13 *Neuroendocrine and Sympathoadrenal Response to Thermal Trauma*

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The previous chapters have described many alterations in secreted hormones and metabolic processes that occur for weeks to months after major burn injury. Interpretation of these alterations can be bewildering; however, many of the findings can be simplified and/or unified to a certain extent if they are viewed as part of an overall alteration in central nervous system (CNS) function characterized by modified control settings.

The Neuroendocrine Reflex Arc

Early work with acute surgical trauma provided the conceptual framework of the neuroendocrine reflex arc.[1,2] In this framework, a signal from an injured area is transmitted by an afferent limb to the brain, which integrates the formation and orchestrates a neural and hormonal output as the efferent limb.

Hume and Egdahl[3] studied dogs anesthetized with ether or Nembutal and with a catheter in an adrenal vein. Upon application of a scald burn, the corticosteroid (CS) secretion rate rose promptly within minutes. This response was blocked by prior section of the medulla oblongata, the spinal cord, or the peripheral nerve innervating the area of the lesion. Subcutaneous injection of ACTH in the denervated burned area provoked a CS response, indicating that if a burn toxin were present and capable of stimulating this acute response humorally, it would likely have been detected. Thus, the acute CS response to a burn did not result from pain per se, which was blocked by the anesthesia, nor from systemic absorption of a humoral toxin from the burned area, but from afferent neural information signaling the presence of an injury. In some experiments, crude measurements of circulating ACTH indicated that the CS response was associated with a surge in endogenous ACTH release. Lesions of the anterior hypothalamus blocked the CS and ACTH responses to operative trauma. These and the cord section experiments indicated that the adrenocortical response was via brain control of ACTH secretion, not via innervation of the adrenals. Nevertheless, activation of the adrenal medullae through the neural route was indicated by observation of elevated catecholamine (CA) secretion rates in the adrenal vein after injury.

Multihormonal Influence on Postburn Hypermetabolism

Sympathetic Nervous System and Catecholamines

The above-described model of response to injury is applicable to the acute response that takes place within minutes to hours. However, elevated plasma

concentrations and urinary excretion of corticosteroids and catecholamines are present days to weeks after a major burn injury, and protracted hypermetabolism (increased O_2 consumption) occurs after an initial delay.[4–20] Plots of postburn plasma norepinephrine (NE) and metabolic rate (MR) are shown in Figures 13–1 and 13–2, respectively. Adrenalectomy[21] or adrenal medullectomy[22] blunts the hypermetabolic response to burn injury in rats. Postburn hypermetabolism is not associated with hyperthyroidism.[16,23] The known capability of catecholamines to mobilize fuels such as fatty acids and to generate hypermetabolism,[17,24,25] the correlation of human postburn resting metabolic rate (O_2 consumption) with circulating concentrations and excretion of both norepinephrine and epinephrine,[8,13,18] and the amelioration of postburn hypermetabolism with β-adrenergic blockade[13] have implicated the sympathetic nervous system (and hence the brain) in the prolonged metabolic and thermogenic response to burn injury. Taylor et al.[26] found that profound narcosis produced by morphine in hypermetabolic burn patients decreased oxygen consumption, pulse rate, core temperature, and ventilatory activity but did not affect blood pressure and blood gases, suggesting mediation of the metabolic responses by the brain. In this study, an agent exerting only a weak suppression of sympathetic outflow (inhaled helium) was without effect on postburn metabolic rate, suggesting that CNS control of the thermogenic drive was reset at a higher level after a large cutaneous burn.

The metabolic rate of normal subjects can be minimized by allowing them to equilibrate at a noncold environmental temperature in the thermoneutral range (around 24 to 25°C). Although postburn hypermetabolism was ameliorated to

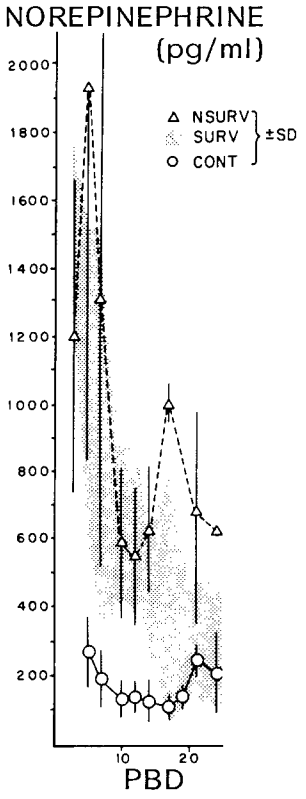

Figure 13–1. Resting recumbent morning plasma norepinephrine concentrations after overnight recumbency in 3 nonsurviving males (NSURV) with burns covering 55 to 93% of body surface, 10 surviving males (SURV) with burn size 18 to 82%, and 8 age-matched controls (CONT) at various postburn days (PBD) beginning on postburn day 3. The elevation of norepinephrine was proportional to burn size. (Data from R. A. Becker et al.: Hypermetabolic low triiodothyronine syndrome in burn injury. Crit. Care Med., *10*:870, 1982.)

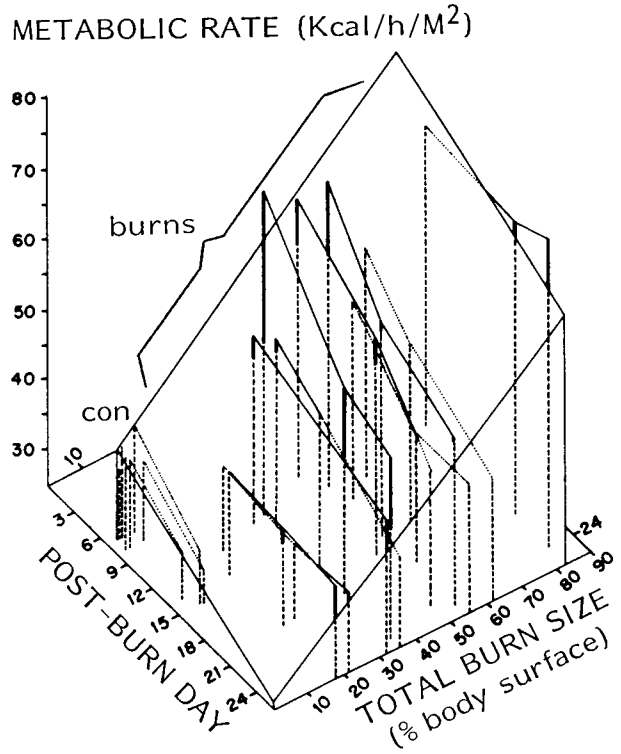

Figure 13–2. Resting metabolic rate (O_2 consumption) in the controls (con) and surviving burn patients described in Figure 13–1 as a function of postburn day and total burn size. Metabolic rate was highly correlated with plasma norepinephrine. (Data from G. M. Vaughan et al.: Cortisol and corticotrophin in burned patients. J. Trauma, *22*:263, 1982.)

some extent by letting patients equilibrate at the elevated thermoneutral temperature (around 30 to 33°C) associated with large burns, Wilmore and his associates[13,27,28] reported that the mean metabolic rate of burn patients at environmental temperatures from 21 to 33°C was never as low as that of unburned controls. In these studies, core temperatures of burn patients remained above those for controls at all environmental temperatures employed. Thus, elevated thermogenesis after burn injury is *not* secondary to a reduction of core temperature despite a known injury-induced augmentation of heat loss (Fig. 13–3*A,B*). The postburn elevation in metabolic rate also is not driven by hyperthermia because in burn patients (including those treated by reduction of heat loss[29] and delivery of an extra heat load by heat lamps[28,30]) metabolic rate is greatly in excess of that explainable by a supposed Q_{10} of 2 (see Chapter 14), and an extra heat load does not further raise the metabolic rate even though body temperature may rise.[28] Postburn hypermetabolism apparently results from a resetting of the thermogenic control for heat production and core temperature at levels (dependent on burn size) higher than normal. Injury hypermetabolism thus is temperature-sensitive but is not temperature-dependent.

Involvement of the sympathetic nervous system in postburn hypermetabolism is suggested by one study on the response of burn patients to cooling the environmental temperature to 21°C.[13,19] Patients who eventually survived their

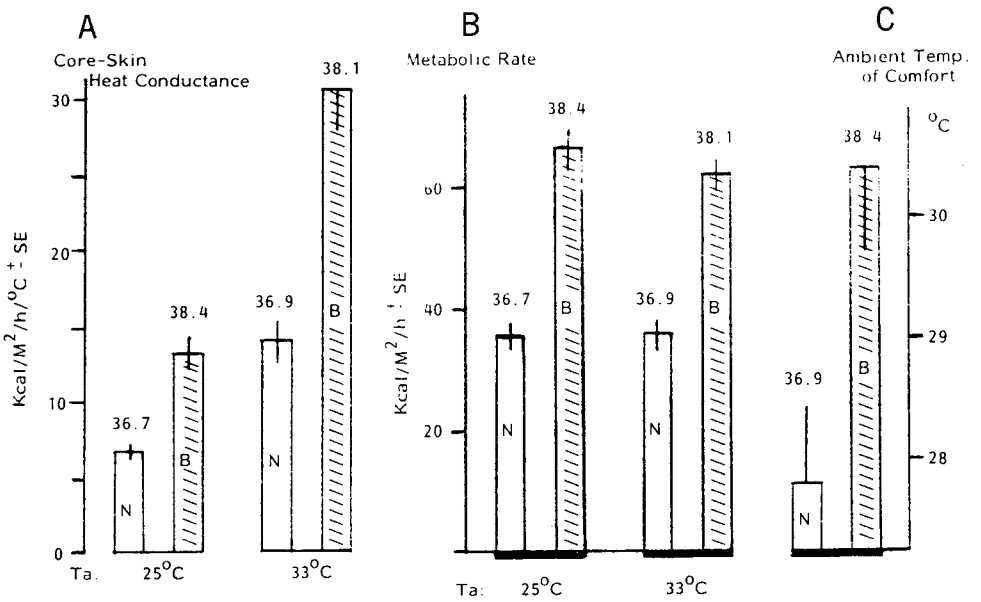

Figure 13–3. Heat conductance *(A)* and metabolic rate *(B)* in burn patients (hatched bars) and normal subjects (open bars) at two ambient temperatures (Ta). Burn patients had a mean burn size of 45% of body surface and were studied on mean postburn day 11. *C,* Self-selected ambient temperature of comfort in normal subjects and patients (mean burn size, 39%) studied on mean postburn day 13. Numbers above all bars indicate mean rectal temperature (°C). Vertical lines represent ± 1 SE. (Data from D. W. Wilmore et al.: Catecholamines: Mediator of the hypermetabolic response to thermal injury. Ann Surg., *180*:653, 1974; and from D. W. Wilmore, T. W. Orcutt, A. D. Mason, Jr., and B. A. Pruitt, Jr.: Alterations in hypothalamic function following thermal injury. J. Trauma, *15*:697, 1975.)

injury responded to the lower ambient temperature with augmented CA excretion and metabolic rate. However, those who subsequently died from complications of their injuries exhibited a fall or no rise in CA excretion and a fall in metabolic rate on exposure to the cooler environment. These patients, who presumably already had undergone maximal metabolic adaptation, had no reserve function and thus exhibited a dysregulated response. Goodall[9] reported that catecholamine stores in patients who died after burn injury and stress appeared to be depleted in the adrenal medulla, nerve endings, and sympathetic ganglia. Other studies[18] did not disclose a fall in basal circulating CA levels in the days and weeks prior to death in nonsurvivors. However, a reduction in tissue responsiveness to catecholamines must occur, as even large doses of CA drugs eventually fail to support the cardiovascular system in nonsurvivors. This rather global change in sympathetic function prior to death in nonsurvivors represents a dysregulation beyond the resetting that is present ordinarily in burn patients and is not yet understood.

This terminal condition is somewhat reminiscent of the so-called ebb phase of injury,[19] which occurs in the first 1 or 2 days after burn when major fluid loss occurs before repair of the capillary leak. The ebb phase is marked by depressed heat production and hypodynamic cardiac function, whereas the subsequent flow phase is characterized by hypermetabolism and elevated cardiac output. Because sympathetic and other hormonal responses typical of the flow phase

presumably also are present during the ebb phase,[3] interpretation of the reduced cardiac and metabolic function (in the presence of reduced effective circulating volume) during the ebb phase is difficult. It is interesting that during the first 1 or 2 days after burn in humans, circulating concentrations of histamine are apparently elevated.[7]

When controls and hypermetabolic (flow-phase) burn patients were allowed to select and maintain an environmental temperature of optimal comfort, burn patients selected a higher mean ambient temperature (30.4 vs 27.8°C), though their mean core and surface temperatures remained higher than those of controls[31] (Fig. 13–3*C*). The sympathetic and hypermetabolic responses to burn injury have been correlated with burn size (see Fig. 13–2), suggesting that the hypothalamus integrates information about the wound. Thus, the concept of the neuroendocrine reflex arc and the role of the hypothalamus have been refined to include an alteration of the settings for control of response elements as the general mechanism underlyng the protracted flow-phase response to injury.[31–33] Whether shifting of control settings also occurs in other locations is open to speculation and investigation.

Glucagon and Cortisol

Circulating glucagon concentrations were found to be elevated in burn patients,[34] and infusions of glucagon elevated the metabolic rate in normal subjects.[35,36] In a series of studies, my associates and I observed glucagon and other circulating hormones under fasting supine conditions in 20 surviving patients with large burns (total burn size, TBS, 18 to 82% of body surface area) and correlated hormonal levels with the resting metabolic rate measured weekly between postburn day 3 and 26.[17,18,25,37] Fasting concentrations of insulin, somatostatin, and growth hormone (GH) were no higher in the burn patients than in controls. However, burn patients had mild hyperglycemia and markedly increased levels of glucagon, norepinephrine, epinephrine, and cortisol, which were directly correlated with elevated metabolic rates. In contrast, total serum cholesterol, thyroxine (T_4), and triiodothyronine (T_3) levels were decreased in burn patients and inversely correlated with metabolic rate. Multiple regression, supported by partitional analysis, suggested independent association of norepinephrine, glucagon, and cortisol variation with residual variation in metabolic rate.[37] Chronic T_3 replacement therapy given to half the patients somewhat lowered NE levels but did not alter the metabolic rate or its pattern of returning toward normal after the second postburn week.

