during surgery in the group that did not receive halo-
though there is a marked hyperglycemia and mobilization of gluconeogenic substrates during and after surgery, it is likely that these substrates are utilized in the perioperative period. They postulate that the primary sources of energy in the surgical neonate are provided by the mobilization of nonesterified fatty acids (NEFAs) from adipose tissue and their conversion to ketone bodies in liver cells. Despite this potential physiological importance, fat metabolism in surgical neonates and infants has received little study. Pinter reported a substantial increase in plasma NEFA values during surgery with a further significant increase postoperatively, whereas Elphick and Wilkinson found no significant changes in NEFAs in the perioperative period. In the latter study, a decrease in plasma triglycerides was documented postoperatively, whereas the plasma concentration of lipoproteins, phospholipids, and cholesterol were unchanged during and after surgery. These responses could be altered, at least partially, by starvation since the neonates in both the above studies received no nutritional support for variable periods before and during the study. Recent studies in term neonates have shown that circulating concentrations of NEFAs, glycerol, and total ketone bodies increased significantly during surgery, but had reverted to preoperative values by 6 hours postoperatively. The significant increase in free fatty acids, glycerol, and total ketone bodies during surgery is indicative of lipolysis and ketogenesis, mediated by intraoperative catecholamine release, as evidenced by the strong correlation between blood glycerol concentrations and plasma adrenaline and noradrenaline levels at the end of surgery. An earlier study in older infants undergoing inguinal herniorrhaphy documented a significant increase in plasma NEFA values during surgery and concluded that this was indicative of lipolysis in response to the stress induced by surgery. In contrast, in studies of neonates undergoing cardiac operations, blood concentrations of total ketone bodies were found to be decreased significantly at the end of surgery and these remained below preoperative values at 6 hours postoperatively. These changes were attributed to the effects of cardiopulmonary bypass (CPB) and two mechanisms were postulated to account for this: 1) the substantial increase in blood glycerol values noted may have been caused by the hepatic output of triglycerides to CPB, secondary to heparin-induced activation of lipoprotein lipase and subsequent breakdown of plasma triglycerides (in addition to the glycerol produced from lipolysis in adipose tissue), and 2) the markedly decreased hepatic circulation and decreased metabolic rate during CPB with deep hypothermia and circulatory arrest (DHCA) would prevent the utilization of this glycerol for gluconeogenesis and the conversion of circulating NEFA's into ketone bodies.

In addition to serving as an energy source, studies of glycerol turnover in newborn infants have shown that 75% of glycerol formed from lipolysis enters the gluconeogenic pathway in the neonatal liver and contributes to 5% of hepatic glucose production. The oxidation of free fatty acids by the neonatal liver may further stimulate postoperative gluconeogenesis through the generation of ATP to support gluconeogenesis, the production of acetyl-CoA which activates pyruvate carboxylase, and the provision of reducing equivalents for glyceraldehyde-3-phosphate dehydrogenase.

In a study on PDA ligation in term and preterm infants, there was a significant rise in blood levels of lactate, pyruvate, total ketone bodies and glycerol by the end of the operative procedures, but by 6 hours postoperatively the levels of all these metabolites had reverted to their preoperative levels. In nonoperated newborn babies who have not yet been fed, the respiratory quotient and the blood glucose level fell while the serum concentration of free fatty acids (FFA) rises, indicating a rapid change from carbohydrate to fat metabolism soon after birth. In addition, liver and muscle glycogen reserves are reduced and the rate of disappearance of glucose administered by intravenous infusion is decreased. It also appears that protein is less easily utilized for energy purposes during starvation at this time. All this indicates that fat, rather than protein or carbohydrate, is being used for energy production in the newborn.

In a recent study, various surgical procedures led to variable changes in the plasma concentration of free fatty acids. In addition, 4 to 24 hours after surgery, the plasma triglyceride level fell by an average of 25%, but later rose. In contrast, in this study during starvation, plasma FFA concentrations rose during the first 2 days of life and were very high between days 3 and 5. Plasma triglycerides, cholesterol, phospholipids, and total esterified fatty acids also increased after birth. These results suggest that during starvation in the neonate there is rapid mobilization of fat from adipose tissue stores and a reduction in the peripheral utilization of glucose. There is no evidence to suggest any impairment of fat mobilization or metabolism even after 7 days of starvation. After surgery, however, even though there is more rapid mobilization of fat, the rate of utilization is greater than the rate of mobilization, resulting in variable and even reduced levels of the various lipids. These results led these authors to speculate that babies of normal birthweight may be more able to cope with starvation and surgical injury than is generally realized through this rapid mobilization of stored fat.