It appears that the resting metabolic rate after burn injury is removed from control by thyroid hormones, which normally regulate it,[38] and placed under the influence of a set of anti-insulin hormones including catecholamines, cortisol, and glucagon, but not GH. It is interesting that in a group of injured patients (some without burns), the suppressive effect of glucose infusions on plasma glucagon concentration was demonstrable but attenuated,[39] indicating an altered setting of control for glucagon secretion. It is theoretically possible that this alteration takes place in the hypothalamus, the origin of sympathetic and parasympathetic pathways that control glucagon secretion.[40] This same effect might also result from the glucagon-secretory effect of catecholamines in the setting of generally elevated sympathetic tone.

Wilmore and his colleagues[15,19,27,32,33,41] extended the neuroendocrine reflex

arc concept, originally developed by Hume and Egdahl[1–3] for the acute adrenocortical response to trauma, to model the longer term (flow-phase) thermogenic response to the presence of burn injury. In this model, the elevated circulating cortisol concentration present after burns was viewed not as the primary drive to hypermetabolism but as a permissive influence facilitating substrate mobilization and utilization.[17,41] Interestingly, to date, there are no studies verifying that the flow-phase adrenocortical response to burns results from a resetting of the ACTH control mechanism, although in one study, plasma ACTH, like cortisol, was elevated in proportion to burn size.[42] Lack of a uniform observation of such proportionality,[17] although not yet understood, might reflect sampling variably during peaks and troughs of pulsatile ACTH secretion, or it might reflect variations in circulating blood volume (volume deficits can activate the ACTH-cortisol axis). Alternatively, the lack of correspondence between cortisol and ACTH responses might result from the combined effect of (1) negative feedback by elevated cortisol released from the adrenal cortices and (2) enhanced adrenocortical sensitivity to ACTH due to chronic stimulation by ACTH. Such a mechanism could explain the relatively small increases in ACTH following burns associated with fairly large increase in cortisol, which might still be ACTH dependent. The observation of a significant nyctohemeral rhythm of cortisol in burn patients with normal rhythm timing (though with a blunted amplitude) suggests that the elevated secretion of cortisol is controlled by the hypothalamus through ACTH[17] (Fig. 13–4). Other studies indicate that burn patients may exhibit a reduced or absent circadian rhythm for circulating cortisol and ACTH (see Chapter 8); even if these hormones are normal in the morning, there is a lack of fall to the low values expected in the late evening.

At first glance, the pattern of adrenal reticular zone androgens (C-19 steroids) would seem to weigh against ACTH control of the adrenal cortex after burn injury. Serum levels of dehydroepiandrosterone sulfate (DHEA-S) and andro-

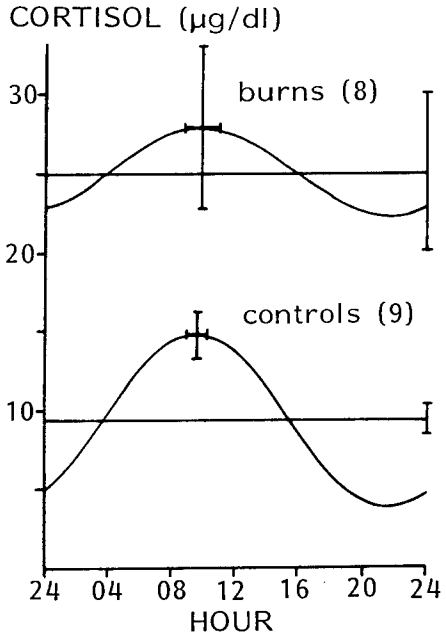

Figure 13–4. Best-fit cosinor curves for plasma cortisol based on samples taken at 2-hour intervals for a 24-hour period from controls and 8 patients with a mean burn size of 39% TBS on mean postburn day 13. The error bars mark the SE of the mean for the magnitude and timing of the acrophase (curve peak) and for the level of the mesor (group curve average, horizontal lines). Among the burn patients, individual mesors were positively correlated with burn size. Although cortisol rhythmicity was significant ($p < .005$) for the burn group, its amplitude was less than half that for the control group ($p < .05$). (Data from G. M. Vaughan et al.: Cortisol and corticotrophin in burned patients. J. Trauma, 22:263, 1982.)

stenedione become depressed in burned men[43] (see Chapters 5 and 6). In other human syndromes of excessive ACTH secretion (e.g., congenital adrenal hyperplasia and ACTH-producing tumors), there is a tendency for increased secretion of C-19 steroids, which are generally controlled in a positive fashion by ACTH.[44] Although the literature pertaining to control of adrenal androgens is difficult to interpret, stimulation of children (particularly for prolonged periods up to 1 to 2 weeks) with the luteinizing hormone (LH)-like hormone chorionic gonadotrophin (hCG) increases serum DHEA, DHEA-S, and androstenedione.[44] Negative studies in adults might reflect lack of basal hypogonadotrophism with no room for a further effect of added gonadotropin, lack of adequate time allowed for development of such an effect, and/or lack of focus on a possible synergy between ACTH and LH activity. It is interesting that these reviewers[44] characterized the influence of ACTH on adrenal androgen secretion as partial and possibly permissive.

Serum bioactive LH drops precipitously and remains low after burn injury in men as does testosterone (see later section on Leydig cell control). However, the decrease in DHEA-S and androstenedione in burned men is much more gradual than is that of testosterone.[43] This pattern suggests that adrenal androgen secretion may be controlled by both LH and ACTH. Hypothetically, it might take some time for the reduction in bioactive LH (or perhaps reduction of some other stimulus) to affect adrenal androgen secretion after burns in the presence of normal or elevated ACTH. Perhaps, ACTH can maintain DHEA-S even for 1 to 2 weeks without bioactive LH, after which cortisol remains elevated but adrenal androgens decrease. Such a scheme, although in need of further support, would be consistent with continued ACTH control of the adrenal cortex after burn injury associated with a relative shift away from C-19 steroids toward cortisol.

Insulin Resistance and Alteration of Metabolic Pathways

The hormones elevated in burn injury—catecholamines, cortisol, and glucagon—are expected to increase glucose production through glycogenolysis and gluconeogenesis. However, these same hormones typically produce insulin resistance to glucose disposal in insulin-dependent tissues, principally muscle. Insulin resistance has been found in uninjured forearms of post-trauma patients.[45] A burn-size-related hyperglycemia occurs without depressed insulin levels,[37,42,46] and total glucose disposal following injury appears unresponsive to rising plasma insulin in the range just above physiologic.[39] Nevertheless, glucose flow (total production and utilization) is markedly elevated in the hypermetabolic (flow) phase of burn injury.[33,41] The nonretarded decay rate of plasma glucose and the normal insulin response seen after an intravenous glucose load[46] suggest that the exit of glucose through a non-insulin-dependent route is increased in burn patients to counterbalance a restricted glucose exit rate into insulin-dependent tissues. Furthermore, low glucose uptake across unburned extremities of burn patients and high uptake across burned extremities (in which lactate production accounts for most of the glucose utilized) are associated with high O_2 extraction in both cases.[33] It is thus apparent that muscle shifts toward nonesterified fatty acids (NEFA) for a fuel source and that the increased glucose disposal in burn patients occurs largely in the skin burn wound, which is not insulin-dependent for glucose uptake. This provides an exaggerated Cori cycling of lactate and glucose between the wound and the liver, possibly for the benefit of the function

of leukocytes, macrophages, and granulation tissue in the wound, although this possibility needs further investigation.

During the flow phase of burn injury, net breakdown of skeletal muscle occurs, providing amino acids as a major contribution to the three-carbon substrate pool that supports the augmented gluconeogenesis. If enough calories and protein are supplied exogenously, insulin secretion is stimulated sufficiently to augment protein anabolic processes and to prevent nitrogen loss.[47] The postburn increase in O_2 consumption (metabolic rate) occurs in liver, skeletal muscle, kidneys, heart, and possibly other tissues[15,33,48,49] principally through increased use of nonesterified fatty acids as substrate, since the respiratory quotient (RQ) is typically depressed. Stimulation of lipolysis mainly by catecholamines and perhaps by glucagon in the setting of hypercortisolemia is thought to make nonesterified fatty acids available.[11] Whether the multihormonal influence might also promote utilization of nonesterified fatty acids and other substrates by separate stimulation of the Krebs cycle and various substrate (futile) cycles also should be considered.[10]

The relative individual contributions of the elevated hormones to the postburn hypermetabolic response is not yet fully understood. Adrenergic blockade blunts O_2 consumption when given at the peak of the hypermetabolic response to large burn injury.[11,13] The failure of Wolfe et al.[50] to find a statistically significant lowering of metabolic rate by beta-blockade in some patients may have occurred for several reasons: (1) assessment of patients at a postburn time when hypermetabolism is only mild, (2) the difficulty in detecting a role for an individual effector component when others may also be active, and/or (3) the unknown time course required for amelioration of the response when the effect of one component is reduced. Nevertheless, these authors found that recycling of nonesterified fatty acids to triglycerides (accounting for 33% of lipolysis in controls and 39% in burn patients) as well as total lipolysis was elevated and both were subsequently reduced in burn patients within 90 minutes of propranolol injection. Glucose appearance not after movement through pyruvate or lactate in the Cori cycle but after cycling from glucose through hexose and triose intermediates (25% of total glucose appearance in controls and burns), as well as glucose appearance other than after cycling through those intermediates, was elevated in burn patients and not diminished after propranolol infusion. The authors suggested that substrate cycling was important in postburn hypermetabolism and that although catecholamines appeared to play a readily detectable role in the component of fat metabolism, the elevated circulating glucagon in burn patients might contribute more to glucose metabolism.

As shown in Figure 13–5, postburn hypermetabolism involves production of excess ATP in many tissues via the oxidation of nonesterified fatty acids and glucose, as indicated from the increased O_2 consumption and CO_2 production and from the elevated glycolysis. At least some of the excess ATP is used in substrate cycling, that is, recycling of nonesterified fatty acids to triglycerides (presumably in liver and adipose tissue), lactate to glucose (liver), and glucose through hexose phosphates back to glucose (liver). The rest of the excess ATP is used for protein synthesis (e.g., in muscle and liver) and perhaps other processes. Even this elevated protein synthesis represents a substrate cycle (not shown), as the protein breakdown rate is also elevated.[51] Some of the breakdown contributes to gluconeogenesis. Thus, the adaptive advantage of hypermetab-

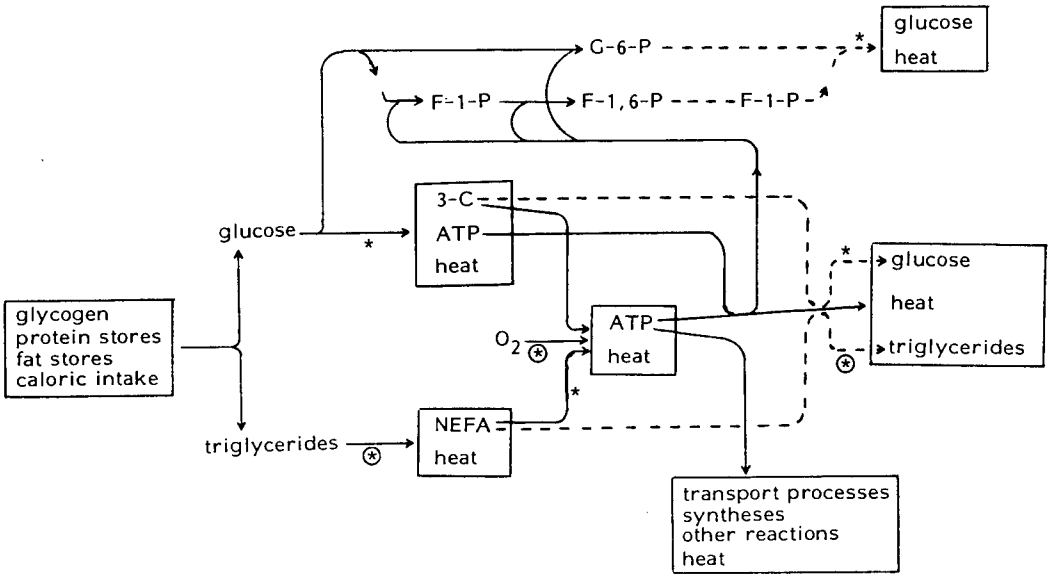

Figure 13–5. Simplified diagram illustrating substrate cycles, which appear to be an important component of postburn hypermetabolism. Processes accelerated in burn patients, presumably by catecholamines, glucagon, and/or cortisol, are indicated by an asterisk (*). Those processes whose acceleration has so far been shown to depend at least partly on increased sympathetic activity in burn patients are indicated by a circled asterisk.[11,13,50] Dashed lines indicate the portion of substrates contributing to recycling. G-6-P, glucose-6-phosphate; F-1-P, fructose-1-phosphate; F-1,6-P, fructose-1,6-diphosphate; 3-C, 3-carbon intermediates such as lactate; ATP, adenosine triphosphate; NEFA, nonesterified fatty acids. Intermediates of less than 6 carbons are not shown for the separate non-Cori glucose and fructose cycles at the top of the diagram. The Cori cycle is represented by the path including the dashed line from 3-C to glucose, much of the 3-C being produced in the burn wound from glycolysis and transported to the liver as lactate for the gluconeogenesis limb of the cycle, where amino acids also contribute to gluconeogenesis. Phosphate, ADP, and other substrates, intermediates and cofactors, and CO_2, H_2O, and other products are omitted for simplicity.

olism (increased O_2 consumption) may lie partly in the provision of ATP for increased substrate cycling, which increases the availability of many metabolic intermediates and perhaps the effectiveness of any alterations in various enzyme activities, which could provide metabolic flexibility in adapting to changes in energy substrate demands.[51] However, this hypothesis is not yet adequately tested.

In uninjured normal subjects, combined infusion of cortisol, glucagon, and epinephrine (sufficient to maintain plasma levels in the range typical of patients with major burns) produced effects that mimicked in some respects the metabolic response to burn.[52] These effects included tachycardia, widened pulse pressure (as seen in burn patients), hypermetabolism, negative nitrogen and potassium balances, hyperglycemia, and insulin resistance. These effects were present throughout the 3 days of infusion and did not progress after the first day. Although these results support the hypothesis that a multihormonal system is involved in the metabolic response to burn injury, the metabolic rate of the infused normal subjects was elevated only 19%, wheres a 50 to 100% increase in metabolic rate is common in patients with large burns (see Fig. 13–3*B*). In

addition, the infused normal subjects showed a slight rise in temperature and fall in respiratory quotient. The absence of norepinephrine in the infusions or the relatively short period of hormonal exposure in this study might explain the failure fully to reproduce the postburn hypermetabolic response. Alternatively, humoral peptides such as interleukin-1, tumor necrosis factor, and others[53–57] (see Chapters 11 and 12), presumably emanating from leukocytes and macrophages in the wound and acting on peripheral tissues along with the other hormones, hypothetically might also be required for full thermogenic expression.

Whether catecholamines, glucagon, and cortisol act additively or potentiatively on each of the many specific metabolic alterations found in burn patients and just how much of the total metabolic response results from their aggregate mediation need further investigation. Nevertheless, at this time the evidence is strong that they participate in the mediation of this response, which is a catabolic resetting of metabolism together with an anabolic component whose control is less well understood. This resetting has two principal effects: (1) increased mobilization of nonesterified fatty acids as fuel for systemically elevated O_2 consumption and thermogenesis by many noninjured tissues; and (2) mobilization of amino acids from muscle presumably for synthetic processes in the wound, liver, bone marrow, and perhaps elsewhere, and more certainly for accelerated production of glucose to be consumed by glycolysis in the wound, and recycling of the lactate for more glucose production.

The teleology of this whole process, with its generalized catabolic energy and heat production and obvious but less well understood redirection of synthetic processes, is not yet fully characterized, but a reasonable hypothesis is available.[10,19] The extra energy (the part produced as chemical equivalents in high energy bonds) might be used for work in the production of new glucose, the prolonged elevation of acute-phase proteins, replenishment of albumin and other proteins lost through the wound, and synthesis of leukocytes and of new dermal, vascular, and epidermal elements for wound healing. The part expressed as heat production may elevate body temperature in order to speed wound healing and improve resistance to infectious organisms. Glycolysis in the wound may be used for leukocytic host defense and/or healing. Involvement of the catabolic hormones and correlation of almost all elements of the response with burn size suggest that the CNS has a role in this general resetting of metabolism.

Growth Hormone

Other findings also indicate that hypothalamic function is altered in burn patients. For example, the increases in circulating growth hormone (GH) that are normally stimulated by arginine infusion and by insulin-induced hypoglycemia were blunted in burn patients[31] (Fig. 13–6). Likewise, the normal GH surge accompanying sleep in the first part of the night was diminished in burn patients.[14] Whether such reduced responses represent a resetting of the GH-release mechanism because of the presence of mild basal hyperglycemia in these patients is not yet known. In contrast to the elevated GH seen acutely after stress and shock, baseline plasma GH usually is normal or near normal in the flow phase of burn injury.[14,37,42] However, because the sensitivity of the GH assay is low near the normal basal range, the possibility of low basal plasma GH in flow-phase burn patients cannot be ruled out. The finding of Coates et al.[58] that

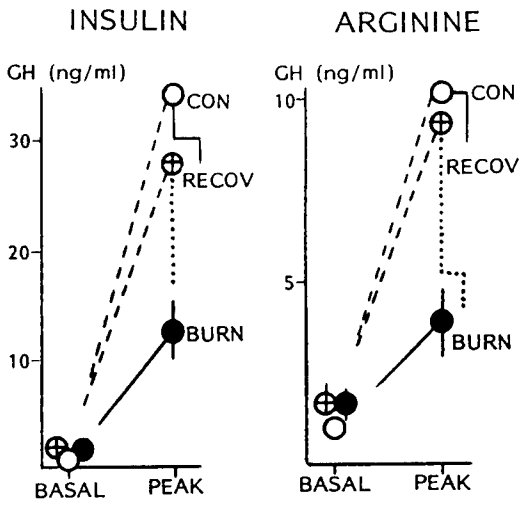

Figure 13–6. Response of plasma growth hormone (mean ± SE) to insulin-induced hypoglycemia and to arginine infusion in normal subjects (CON), recovered burn patients (RECOV), and nonrecovered burn patients (BURN) with a mean burn size of 52% of body surface. Both the controls and recovered burn patients were injected with insulin at 0.15 units/kg body weight; burn patients received 0.30 units/kg on mean postburn day 12. These dosages produced mean blood glucose decrements of 71%, 64%, and 62%, respectively, in control, recovered, and burn groups. Subjects were infused with 30 g of arginine over 30 minutes. (Data from D. W. Wilmore, T. W. Orcutt, A. D. Mason, Jr., and B. A. Pruitt, Jr.: Alterations in hypothalamic function following thermal injury. J. Trauma, *15*:697, 1975.)

circulating levels of bioactive somatomedin were depressed in burn patients may provide indirect evidence for a concomitant depression in plasma GH.

Injured patients do not lose their ability to respond to GH. After surgical or orthopedic trauma, injections of GH elevated plasma nonesterified fatty acids and increased the proportion of calories expended from fat relative to those from carbohydrate.[59] Wilmore et al.[47] demonstrated that administration of GH for 1 week to hypermetabolic burn patients further elevated their plasma NEFA concentrations; reduced their serum cholesterol; markedly elevated their serum insulin and magnified its response to glucose loading without augmenting their mild hyperglycemia or causing a change in glucose tolerance (i.e., GH caused insulin resistance); and reduced their nitrogen loss in proportion to a reduction in potassium loss (a sparing effect on muscle protein). The authors noted that a previous study had shown little or no protein-sparing effect of GH in patients receiving inadequate calories and nitrogen and suggested that the beneficial effect of GH administration depends upon adequate nutrition and an intricate relationship among food intake, insulin response, and protein sparing. In fact, because adequate nutritional intake alone can insure positive nitrogen and caloric balances, the general use of GH to offset hypercatabolism in burn patients seems inappropriate at this time. Whether an added benefit of exogenous GH might be to prevent elements of multiorgan failure by local anabolic effects to protect vital tissues in the general catabolic milieu of critical injury and illness remains an interesting question.

Afferent and Efferent Signals Following Burn Injury

Afferent Limb

The Hume-Egdahl model of the neuroendocrine reflex arc posits a *neural afferent* mediation of acute pituitary-adrenal activation following injury. Various observations, however, suggest that the long-term hypermetabolic response to burn injury may depend, at least in part, on a *humoral afferent* signal from the

burn wound. For example, an elevated postburn metabolic rate was observed in a patient whose spinal cord was transected at a level above the burn; also, postburn hypermetabolism was not ameliorated by topical wound or spinal anesthesia.[41] Aulick and Wilmore[19] have reviewed evidence for a circulating factor(s) that may act centrally. Microaliquots of plasma from normal subjects produced very little if any hyperthermic response when injected into the anterior hypothalamus of rabbits; however, samples from 9 of 13 burn patients elicited a febrile response. This effect was attenuated after heat treatment of the samples, suggesting mediation of the response by peptidic endogenous pyrogen(s). However, the absence of differences in prostaglandin levels measured in the circulation across burn wounds suggests that although these substances may have local metabolic and circulatory effects in the wound or be involved locally in alteration of brain mechanisms, other techniques may be required to determine whether circulating prostaglandins have any role in the responses to injury. Other candidates as circulating mediators include peptide mediators (e.g., interleukin-1, tumor necrosis factor, and others), which might be derived from reparative elements or from monocytes or macrophages accumulating in the wound and releasing their products to act via the circulation on the CNS[53–57] (see Chapters 11 and 12). Sympathetic, adrenocortical, and thermic responses similar to those seen after burn injury or after endotoxin adminstration can be elicited in human subjects by administration of tumor necrosis factor (D. W. Wilmore, personal communication).

Another potential afferent mediator is a deficit in effective circulating volume from an arteriovenous shunt in the burn wound, which theoretically could contribute to elevation of many of the hormones found to be elevated after thermal injury. Most measurements have focused on the period well after resuscitation, when plasma and blood volumes are expected to have normalized with modern-day treatment.[60] However, normal blood volume might partly reflect the result of many compensatory hormonal adjustments to persistent wound-induced alterations of the vascular bed, or it might be viewed as inadequate for a possible relative increase in vascular capacity. These issues are not yet resolved.

Interestingly, splanchnic blood flow and, in the absence of sodium deprivation, renal blood flow are typically increased in burn patients.[48,49] These and other clinical indices discussed in the next section may reflect adequate or enhanced effective volume accompanying many of the measurements of volume-responsive hormones. Alternatively, they may suggest the presence of circulating vasodilator(s) causing a relative reduction in effective circulating volume in spite of normal or elevated total volume and elevated visceral and wound flow. If the latter vasodilator mechanism plays any role, it must be operating viscerally perhaps for redistribution of volume to internal organs, where it also might generate a signal of reduced effective volume. This is an unlikely mechanism for stimulation of renin secretion, however, because glomerular filtration rate is typically elevated or normal in flow-phase burn patients (see below). In one study of burned children, circulating catecholamines, renin, and aldosterone were elevated; in some cases, these elevated levels were associated with hypertension and high total peripheral resistance inappropriate for the measured hypervolemia.[61] In studies of burned adults (see Chapter 8), renin axis hormones were found to be always elevated in those with high blood pressure and sometimes in those without elevated blood pressure. Thus, at the present time, it seems unlikely

that reduced effective volume is a major afferent signal following burn injury. Further studies of regional blood flow to sites of endocrine secretion would be helpful in determining whether decreased or increased blood flow or perfusion pressure contributes to the overall afferent signal(s) determining the final observed alteration in hormonal secretion in burn patients. One wonders how simple or how complex the afferent signal(s) might be, for the ultimate hormonal responses are quite multifaceted.

Efferent Limb

Although the efferent limb of the postburn neuroendocrine reflex usually has been discussed in terms of mediating hypermetabolism, it now appears to include many hormonal outputs, some without any yet demonstrated effect on the metabolic rate.

The elevated secretion of catecholamines in burn patients (see Fig. 13–1) almost certainly represents a neural component of the efferent limb because norepinephrine originates in postganglionic sympathetic endings in many organs, and both norepinephrine and epinephrine originate in the adrenal medulla. Postburn hypermetabolism appears to be at least partly a response to catecholamines. Whether some elements of the efferent limb might also, in effect, constitute the afferent signals for other efferent elements is not yet clear. For example, some efferent components, such as persistent activation of glucagon and vasopressin secretion and inhibition of the pituitary-thyroid and -gonadal axes, may also be partly a response to catecholamines or substrate intermediates. Whether relative TSH deficiency or a decrease in peripheral T_4 to T_3 conversion partly results from excessive cortisol, catecholamines, or mobilization of fatty acids needs further study.

With respect to sympathetic effects, influence could be exerted humorally through circulating epinephrine and norepinephrine (NE) from the adrenal medullae and through NE released from peripheral and visceral nerve endings, producing potentially widespread effects in any tissue with CA receptors. On the other hand, influence potentially might be exerted more discretely through local neuronally derived NE acting as a neurotransmitter in an innervated tissue (e.g., in the cardiovascular system for elevated cardiac output, in liver for heat production, in pancreatic islets for glucagon secretion, in the renal juxtaglomerular apparatus for renin secretion, or in the pineal for melatonin secretion). The relative contributions of these two general routes need further investigation. How much the sympathetic nerve endings in various tissues take up (and inactivate) NE and epinephrine entering from the circulation (thus providing protection from stimulation by humoral catecholamines) is also uncertain. Potential interactions between the neural and humoral components of the efferent limb of the response to burn injury are yet to be characterized.

Experiments also are needed to determine directly whether all components of the efferent limb are dependent upon the brain and spinal cord and which CNS loci are primarily responsible for which response. Stereotaxic lesions as well as implantation of specific substances in the CNS may be used in the future to study these questions, which are still unresolved. However, as discussed above and subsequently, indirect evidence already points to involvement of the brain and hypothalamus for many of the responses to burn injury.

Water and Electrolyte Metabolism

Vasopressin (Antidiuretic Hormone)

Hyponatremia and exaggerated antidiuresis (the latter more prominently expressed as dilution of plasma than as oliguria) are often seen in burn patients days and weeks after injury. In a group of burn patients studied well after resuscitation, Soroff et al.[62] noted that a fall in serum sodium concentration was associated with administration of greater amounts of electrolyte-free water than in other burn patients. The presence of adequate urine flow, appreciable sodium excretion and a positive sodium balance indicated that a deficit of fluid volume or of sodium was not the likely cause of water retention in these patients. Soroff et al. suggested that hyponatremia in the presence of burn injury is dilutional and speculated that it results from an osmoregulatory mechanism set at a lower than normal plasma tonicity. Based on similar observations, Collentine et al.[63] suggested that burn injury could cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH), previously thought to be a phenomenon restricted to a few patients with cancer or diseases of the lungs or of the CNS.[64]

Although Doleček[10] found elevated bioassayable ADH in the circulation mainly during and just after resuscitation, he also reported elevated levels in a few apparently sodium- and volume-replete burn patients after resuscitation. Subsequent studies using more precise immunoassays to determine plasma arginine vasopressin (AVP) of burn victims[65,66] were limited to the first postburn week and demonstrated very high concentrations of AVP in the presence of high plasma tonicity. The initial high plasma osmolality may have resulted from the fluid shifts that occur just after injury and resuscitation when evaporative (free) water loss becomes great. However, by postburn day 4 to 6, the data suggest that low plasma tonicity was present at a time when AVP was still elevated. In these two reports,[65,66] serum sodium concentrations were not presented, although Hauben et al.[65] stated that serum sodium stayed within normal limits. Because of the uncertain status of serum sodium and the mostly elevated plasma tonicities (a normal stimulus for AVP secretion), the possibility of SIADH was not well addressed in these studies. However, the presence of some measurable mean AVP associated with an apparently low-normal plasma tonicity suggests the possibility that SIADH had developed by the end of the first postburn week. One interesting finding was that despite the very high levels of AVP (perhaps even in the vasoconstrictor range, > 15 pg/ml) in these patients, they produced large urine volumes (3 to 9 L/day).