Pinter demonstrated that the average plasma FFA level showed a slight but significant increase at the end of surgery. At the 6th and 12th postoperative hour this increase was already more pronounced. The plasma FFA level, however, showed great individual variation. Although, in most cases, a marked increase in plasma FFA concentration occurred, the average increase, because of the significantly different initial levels, did not achieve statistical significance. At 24 hours postoperatively, the increase still persisted. As an explanation for the occasional absence of an increase in FFA postoperatively, Pinter postulates that pronounced hyperglycemia directly or indirectly inhibits the mobilization of FFA. The fact that, after surgery, a rapid fall in blood glucagon
concentration is accompanied by a rise in plasma FFA levels lends support to this explanation.

Pinter\textsuperscript{215}, in a study of 29 newborns being operated upon for congenital anomalies, described their metabolic characteristics between the 1st and 7th postoperative day. In these investigations, a decreased free fatty acid level was observed between the 2nd and 7th days, whereas during the operation, as well as on the first postoperative day, a well-defined increase in the FFA level took place, which might have been caused by the response to the anesthetic and surgery (increased release of catecholamines and steroids, metabolic effects of anesthetics, hypoxia, hypothermia, acidosis, etc). Although the FFA level showed a tendency to decrease postoperatively, it still remained higher than the preoperative value. This pattern of fat metabolism can be explained by two facts: 1) in the postoperative period the complex hormonal and metabolic changes evoked by surgery are returning to the preoperative level, and 2) the state of hypoalimentation. These combined hormonal and metabolic processes, which are also typical of the adaptation to extrauterine life, explain why it is difficult to find a reciprocal relationship between glucose and FFA metabolism.\textsuperscript{240, 241} Elphick also failed to demonstrate a relationship between glucose and FFA levels in newborn infants following surgery.\textsuperscript{242}

Studies in adults have indicated that the concentration of circulating free fatty acids varies in response to surgical stress.\textsuperscript{243} Talbert et al's\textsuperscript{83} study examined infants undergoing bilateral inguinal hernia repair. Eleven of 13 patients demonstrated a significant elevation in free fatty acid levels following surgery. The plasma-free fatty acids have been identified as the major metabolite from the mobilization of body adipose tissue/depot fat to be used as an energy source.\textsuperscript{240, 244} The hydrolysis of triglycerides is the major biochemical reaction in fat stores for the production of energy precursors. Mobilization of fatty acids is mediated by three central mechanisms: metabolic, hormonal, and neural.\textsuperscript{245} Under conditions of starvation a net release of FFA from the peripheral fat depots is observed. Various hormones have been demonstrated to be active in the regulation of fatty acid mobilization.\textsuperscript{246} Among the most important of these hormonal regulators are the catecholamines. These compounds have been recognized as potent stimulants of FFA mobilization.\textsuperscript{247} Concomitant increases in the rate of glycerol production verify the fact that elevations in plasma-free fatty acids are due to an absolute increase in the rate of hydrolysis of triglycerides. Animal experiments have emphasized the importance of this mechanism in producing postoperative elevations in plasma FFAs.\textsuperscript{249} The importance of the innervation of fat stores in facilitating free fatty acid mobilization has been verified by experiments with innervated and denervated tissues.\textsuperscript{245} The sympathetic nervous system is a critical component of this process. Since norepinephrine is the chemical mediator at the postganglionic sympathetic nerve ending, the final mechanism of action may be similar to that observed following the parenteral administration of this compound. The importance of this system as a mechanism for mobilizing free fatty acids has been documented in adults during emotional stress.\textsuperscript{249} It is evident that circulating levels of free fatty acids are regulated by a variety of factors, many of which also participate in the infant’s response to stress. The importance of this composite action is suggested in Talbert’s experiments in which he demonstrated an increase in plasma FFA in the absence of a discernible increase in circulating catecholamines. Previous investigators have demonstrated an elevation of FFA in adults following cholecystectomy and inguinal herniorrhaphy.\textsuperscript{240} These results substantiate the sensitivity of free fatty acid mobilization to the stimulus of surgical trauma and suggest the usefulness of the plasma-free fatty acid level as an index of the infant’s stress response.

In addition to the outlined mobilization of body fat stores, renewal of these stores has been suggested. Winthrop et al\textsuperscript{78} showed that body fat increased postoperatively from day 0 to day 7 from 12.9 ± 0.6% to 14 ± 0.06% (p < 0.05) in 13 full-term infants undergoing surgery at approximately 10 days of life. Although this is a small but statistically significant increase in the body fat, the magnitude of the change falls within the range of experimental error for anthropometry. In this study, fat accounted for almost 60% of the new solid tissue synthesized, which is in agreement with Fomon et al’s figure of 56.6%.\textsuperscript{250}

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