Shirani et al.[67] studied nine hyponatremic (mean Na^+, 130 mEq/L) burn patients on postburn days 4 to 21, well after the initial fluid resuscitation. These patients exhibited no pain, nausea, hypotension, sepsis, pneumonia, or intracranial, renal, adrenal, or thyroid disease. They had hypertonic urine (mean flow, 2.7 L/day; Na^+, 80 mEq/L; osmolality, 500 mOsm/kg) and low-normal blood urea nitrogen (mean, 12 mg/dl), despite an elevation in gluconeogenesis and hence ureagenesis (mean fasting serum glucose, 130 mg/dl) that is expected during this time after burn injury. This clinical picture qualifies these patients for the diagnosis of SIADH.[64] Indeed, their plasma concentrations of AVP measured by a sensitive and specific radioimmunoassay were markedly elevated (mean, 6.8 pg/ml); the expected normal for subjects with hypotonic plasma is

undetectable (less than 0.5 pg/ml). Five of these patients received a water load, which was excreted slower than normal (Fig. 13–7). Their plasma was diluted further, and their plasma AVP and urine tonicity fell. One patient's plasma tonicity returned toward normal during a 5% NaCl infusion. Plasma AVP in these patients varied with plasma tonicity with a slope not much different from normal but shifted by some 20 mOsm/kg of plasma tonicity lower than normal (Fig. 13–8).

Because the control mechanisms for AVP release are centered in the hypothalamus, these results implicate the CNS in the response to burn injury and indicate that control of AVP secretion by plasma tonicity is reset. Some of these patients received fluids only orally, thus implicating excessive thirst as part of their response to injury, again implying involvement of the hypothalamus. However, the AVP pattern could be an appropriate response to reduced effective volume even without a total volume deficit. Although the elevated splanchnic and renal blood flow typical of flow-phase burn patients speaks against a reduced effective volume due only to a vascular shunt effect of the burn wound, dilated visceral beds could signify vasodilating mediators producing a relatively low effective volume at sites controlling AVP secretion. Whether such mediators

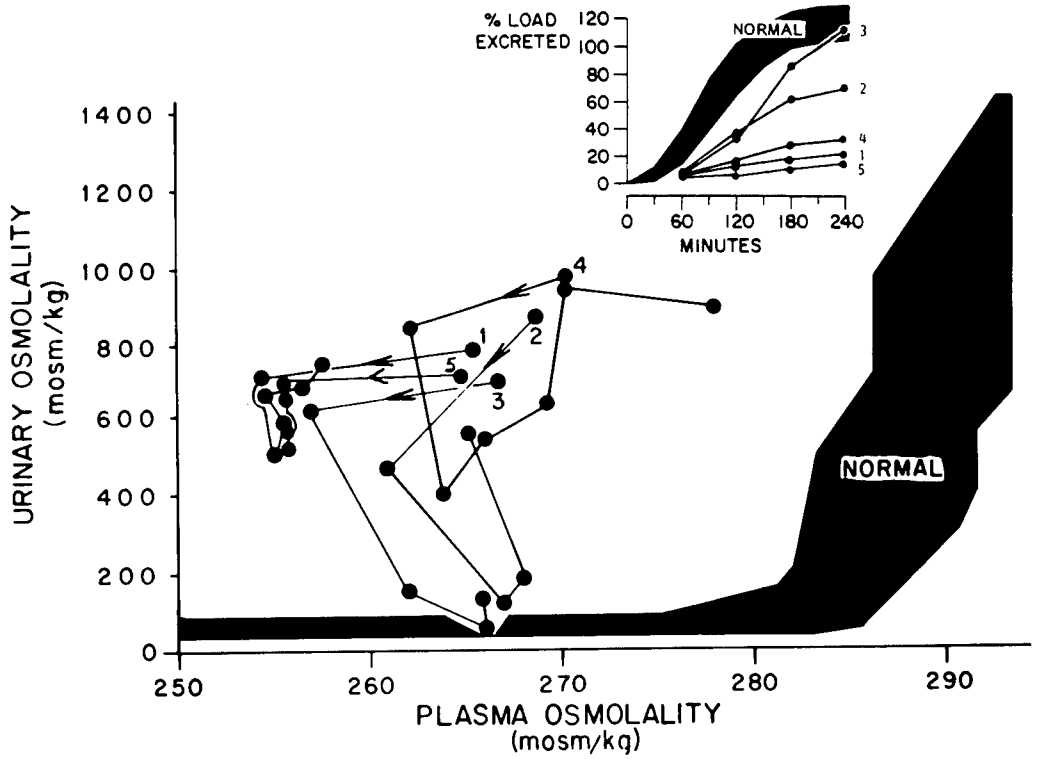

Figure 13–7. Plasma and urine tonicity in sequential samples taken during an oral water-loading test (20 ml/kg body weight) in five hyponatremic burn patients. In this figure, individual patients are identified by number; data from some of these patients have been presented previously.[67] Total burn size ranged from 21 to 42% of body surface. The studies took place on postburn day 9 to 37. The insert shows the volume excretion pattern, and the normal response to water loading is indicated by the black areas. (From G. M. Vaughan, unpublished data.)

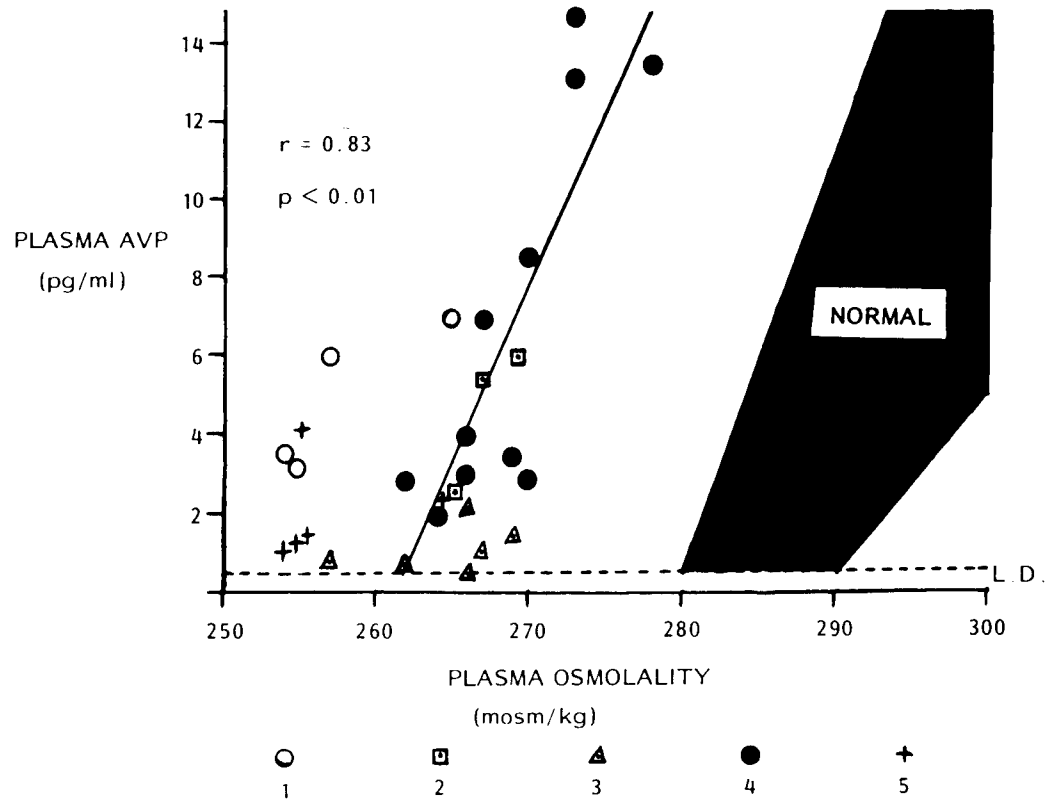

Figure 13–8. Plasma arginine vasopressin (AVP) during the water-loading test for some of the samples from the burn patients described in Figure 13–7. A regression line is drawn through the values for one patient who also received a 5% hypertonic saline infusion (●). The normal relationship between plasma tonicity and plasma AVP is indicated by the black area. (From G. M. Vaughan, unpublished data; AVP assays performed by Dr. Gary Robertson.)

include elevated temperature, glucagon, epinephrine, or prostaglandins should be investigated. Alternatively, altered control of AVP might reflect the action of peptide mediators from the burn wound on brain centers.

Renin-Angiotensin-Aldosterone Axis

Elevated plasma renin activity and aldosterone[61,68–74] (see Chapter 8) and angiotensin-2 concentrations[68,72] have been noted in burn patients well after the period of resuscitation. Except in one study,[61] their volume status was usually not described.

Shirani et al.[73,74] studied a group of burned men (TBS 20 to 44%) without medical or surgical complications for 4 weeks beginning on postburn day 4. In conformity with the previously reported elevation of Glofil-determined glomerular filtration rate (GFR) in burn patients,[75] endogenous creatine clearance (CRCL) in these patients usually remained normal to elevated in proportion to burn size (Fig. 13–9) with no evidence of reduced renal function related to Na^+ retention (Fig. 13–10). On postburn day 5 to 11, six of these patients (mean TBS 34%) received a 2-hour infusion of 5% saline sufficient to normalize serum Na^+ (initial mean, 134 mEq/L) and plasma tonicity (initially mean, 276 mOsm/

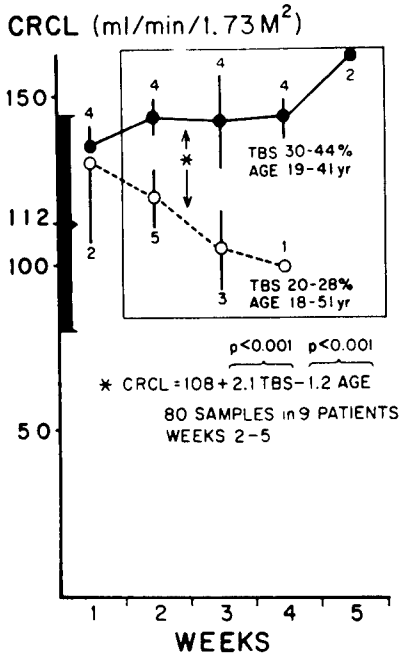

Figure 13–9. Creatinine clearance (CRCL) in burned men (total $n = 9$) with burn size of 20 to 44% of body surface plotted against weeks postburn. Means of within-patient means (± SE) for values obtained within a given week are shown. The thickened area on the ordinate represents the normal range (mean ± 2 SD) for CRCL in healthy individuals of similar age.[76,77] As shown, multiple regression analysis indicated significant positive variation of CRCL with burn size (TBS) after accounting for the variation due to age. The numerals near each data symbol indicate the number of patients represented during a given week. (Data from K. Z., Shirani, G. M. Vaughan, A. D. Mason, Jr., B. A. Pruitt, Jr., and J. D. J. Bullard: Elevation of plasma renin activity, angiotensins I and II, and aldosterone in burn patients: Na^+/volume-responsive but not -dependent. Surg. Forum, *35*:62, 1984.)

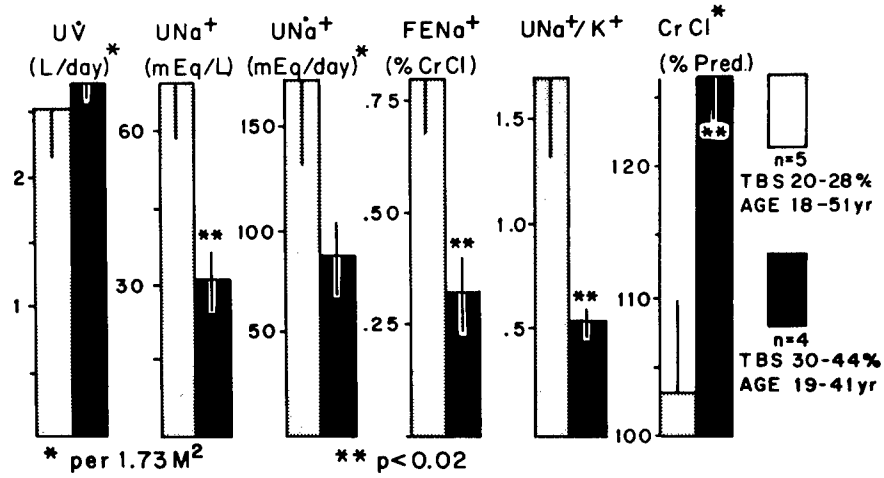

Figure 13–10. Various other indices of renal function in the nine uncomplicated patients of Figure 13–9. A mean value for each patient (five with smaller and four with larger burns) was calculated from all individual values obtained from postburn days 5 to 28, and these within-patient values were combined and plotted as the group mean ± SE. Variables shown are as follows: UV̇, daily urine volume; UNa^+, urinary sodium concentration; $U\dot{N}a^+$, daily excretion of urinary sodium; $FENa^+$, fractional excretion of the filtered sodium; UNa^+/K^+, urinary sodium/potassium ratio; and CrCl, creatinine clearance as % of that predicted as normal for age.[76,77] Significant differences between group means ($p < .02$) are indicated by double asterisk (**). Creatinine clearance in the group with larger burns not only was greater than in the group with smaller burns but also was greater than that predicted as normal for age ($p < .01$). (Data from K. Z. Shirani, G. M. Vaughan, A. D. Mason, Jr., B. A. Pruitt, Jr., and J. D. J. Bullard: Elevation of plasma renin activity, angiotensins I and II, and aldosterone in burn patients: Na^+/volume-responsive but not -dependent. Surg. Forum, *35*:62, 1984.)

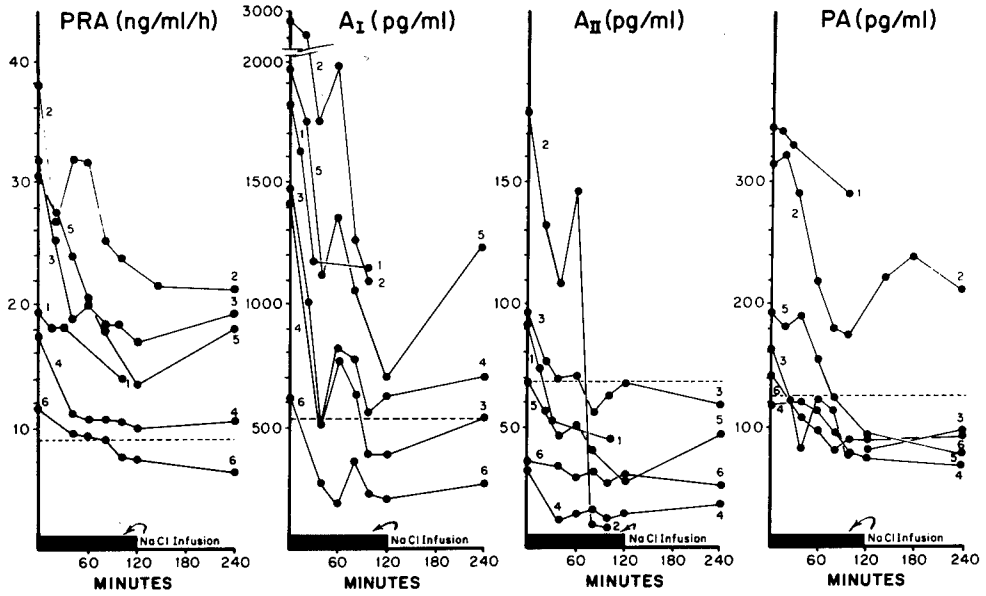

Figure 13–11. Plasma renin activity (PRA), angiotensin-I (A_I), angiotensin-II (A_{II}), and plasma aldosterone (PA) in six volume-replete overnight recumbent burn patients during and following a 2-hour infusion of 5% saline. Mean burn size was 34% of body surface; studies were conducted on postburn day 5 to 11 after completion of adequate postinjury fluid and electrolyte resuscitation. The numbers by each curve identify individual patients. The horizontal dashed lines indicate the upper normal limit (mean + 2 SD) based on 12 random samples from 7 normal laboratory personnel who were not recumbent but sitting for various times after standing; these upper limits of normal thus are likely to be overestimates. A_I and A_{II} were measured by radioimmunoassay after column extraction in carefully characterized procedures.[73] (A_{II} antibody was provided by Dr. Kevin Catt. Data from K. Z. Shirani, G. M. Vaughan, A. D. Mason, Jr., B. A. Pruitt, Jr., and J. D. J. Bullard: Elevation of plasma renin activity, angiotensins I and II, and aldosterone in burn patients: Na^+/volume-responsive but not -dependent. Surg. Forum, *35*:62, 1984.)

kg) in order to provide a mild volume stimulus without elevated tonicity. The mean baseline Na^+ excretion (5.4 mEq/h) and creatinine clearance (214 ml/min/1.73 M^2) indicated at least adequate volume expansion before the infusion, although plasma levels of renin activity (PRA), angiotensins (A1, A2), and aldosterone (PA) were usually elevated above values for normal subjects (Fig. 13–11).

Plasma levels of PRA, A1, A2, and PA in these patients all significantly decreased during saline infusion by about 50% (Fig. 13–12). The rate constant for the PA decline was negatively correlated with TBS (Fig. 13–12, insert), suggesting a slower PA fall with greater burn size. Thus, the renin-angiotensin-aldosterone system remains responsive in burn patients, and the elevated level of function that occurs after thermal injury appears to result from a burn-size-dependent resetting of control mechanisms. Because renin release depends in part on sympathetic tone, the excess sympathetic activity of burn injury may be a factor altering the renin system, an alteration that might occur at the level of the CNS. This hypothesis has not been tested, however.

After resuscitation, renal K^+ losses are accentuated in burn patients.[78] Although the specific contributions of the large Na^+ load from resuscitation and its subsequent filtration and of the altered control of the renin system and the

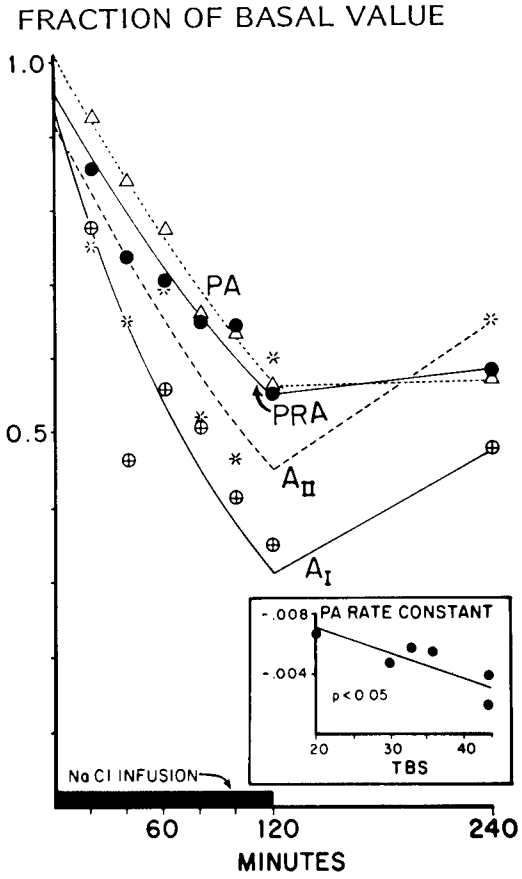

Figure 13–12. Mean plasma renin activity (PRA), angiotensin-I (A_I), angiotensin-II (A_{II}), and plasma aldosterone (PA) during and after saline infusion for the patients whose individual values are shown in Figure 13–11. Exponential regressions showed a significant fall ($p < .001$) in each plasma variable during saline infusion. Correlation of the exponential rate (decay) constant for PA with burn size (TBS) was significant (insert). (Data from K. Z. Shirani, G. M., Vaughan, A. D. Mason, Jr., B. A. Pruitt, Jr., and J. D. J. Bullard: Elevation of plasma renin activity, angiotensins I and II, and aldosterone in burn patients: Na^+/volume-responsive but not -dependent. Surg. Forum, *35*:62, 1984.)

elevated levels of aldosterone are not yet known, they probably play roles in postburn kaliuresis. Alkalosis and the renal effect of Sulfamylon cream may further increase K^+ loss. Use of 0.5% $AgNO_3$ soaks may produce large transeschar K^+ losses. Even without the latter, potassium requirements up to several hundred mEq/day may be variable, and daily determinations of serum K^+ concentration are necessary to alter the amount of K^+ added to intravenous fluids in order to prevent hypokalemia. Sepsis, acidosis, and renal failure may raise serum K^+ and necessitate reduction or elimination of K^+ administration.

Fluid Balance

The principles of fluid administration in the 24 to 48 hours immediately after burn injury have been reviewed by Pruitt.[78] The aim of resuscitation is to replenish fluid and salt lost mainly from the disrupted capillary system, and the endpoints are mainly hemodynamic and renal. Although hormonal responses may occur during this early postburn period, they may have less direct bearing on fluid management at this time than later. The altered control of hormones directly regulating water and Na^+ may have some relevance for management of burn patients when a large fluid load containing much salt has already been given for resuscitation. Fluid replacement then must compensate for a host of factors, many ultimately derived from indirect actions of other hormones, but all potentially contributing to disruption of optimal fluid balance. The often

prodigious magnitude of evaporation from the disrupted skin lipoprotein water vapor barrier magnifies insensible water loss, which can be estimated in milliliters per hour as total body surface area in $M^2 \times (25 + \%$ of body surface burned).[79,80] Additional losses into urine and wound pads typically bring total water losses to 2 to 3 ml/% body surface burned per kg body weight per day.[79] Water loss can be altered by fever, hyperventilation, environmental climatic conditions, method of wound care, and progression of wound healing.

Evaporative water losses are conceptually electrolyte free, as are some urinary losses. For example, hyperglycemia and sometimes glycosuria[81,82] and the large urea load from the characteristic postburn exaggeration of gluconeogenesis often accentuated by the nitrogen load of hyperalimentation may contribute to osmotic diuresis. By their catabolic influence and promotion of gluconeogenesis, postburn endocrine responses (e.g., high levels of catecholamines, cortisol, and glucagon and insulin resistance) may underlie generation of osmotic factors including amino acids, lactic and fatty acids, glucose, and especially urea. Sepsis can accentuate evaporative and osmotic losses.[78,83]

Warden et al.[83] observed another potential cause of renal free-water loss in two burn patients who developed hypernatremia in the face of relatively dilute urine and who responded to AVP injection. In that this diabetes-insipidus-like condition with apparently deficient AVP secretion resolved, it may represent the opposite extreme of a potential spectrum of osmotic AVP dysregulation in which the more common form is excessive vasopressin secretion and a propensity for dilutional hyponatremia.

These considerations suggest potential postburn loss of predominantly electrolyte-free water, despite the often activated vasopressin mechanism to limit renal water loss. This phenomenon, together with the fact that total exchangeable body Na^+ is elevated following resuscitation, implies that solutions hypotonic with respect to electrolytes should be administered after resuscitation. However, it must be realized that postburn evaporative water loss may be quite variable and that variable Na^+ loss also occurs through the wounds, up to 300 mEq/day for patients treated with dressings and more if 0.5% $AgNO_3$ soaks are used.[78] Variable Na^+ loss also occurs in the urine.

Depending on burn size and other variables, water and electrolytes mobilized from the burn and tissue edema provide an additional source of water and salt for the intravascular compartment during the week after resuscitation.[78] During this time, as the patient loses this fluid and approaches preburn weight, administered fluid (mostly Na^+ free) is given in sufficient quantity to prevent hypernatremia and is restricted if serum Na^+ falls below 135 mEq/L. As preburn weight is approached and thereafter, enough total fluid to cover predicted losses is given, with only enough Na^+ (if indicated) to maintain urinary Na^+ excretion above 50 mEq/day and adequate blood pressure. Again, the amount of electrolyte-free water given is varied to control serum Na^+ concentration.

The many variables that affect water and salt balance in burn patients include the following:

- Postresuscitation mobilization of edema fluid
- Potentially prodigious evaporative and other transeschar water and Na^+ losses, which vary with the thermal status of the patient, environmental temperature and humidity, and type of wound treatment
- The Na^+ and osmotic loads delivered with calories, the metabolically derived

osmotic load, and the loss of water accompanying excretion of nonelectrolyte osmoles
- Alteration in control of AVP secretion and the frequently reduced ability to dilute urine
- Alteration in control of the renin-angiotensin-aldosterone system and potential changes in renal blood flow, urine volume, and urinary Na^+ excretion
- A tendency toward elevated glomerular filtration rate (unless renal failure develops)
- Sepsis, which can have adverse effects on any of these variables

Because of the number and interactions of these variables, the use of formulae designed to aid in the prediction of postresuscitative fluid needs is restricted to crude range-finding procedures. Adjustments in volume and Na^+ delivery must be made based on monitoring of renal function, urine volume and osmolality, urinary Na^+ excretion, and body weight. However, the single most important variable in monitoring the fluid status of burn patients is serum Na^+ concentration,[67,78,83] which guides delivery of appropriate amounts of electrolyte-free water so as to avoid the complications associated with hypernatremia due to dehydration (acidosis, prerenal failure, obtundation, and shock) or severe hyponatremia due to overhydration (cerebral and pulmonary edema and congestive heart failure).

The normal serum Na^+ concentration for patients with extensive burn injury has not been rigorously defined, but the usually observed and recommended 132 to 138 mEq/L[83] is often associated with adequate renal function and the absence of pulmonary edema. This mild plasma dilution (despite urine osmolality above 100 mOsm/kg) probably results from persistent AVP secretion[67] in the face of water loads clinically judged necessary to maintain adequate renal function and excretion of the osmotic load.[62] Specification of the optimal serum Na^+ concentration (and hence free-water load) in terms of renal function and how this might be altered in the presence of complications such as inhalation injury, pneumonia, and myocardial insufficiency needs further investigation. Dangerous hyponatremia is most apt to occur in children, in whom rapid administration of hypotonic (electrolyte-free) fluids into relatively small intravascular and extracellular compartments may lead to seizures.[84] Significant hyponatremia, however, can occur in any burn patient as a result of an overload of electrolytically hypotonic fluids if evaporative water loss is suddenly reduced by application of occlusive dressings, biologic dressings, or cutaneous autographs and the fluid input is not correspondingly reduced.[78]

Alteration of TSH Control and of Thyronine Interaction with the CNS

The depression of circulating concentrations of the thyroid hormones (TH) thyroxine (T_4) and triiodothyronine (T_3) in burn patients is now well known[16,18,20,72,85–87] (see Chapter 7). These thyroid hormones are depressed in proportion to burn size and for a given burn size are lower in patients who ultimately do not survive. There is almost always less postburn depression of T_4 (little or none with small injuries) than of T_3, which can even become undetectable (<10 ng/ml) in nonsurvivors with extensive injury. These same patterns apply

to the free indices (FT_4I and FT_3I, products of T_4 or T_3 with T_3U), and low free T_4 concentration by dialysis (FT_4) can also be seen. The free indices likely better represent the concentrations of hormones available to tissues than do the free concentrations (see Chapter 14). In other (nonburn) forms of critical nonthyroidal illness (NTI), low T_4 and T_3 are associated with accelerated metabolic clearance of these hormones, suppressed production of T_4 and T_3,[88] and low serum levels of thyroid-stimulating hormone (TSH) in some but not all patients when measured with a sensitive and specific RIA.[89] Return of serum thyroid hormones toward normal levels in surviving patients with burns[90] and other NTI[91] is associated with prior rises in thyrotropin (TSH) to values at or around the upper limit of normal. Although such studies imply a role for inadequate TSH in the thyroidal failure of NTI, the conditions in which frankly low immunoreactive TSH may be found are not yet defined. Even the use of sufficiently sensitive and specific immunoassay procedures does not necessarily insure observation of low TSH prior to recovery from NTI.

The apparent absence of a definitive depression of serum TSH in some studies of nonburn NTI patients with low T_3 and/or T_4 and in others of burn patients with low free T_4 and T_3[85,87] may have resulted partly from the lack of sensitivity and specificity of the common RIA methods in the low and normal range of TSH. However, the presence of uncompensated (nonelevated) TSH values may suggest altered control of TSH secretion such that a *relative* inadequacy of TSH might contribute to depression of TH secretion. Additionally, if TSH concentration is normal (not low) based on a sensitive and specific assay, then factors other than a relatively inadequate serum TSH might also contribute to low TH levels, including an accelerated TH metabolic clearance rate. During resuscitation, extravasation of protein-bound thyroid hormones into the wounds and dilution of the plasma compartment might further contribute to low TH levels. The contribution of this theoretical mechanism to the early reduction in serum TH levels has not been tested.

Beginning after resuscitation in burn patients, my associates and I[92–94] evaluated thyroid function by serial measurements of T_3, T_4, and TSH. The latter was measured with a highly sensitive and specific double monoclonal immunoradiometric assay (Serono kits) capable of detecting depression of TSH below the normal range (usually undetectable) in all thyrotoxic subjects tested in a preliminary study in which all the values for normal subjects were well within the detectable range. Values from 7 surviving and 5 nonsurviving burn patients were compared with those obtained in 10 healthy controls (Fig. 13–13). Whereas mean T_4, T_3, FT_4I, FT_4, and FT_3 were low in the first postburn week, mean TSH was normal at that time in both groups of burn patients. Thereafter, in survivors, mean TSH rose to the upper normal limit where it persisted as T_4 and T_3 continued to rise toward the normal mean. In contrast to this pattern in survivors, mean TSH fell to low levels in nonsurvivors, paralleling decreases in total and free T_3 and T_4 to very low levels. These differences in the responses of survivors and nonsurvivors were evident during the first 2 postburn weeks (before any dopamine was given to nonsurvivors) as statistically significant differences in the slopes of TSH and the thyroid hormones versus time; in nonsurvivors, the slopes were negative.

These results demonstrate that low TH levels can be associated with nondepressed serum TSH in burn patients and imply accelerated TH disposal pe-

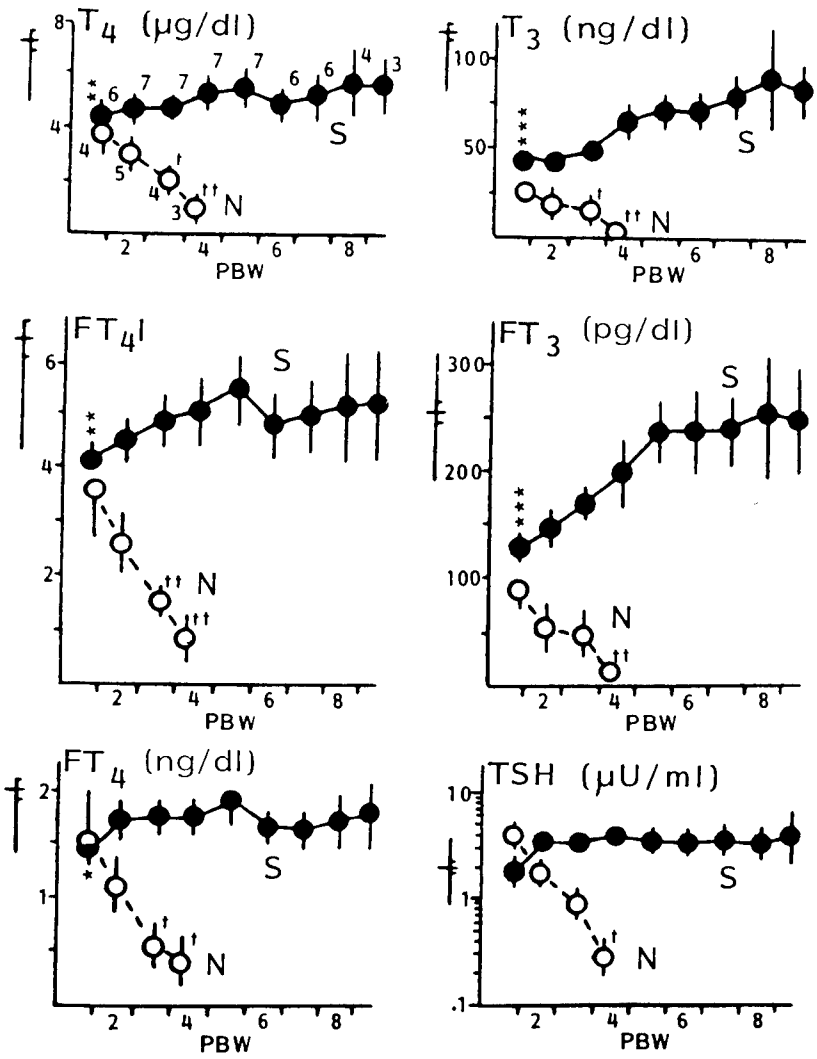

Figure 13–13. Mean values ± SE for various indices of thyroidal function in 7 surviving (S) and 5 nonsurviving (N) burn patients with a mean total burn size of 47% and 48%, respectively. The variables shown are as follows: T_4, plasma thyroxine; FT_4I, free-thyroxine index; FT_4, dialyzable thyroxine; T_3, plasma triiodothyronine; FT_3, dialyzable triiodothyronine; and TSH, plasma thyroid-stimulating hormone. The values plotted are the means of the within-patient means for a given postburn week (PBW) for each group. The numerals near the data symbols in the T_4 plot indicate the number of patients represented during each sampling period. The configuration to the left of each ordinate represents values for 10 normal controls: mean ± SE (horizontal marks) and 2 SD (vertical extent). One control and one surviving patient were women; all other subjects were men. Significant differences between corresponding mean values for surviving and nonsurviving groups are indicated by daggers: † $p < .05$; †† $p < .01$. Significant differences between mean values for survivors at postburn week 1 and corresponding control values are indicated by asterisks: *$p < .05$; **$p < .01$; ***$p < .001$. (From G. M. Vaughan, R. A. Becker, K. A. Shirani, B. A. Pruitt, Jr., and A. D. Mason, Jr.: Roles of thyroid hormones in burn pathophysiology: Two patterns of thyrotrophin alteration and lack of change in thyronine binding globulin. *In* Annual Research Progress Report, 1987, U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas. Washington, DC, U.S. Army Research and Development Command.)

ripherally, inability of the thyroid to respond to TSH, or reduced bioactivity of the circulating immunoactive TSH. These possibilities have not been investigated thoroughly, but the thyroid glands of burn patients respond in a qualitatively normal fashion to injected bovine TSH, with rises of serum T_4 and T_3 into or above the normal range.[72] Extrapolation from studies of other kinds of critical NTI[88] supports the likelihood of accelerated T_4 and T_3 disposal and reduced production rates in burn patients. Thus, abnormalities below the level of the pituitary probably contribute to the low TH concentrations, in particular an inhibition of peripheral conversion of T_4 to T_3, which would account for the greater depression of T_3 than of T_4 in burn patients.

There also seems to be a deficiency of TSH secretion in extensively burned patients. This is most evident in nonsurvivors, whose basal immunoactive serum TSH falls from normal to low after the first postburn week while their T_4 and T_3 fall from low to very low levels[92–94] (Fig. 13–13). The response of serum TSH to injection of thyrotropin-releasing hormone (TRH) in such patients is markedly blunted,[18] and flattened follicular epithelial cells sometimes associated with unfilled spaces within the colloid are often seen in histologic sections of the thyroid at autopsy, particularly in cases of death after 2 weeks postburn R. A. Becker and S. Kim, personal communication; see Chapter 16). In survivors, the TSH deficiency is more subtle and is manifested mostly by the absence of a greatly elevated basal serum TSH[18,85,87,92–94] and absence of an augmented serum TSH response to TRH[18] despite low levels of T_4 and T_3 and their free indices. In such patients, studied with close-interval sampling during the recovery period, occasional bursts of TSH rising transiently into the high range are closely followed by identifiable increments of T_4,[90] implying partial recovery at those times from relatively suppressed TSH secretion.

Thus, at least a relative deficiency of TSH appears to exist in burn patients. This deficiency is manifested partly as lack of full compensatory responsiveness of TSH secretion to low TH levels, which resolves with time in survivors but becomes accentuated in nonsurvivors with frank lowering of immunoactive TSH despite very low levels of thyroid hormones. Because of the multiplicity of possible influences on TSH secretion, the behavior of serum TSH is best considered in light of some of these relationships. For example, by negative feedback at the pituitary, the thyroid hormones normally tend to depress serum TSH. A relative deficiency of TSH can be viewed as overly effective suppression of TSH secretion accomplished even by low TH levels. Thus, the thyroid axis in burns might exhibit a change characterized in a functional sense by a resetting of the negative feedback system; the resulting relatively deficient TSH then also would contribute to depression of T_3 and T_4.

The mechanism of this change might involve other known influences on TSH secretion.[95] For example, TRH from the hypothalamus, which promotes TSH secretion, would be expected to lessen the effectiveness of negative feedback, whereas factors that inhibit TSH secretion (e.g., deficient TRH or elevated circulating corticosteroids and dopamine, which occur in burn patients[25]) would increase the effectiveness of negative feedback. Thus, the thyroid axis changes seen in burn patients could result partly from deficient TRH or from excessive cortisol and dopamine. Indeed, Becker et al.[18] found that FT_4I and FT_3I correlated negatively with the elevated plasma dopamine concentrations among burn patients; they also found that dopamine, TSH, FT_4I, and FT_3I were altered

to a greater extent in nonsurvivors than survivors for a given burn size. Further support for the hypothesis that TSH is responsive to thyroid hormones, but at an altered feedback setting, following burn injury is provided by the observation of further decreases in already modestly low mean serum T_4 (and in one study in TSH) during administration of sufficient T_3 to burn patients to normalize their initially quite depressed serum T_3.[16,18]

This formulation of an altered feedback response also has been supported by results of studies with the burn rat model, which exhibits depressed FT_4 and FT_3.[96] In one study, Vaughan et al.[94] determined the effect of burn injury on T_4 feedback inhibition of TSH. In this study, rats with a full-thickness scald burn on 50% of their skin surface received a continuous subcutaneous T_4 infusion by osmotic pump at one of two dose levels (or no T_4); each dose was given for 6 days prior to sampling. Serum T_4, T_3, and TSH were measured on day 8 (Fig. 13–14). Unburned thyroidectomized rats treated in the same way served to indicate the normal response of TSH to increases in T_4. A control group receiving no procedure or treatment was used to indicate normal hormone levels. At the time of measurement, mean serum T_4 values, which were low in the conditions of burn and thyroidectomy without T_4 treatment, had risen in a dose-related fashion to at least normal levels with T_4 treatment in both conditions. The range of mean T_4 values in the burn groups was bracketed by the range of mean T_4 values among the thyroidectomized groups. The elevated mean TSH in thyroidectomized rats and the low-normal mean TSH in burned rats, seen in the respective T_4-untreated groups, were both significantly lowered by T_4 infusion in a dose-related fashion. Serum T_3 was not significantly different between the burn and thyroidectomy conditions in the T_4-treated groups. Plots of serum TSH as a function of serum T_4 (Fig. 13–15) show that the burned rats had much lower TSH for any given serum T_4 concentration than is normal (as indicated by thyroidectomized group).

This altered feedback control could be caused either by an excessive negative influence of T_4 on pituitary TSH secretion resulting from excessive postburn levels of other circulating hormones or by deficient stimulation of TSH by the hypothalamus (presumably through TRH). The relative contributions from these potential influences are not known, but work by Scott et al.[97] suggests that an alteration of CNS function plays a role in this resetting. These authors found that in rats with 60% TBS burns, serum T_4 was depressed already by 6 hours postburn and more so by 24 hours. At 48 hours postburn, T_4 exhibited a partial return toward normal, only to regress again to very low levels by postburn days 7 and 14. This same pattern was seen for FT_4I (Fig. 13–16). Serum T_3 remained depressed at all time points in the burned rats. At 6 and 24 hours after burn, and at any time point in all the sham-burned and unshammed controls, the floor of the third ventricle overlying the medial basal hypothalamus appeared normal by scanning electron microscopy. However, by 48 hours after burn, numerous ectopic supraependymal neurons were visible in this area and were present at least up through postburn day 14. These neurons were interconnected by large numbers of cell processes exhibiting varicosities at sites of connection. Subsequent to publication of these results, TSH was determined on the serum samples of these animals; these results also are shown in Figure 13–16. Whereas TSH was able to respond in a qualitatively normal manner to the low TH levels by postburn day 1 (24 hours), perhaps contributing to the reversal in the fall in T_4

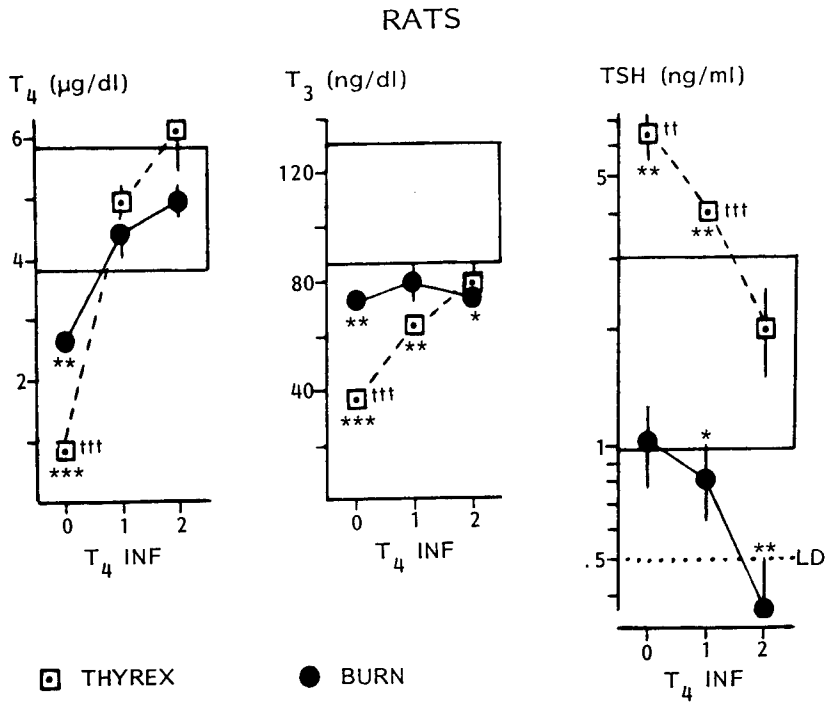

Figure 13–14. Effect of thyroidectomy (THYREX) and experimental burn injury (full-thickness scald burn on 50% of skin surface) in adult male Sprague-Dawley rats on serum T_4, T_3, and TSH levels and on the TSH response to increased T_4 (mean ± SE). The abscissa represents T_4 infusion dosage: 0 (none); 1 (1.1 μg/100 g body weight/day); and 2 (11 μg/100 g body weight/day). T_4 was infused in saline from implanted osmotic pumps, which were present for 6 days up to the time of sampling in implanted animals. Sampling was at 12 days after THYREX or 8 days after BURN. Pumps were not implanted in animals that received no T_4. Values for a control group, which received no treatment, are represented by the boxes with the vertical extent indicating the mean ± 2 SD. $n = 5$ for each experimental group. Significant differences between BURN or THYREX values and control values are indicated as follows: $*p < .05$; $**p < .01$; $***p < .001$. Significant differences between BURN and THYREX values are indicated as follows: $\dagger\dagger p < .01$; $\dagger\dagger\dagger p < .001$. T_4, T_3, and TSH in thyroidectomized animals and T_4 and TSH in burned animals correlated significantly ($p < .05$ or better) with T_4 infusion dosage; the correlation was negative for TSH and positive for T_4 and T_3. T_3 did not change with T_4 infusion in the burned animals. LD, least detectable TSH. (Data from G. M. Vaughan et al.: Control of TSH after burn injury. Paper presented at 4th Annual U.S. Army Regional Meeting of the American College of Physicians, San Francisco, October 1987.)

and FT_4I on day 2 (48 hours), this elevation of TSH was lost beginning at 48 hours. TSH fell further thereafter in parallel with T_4 and FT_4I. Thus, a major alteration in the control of TSH was evident by 48 hours just when the morphologic changes related to the hypothalamus became apparent, suggesting that reduced CNS support plays a role in maintaining deficient function of the TSH-thyroid axis after postburn day 2.

As mentioned previously, a relative TSH deficiency might be caused by a reduction in the bioactivity of circulating TSH; this possibility has not been investigated in burn patients. However, some nonburn patients with hypothyroidism attributed to a functional hypothalamic lesion have normal levels of

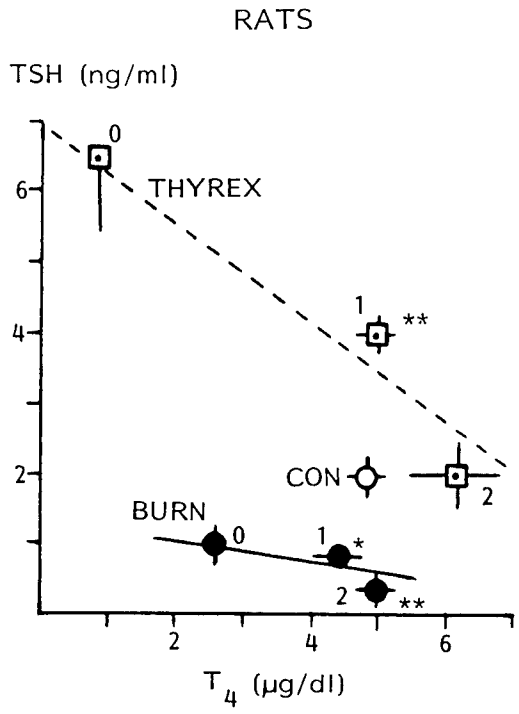

Figure 13–15. Serum TSH plotted against serum T_4 (mean ± SE) based on data in Figure 13–14 for thyroidectomized (THYREX), burned (BURN), and control (CON) rats. Numerals near the data points are T_4 infusion dosage numbers (see Fig. 13–14). Significant differences between experimental groups and controls with similar T_4 means are indicated as follows: $*p < .05$; $**p < .01$. T_3 means for THYREX and BURN groups did not differ significantly at T_4 INF of 1 or 2, but T_3 means in THYREX at INF 1 and in BURN at INF 2 were significantly lower than in controls (see Fig. 13–14). Thus, at equivalent levels of T_4, TSH is lower in burned rats than in thyroidectomized rats despite both groups having equivalent T_3; TSH in burned rats also is lower than in controls even though the latter have higher T_3. The known reported 35% elevation of the T_4 dialyzable fraction in rats at this time after a burn of this size[96] would not have elevated the free T_4 levels in the burned rats in this study to the control levels. (Data from G. M. Vaughan et al.: Control of TSH after burn injury. Paper presented at 4th Annual U.S. Army Regional Meeting of the American College of Physicians, San Francisco, October 1987.)

circulating immunoactive TSH that exhibits markedly deficient bioactivity.[98,99] Administration of TRH[99] restored bioactivity toward normal in correlation with a rise in serum T_3. The implication of these findings is that secretion of TSH in its bioactive form requires normal hypothalamic secretion of TRH. Obviously, if levels of bioactive TSH are reduced significantly in burn patients, the apparent discrepancy between low T_3 and T_4 in the presence of normal TSH as determined by RIA might disappear. One function of TRH is to promote proper glycosylation of TSH, which determines its bioactivity. Evidence of reduced mannose content of serum TSH in severely ill patients[100] indirectly suggests that hypothalamic alteration in ill patients can lead to reduced bioactive TSH.

It has become clear that the normal response of the rat brain to low circulating TH levels is a dramatic elevation of brain tissue capacity to convert (monodeiodinate) T_4 to T_3, through a rise in activity of type II 5′-deiodinase (5′-DI).[101] This rise constitutes an index of the brain's ability to recognize deficient circu-

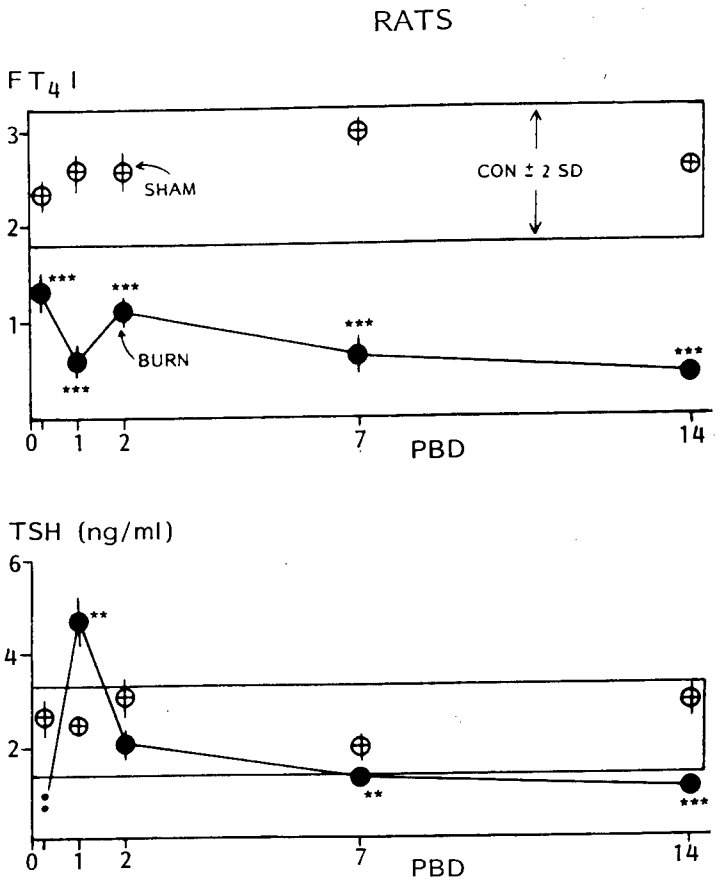

Figure 13–16. Serum FT_4I and TSH (mean ± SE) in controls (CON), sham burn, and burned (60% body surface, full-thickness) rats at various postburn days (PBD). There were 5 rats per group. Enough serum from only 2 burned rats was available for TSH determination at PBD 0.25 (6 hours). Significant differences between experimental groups and controls are indicated as follows: $**p < 0.01$; $***p < 0.001$. The qualitatively normal TSH response to low FT_4I in burned rats at PBD 1 is not seen on PBD 2, and TSH is depressed at PBD 7 and 14 despite FT_4I approaching its level on PBD 1. Although the FT_4I is likely the best indicator of the T_4 available to cells (see Chapter 14), total dialyzable free T_4 and T_3 concentrations are also depressed on PBD 8 and 14 in 60% burned rats.[96] TSH antibody and standard were supplied by NIAMDDK; sample volumes were 200 μl. (From D. E. Scott, G. M. Vaughan, and B. A. Pruitt, Jr.: Hypothalamic neuroendocrine correlates of cutaneous burn injury in the rat. I. Scanning electron microscopy. Brain Res. Bull., *17*:367, 1986; TSH values in Figs. 13–14, 13–15, and 13–16 obtained through collaboration with Dr. Mary K. Vaughan.)

lating TH concentrations much as elevated serum TSH is an index of the pituitary's ability to detect low TH levels. Vaughan et al.[102] determined the serum TSH and whole brain 5′-DI status in 60% burned rats and in thyroidectomized rats, whose serum TH levels are lowered. Sham burned rats and controls with no procedure had equivalent normal hormone levels. Serum thyroid hormones (T_4, FT_4I, T_3, and rT_3) were severely depressed in the burned rats as they were in the thyroidectomized rats. In contrast, the expected elevation in serum TSH and brain 5′-DI, which was evident in the thyroidectomized rats, was dramatically absent in the burned rats (Fig. 13–17). Thus, following burn injury, neither the

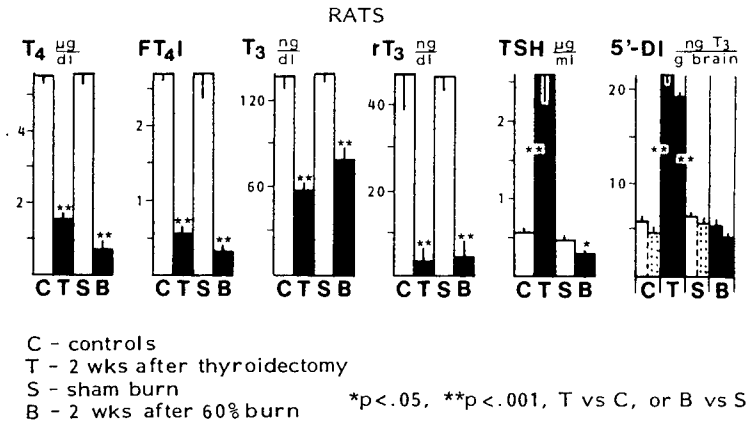

Figure 13–17. Serum thyroid hormones, serum TSH, and in vitro brain 5′-deiodinase (5′-DI) activity (T_4 to T_3) in adult male rats subjected to thyroidectomy, 60% full-thickness burn, or sham burn (mean ± SE). Activity of 5′-DI was taken as the difference in T_3 (RIA of ethanol extracts) for a brain homogenate between separate aliquots with T_4 (1 μg/ml) added before and after incubation; the 2-hour incubation always included 25 mM dithiothreitol. In the 5′-DI plot, the left side of each bar represents incubation without and the right side with 1 mM propylthiouracil. The predominance of propylthiouracil-resistant 5′-DI activity in all groups and the similar pattern between this and total activity across groups suggest that the 5′-DI changes mainly reflect the type II 5′-DI enzyme typically predominant in brain. (Data from G. M. Vaughan et al.: The thyroid axis and brain 5′-monodeiodination of thyroxine in the burned rat model of nonthyroidal illness. Neuroendocrinol. Lett., *8*:221, 1986.)

pituitary nor the brain recognizes the low circulating levels of thyroid hormones as low. Although a causal relationship between alterations in responsiveness of brain 5′-DI and serum TSH has not been established, these findings provide another indication that postburn depression in TSH secretion is related to altered CNS function.

In burned humans, depressed serum T_4, FT_4I, T_3, and FT_3I have been closely correlated with depressed CNS function measured as obtundation on a six-point scale.[87] CNS dysfunction is not a likely direct result of the low TH levels. In patients administered T_3 throughout their course in sufficient quantity to prevent low T_3 levels and in those receiving placebo instead,[18] the same fraction died, with nonsurvivors exhibiting the typical obtundation prior to death.

Regulation of the thyroidal system and the sympathetic nervous system may be interrelated in normal and various disease conditions. For example, in conditions marked by primary alteration of thyroid function (thyrotoxicosis and hypothyroidism), the observed levels of urinary and plasma norepinephrine (but not epinephrine), plasma dopamine-β-hydroxylase (an independent index of norepinephrine release), and cardiac norepinephrine turnover indicate that generally thyroid hormones suppress sympathetic nervous system activity, whereas TH deficiency elevates it.[24,25] Teleologically, this relationship is understandable in terms of the goal of preserving normal metabolism because thyroid hormones and β-adrenergic activity promote similar effects (e.g., elevated cardiac output, lipolysis, and hypermetabolism indicated by elevated O_2 consumption). In the cardiovascular system, TH and catecholamine actions may only be additive, but in other systems (e.g., lypolysis), thyroid hormones potentiate the effect of cat-

echolamines. Interestingly, TH-induced changes in catecholamine receptors do not follow a general pattern consistent with TH effects on CA-responsiveness of tissues.[103]

Among patients with burns of varying sizes, plasma catecholamine concentrations are correlated negatively with serum T_3 ($p < .001$), suggesting that a qualitatively normal inverse interrelationship between these systems remains after burn injury. Furthermore, raising serum T_3 to normal in such patients by T_3 administration for days to weeks partially lowers plasma norepinephrine (but not epinephrine) concentrations, with no effect on metabolic rate.[16,18] Long-term T_3 replacement therapy throughout recovery does not alter the rate at which the metabolic rate returns to normal. Basal epinephrine levels are elevated and inversely related to endogenous serum T_3 in burns. However, there appears to be a relative lack of variation in epinephrine secretion with primary thyroid-disease-induced alteration in TH levels or experimentally induced alteration in TH levels within the setting of burn injury. This suggests that the inverse thyroid-sympathetic pattern probably is not the result of a nonspecific influence, such as volume status, and that postganglionic sympathetic elements outside the adrenals are involved. For a review of the role of norepinephrine in stimulated thermogenesis in mammals including humans, see the concluding comments of Vaughan et al.[17]

One reasonable hypothesis is that some afferent signal representing burn size stimulates a proportional efferent drive in sympathetic tone, at least partially determining the rise in metabolic rate and the set-point for its control. The postburn fall in thyroid hormones then might result from signals controlling hypothalamic TRH secretion and/or from sympathetic or other signals interacting at pituitary or peripheral levels in the thyroid axis. Even if this thyroid adaptation is intercepted with exogenous T_3, adjustments are possible that appear (only partially) to reduce noradrenergic output while maintaining an elevated metabolic rate at the predetermined setting based on the size of the burn. Although this hypothesis needs further testing, the evidence so far suggests that the thyroid-sympathetic interaction continues in burn injury, but with an altered relationship associated with a large contribution of nonthyroid-mediated hypermetabolism.

At an ambient temperature of 32°C, metabolic rate was higher in burned than in nonburned rats even if both groups were previously thyroidectomized; however, burning after thyroidectomy did not raise the metabolic rate to as high a level as it did without thyroidectomy.[21,104] Thus, the postburn surge of O_2 consumption can occur independently of thyroid hormones. However, in burned animals with intact thyroids, even the burn-suppressed TH levels apparently still interact with the effector system for the full-blown response. Accelerated lipolysis is reflected in burn injury by elevated levels of circulating nonesterified fatty acids.[105,106] That this elevation often is relatively mild despite marked elevations of hormones known to promote profuse lipolysis (mainly catecholamines but also glucagon and cortisol) might reflect a reduction of thyroid hormones and hence of their well-known profound influence on CA-mediated lipolysis.[107] Indeed, CA-stimulated lipolysis in incubated adipocytes from rats with a large burn was blunted compared to normal[108] (Fig. 13–18). Thus, although further verification is necessary, it is at least possible that suppression of the thyroid axis in burn injury might serve to ameliorate some of the sympathetic effects. Whether

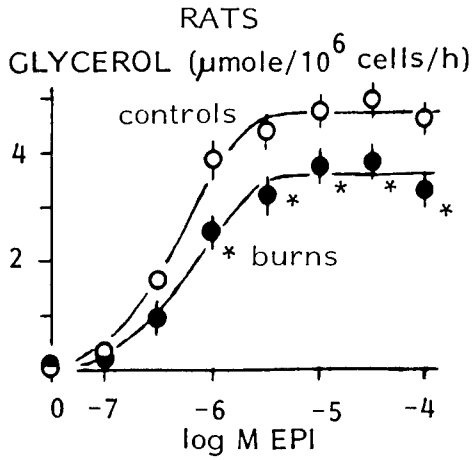

Figure 13–18. In vitro lipolysis (as glycerol production) plotted against concentration of added epinephrine (EPI) in dispersed peri-epididymal adipocytes taken from rats with 60% TBS burns on postburn day 12. *$p < .05$, burns vs. controls. Adipocytes from burned rats also had a significantly blunted response to dibutyryl cyclic adenosine monophosphate. (Data from D. R. Strome et al.: Mechanisms of reduced lipolytic response in rat adipocytes following thermal injury. Surg. Forum, *34*:103, 1983.)

the maintenance of some residual thyroid function is necessary for the redirection of synthetic processes (see above) is not yet known.

Reduction of circulating thyroid hormones (particularly lower T_3) in another catabolic state, starvation, lessens muscle breakdown[109–112] and has been considered protective.[113] Postburn reductions in thyroid hormones may also protect against excessive catabolism. Because of the apparently adaptive nature of the chemical hypothyroidism in burn injury, the lack of a beneficial effect on mortality of administration of T_3 to burn patients[18] and T_4 to other ill patients,[114] and the adverse effect of T_4 administration in a rat sepsis model,[115] thyroid replacement therapy in burn patients without pre-existing hypothyroidism is not recommended.

Central Alteration of Leydig Cell Control

Scrutiny of the reproductive system (see Chapter 6) also yields evidence for involvement of the CNS in burn injury. Burned men have extremely low circulating concentrations of total and free testosterone, although their levels of luteinizing hormone (LH) are usually reported to be normal or, less frequently, depressed or elevated.[14,42,43,72,116–118] Such results have been obtained by use of radioimmunoassays measuring immunoactive LH (iLH) and at first appear to offer no explanation for the extremely depressed testosterone concentrations. Nevertheless, Doleček et al.[116] found that the system behaved in a way characteristic of hypothalamic hypogonadism. That is, in burned men, serum testosterone responded to exogenous gonadotropin, indicating the absence of a major lesion at the level of the Leydig cells, and serum iLH responded to injected LH-releasing hormone (LH-RH), suggesting qualitatively normal pituitary responsiveness. These findings imply a deficiency of LH-RH in burn patients, but raise the question of why postburn testosterone levels are so low if concentrations of the presumed intermediary hormone, LH, are normal.

From studies unrelated to burn injury, it is becoming clear that in any condition characterized by relative deficiency of LH-RH or its activity, the secretion of bioactive LH (bLH) is preferentially depressed with relative sparing of circulating iLH concentrations. In this condition, gonadal function seems better related to the status of bLH. Predominantly low bLH (compared with iLH) is normally

found before puberty.[119–121] In adults, hypogonadism, presumably in the setting of reduced secretion or action of LH-RH and marked by low bLH and in some cases near-normal or normal iLH, has been associated with a pituitary lesion,[122] excessive estrogen exposure in men,[123,124] and administration of LH-RH analogues that mask or block the normal pulsatile exposure of pituitary luteotrophs to LH-RH.[125–128] In addition, several studies have demonstrated a preferential release of bLH within serum LH pulses generated normally or through injection of LH-RH.[122,129] Thus, it appears that the actions of LH-RH on the pituitary possibly include transformation of LH to a bioactive form and/or the generation and release of a pool of bLH.

Before these findings on the normal LH-RH control of the quality of circulating LH were reported, Doleček's results led him to suspect that the Leydig cell failure in burn patients represented an hypothalamic defect and that circulating bLH would be low.[116] As it has turned out, finding low bLH in burn patients would actually constitute evidence for involvement of the hypothalamus. In fact, Plymate et al.[130] have recently demonstrated very low serum concentrations of bLH (worse with greater burn size) in burned men using the mouse Leydig cell bioassay, along with severe reductions in serum concentrations of total testosterone and the bioavailable testosterone calculated from measurements of sex hormone binding globulin. These results and the findings of low follicle-stimulating hormone (FSH) levels and disrupted spermatogenesis[116] indicate hypothalamic hypogonadism in burned men. In that serum estradiol levels are elevated in these patients,[72,130] perhaps partly as a result of their augmented adrenocortical function, it is possible that elevated estradiol might contribute to an abnormality of LH-RH secretion. These hypotheses need further investigation, particularly in light of the observed decrease in potential estradiol precursors such as dehydroepiandrosterone sulfate, androstenedione, and testosterone in burned men.[43] Although an adrenal origin for this excess estradiol is assumed, it has not yet been demonstrated. Whether a rise in peripheral aromatase activity, also not yet demonstrated, could account for elevated estradiol levels in the presence of decreased precursor levels is not yet known.

The relatively catabolic state of burn patients raises the question of androgen therapy.[116,118,131] However, because any role of testosterone deficiency in wound healing and postburn protein wasting remains uncertain, administration of anabolic steroids to burn patients should await the results of controlled clinical trials.

Pineal Function

The pineal gland normally synthesizes an indoleamine hormone (melatonin) in a nyctohemeral rhythmic fashion. Thus, melatonin content of the mammalian pineal gland is highest during the dark phase of the light/dark cycle. In humans, this nocturnal surge of melatonin synthesis is reflected in a nightly elevation of circulating melatonin concentrations. Further, as in lower animals, the human nocturnal melatonin surge is directed by a neural pathway beginning in the suprachiasmatic nucleus of the hypothalamus (where the melatonin rhythm is entrained to photic cycles with information conveyed from the retinae), then traversing the brain stem and cervical cord, to exit via the sympathetic nervous

system, which sends postganglionic fibers to stimulate pinealocytes through a β-adrenergic mechanism involving norepinephrine neurotransmission.[132,133]

Because burn patients have a marked elevation of general systemic activity in the sympathetic nervous system, my associates and I wondered if this would be reflected by elevated melatonin levels, particularly during the daytime when they should be low. However, neither burned rats or hamsters (pineal melatonin content) nor burned humans (serum concentration) had elevated daytime melatonin. Thus, the sympathetic pathway to the pineal does not share in the general sympathetic activation following burn injury,[134] which conforms with previous evidence that melatonin is not an index of general sympathetic tone.[132] Further, in burned humans the nocturnal surge of serum melatonin, though still evident, is blunted[134] (Fig. 13–19). This suggests the possibility of hypothalamic involvement, as the neural pathway to the pineal originates in the hypothalamus. However, a blunted nocturnal melatonin surge is also seen in psychiatric depression and in Cushing's disease.[133,135] A common element in these conditions and burns is activation of the ACTH-cortisol axis, which also characterizes illness generally. Whether the nocturnal melatonin deficiency represents an hypothalamic abnormality or an ability of cortisol to inhibit pineal function is not yet known.

In Syrian hamsters, it is known that the pineal gland can be stimulated by light deprivation to inhibit both the reproductive and the thyroid axes.[136–140] These actions require intact sympathetic innervation of the pineal. Thus, the question arises of whether in burn injury, with its generalized (systemic) sympathetic activation, the reduced reproductive and thyroidal function is a consequence of pineal action. However, burn injury in Syrian hamsters produced the same reduction in serum T_4 and testosterone whether or not they were pinealectomized 2 days prior to the experiment.[141] These studies should be extended to animals pinealectomized even further in advance of experimental burn injury in order to rule out some unexpected residual pineal influence lasting longer than several days, even though the half-life of circulating melatonin is in minutes, not days.

The composite results to date indicate a striking pattern of specificity with regard to pineal function. The portion of the sympathetic nervous system innervating the pineal is controlled separately from general sympathetic activity, and the pineal's influence over the thyroid and reproductive system is restricted mainly to mediation of the effects of the light/dark cycle. The endocrine effects

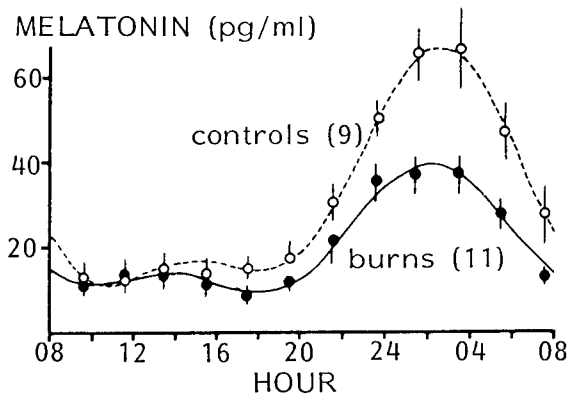

Figure 13–19. Circadian rhythm of serum melatonin (mean ± SE) in 11 burn patients (mean TBS 41%) and in 9 control subjects. Burn samples taken on mean postburn day 15. (Data from G. M. Vaughan, T. J. Taylor, B. A. Pruitt, Jr., and A. D. Mason, Jr.: Pineal function in burns: Melatonin is not a marker for general sympathetic activity. J. Pineal Res., 2:1, 1985.)

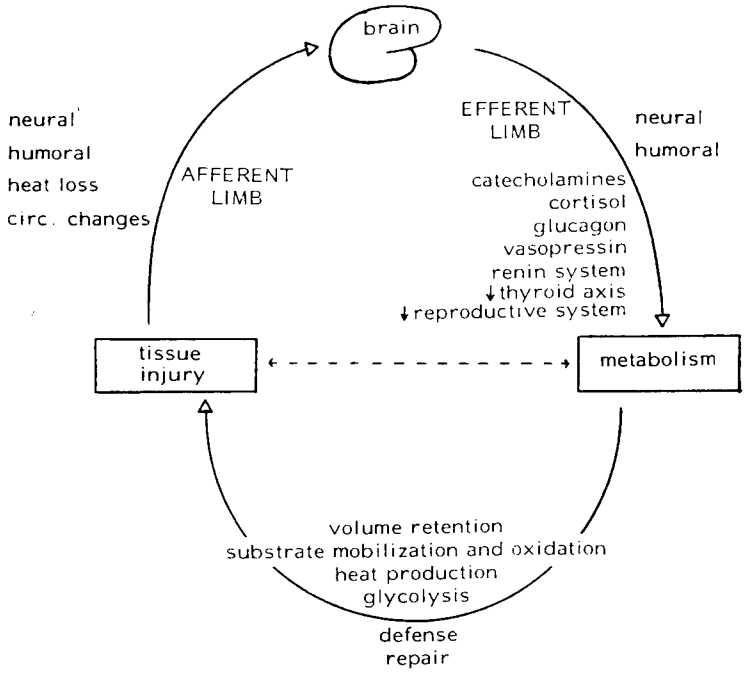

Figure 13–20. Modified neuroendocrine reflex arc model of the flow-phase response to burn injury and other illness. See text for discussion. Numerous additional interconnections are possible, one of which is indicated by the dashed line.

of burn injury probably are not mediated by the pineal gland but for the most part by the hypothalamus.

Conclusion

Many of the findings discussed in this chapter suggest that the neurophysiologic response to burn injury can be conceptualized in terms of an integrated neuroendocrine response cycle, as diagrammed in Figure 13–20. The afferent limb (to the CNS) appears to have a humoral mediator component (perhaps monokines), which signals the presence and severity of injury, although messages carried neurally (e.g., pain and anxiety) or sensed as a loss of heat or effective volume also may be integrated to enhance parts of the response. Many aspects of the neural and hormonal components of the efferent response can be interpreted as resulting from hypothalamic perturbations involving a resetting of various control mechanisms. The efferent hormonal response produces complex metabolic changes resulting in postburn hypermetabolism and other effects. It also seems plausible that these responses promote tissue repair, although just how such increased anabolic activity is orchestrated in the overall postburn catabolic setting requires further investigation.

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