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Cortisol and Corticotrophin in Burned Patients

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In a study of 36 men burned in a fire, based on sequential early morning samples, plasma cortisol concentration was elevated in proportion to burn size. Plasma corticotrophin (ACTH) was not correlated with burn size, suggesting that factors other then ACTH contribute to the elevated cortisol. Cortisol levels did not fall on the days preceding death in nonsurvivors. During 24-hr sampling, burned patients exhibited a fitted cortisol curve mean that was elevated in proportion to burn size, a rhythm amplitude that was significantly less than that in uninjured controls, and a normal peak time. Metabolic rate, rectal temperature, and urinary catecholamine excretion were also elevated in proportion to burn size. Although plasma cortisol was positively correlated with metabolic rate and with temperature, this appeared to result from a common relationship of these variables with burn size. On the other hand, urinary catecholamine values significantly reduced the residual variance of metabolic rate and temperature after accounting for variance related to burn size. Cortisol appears to be less prominent than catecholamines as a possible mediator of the elevated thermogenesis.

Burn injury results in hypermetabolism that has been thought to result from elevated catecholamine secretion (28). However, enhanced adrenocortical secretion after burns has also been shown by increased urinary corticoid excretion (13) and plasma cortisol concentration (17, 21, 23, 32). Such a response is expected as an immediate result of stress and is reflected in the rise of plasma cortisol within 8 hours of various types of injury (24). However, like the ensuing hypermetabolism, the adrenocortical response to burn injury extends well past the immediate post-traumatic period (31) and thus represents another feature of the altered internal milieu that characterizes the body's reaction to severe injury. Furthermore, it has recently been proposed that cortisol is the major hormonal determinant of the postburn metabolic response (1).

Plasma corticotrophin (ACTH) concentration varies widely but is often normal after major burns (12). Although simultaneous cortisol levels were not reported, this suggests a lack of correlation between ACTH levels and expected excess cortisol secretion after burns. In addition, previous studies in subjects without burn injury (10, 14, 15, 18, 19) have suggested that plasma cortisol rises in response to a rise in core temperature. In order to assess the relationships of plasma cortisol to ACTH, core temperature, metabolic rate, urinary catecholamine excretion, and severity of injury, we have used multiple regression analysis to evaluate these variables measured in the same patients during their postburn course.

PATIENTS AND METHODS

Thirty-six men, aged 17 to 23 years and burned in a single accidental gasoline fire, were air transported for treatment 123° longitude (7,000 miles) to the east from the site where they had been stationed and injured. They were admitted to this burn center on the second postburn day (PBD). Because of the suppression of thyroid hormone levels that occurs after burn injury, particularly in deteriorating patients (9), they were entered into a study to evaluate the effect of triiodothyronine (T_3) administration. Eight of these patients had small burns over 2 to 7.5% of body surface and were designated as controls (CONT), since this degree of injury is not associated with measurable alteration in metabolic rate (28). The remaining 28 had a total burn size (TBS) of 18 to 93% of body surface and were randomly assigned in a double-blind fashion to treatment with either a placebo or T_3, 200 μgm per day orally or by nasogastric tube, until their wounds were healed. This dose had previously been

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Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Reg 70-25 on Use of Volunteers in Research.

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found to normalize T_4 levels in burned patients. Because four patients died while receiving placebo (NSURV) and four while receiving T_4 treatment (NSURV-TX), the data were analyzed within the five groups characterized in Table I.

Beginning on PBD 3-5, and then approximately thrice weekly between 0500 hr and 0700 hr when the patients were under resting conditions in the supine position, blood was collected in plastic syringes, placed into heparinized plastic tubes on ice and centrifuged at 4°C. The plasma was then frozen at −70°C. Cortisol (supplies from Clinical Assays, Boston, MA) and corticotrophin (ACTH) levels (2) were measured by radioimmunoassay. Results of plasma thyroid hormone and catecholamine studies will be presented elsewhere. On the days of sampling, 24-hr urine collections were obtained for measurement of creatinine and total catecholamines (26). The rectal temperature on the morning of sampling was recorded. Ward ambient temperature was 28–30° C. Wounds were treated with alternating topical applications of mafenide acetate and silver sulfadiazine. Clinical sepsis (obtundation or ileus) was recorded if present at the time of sampling. At weekly intervals, following at least 8 hr free of caloric intake, resting metabolic rate (MR) based on O_2 consumption (6) was measured in all surviving patients.

Data analysis was focused on the PBD 3–26 period, because a major decrement in catecholamines and MR occurred by PBD 26, the control patients were available for varying periods up to this time, and all survivors were sampled throughout this time (Table I). All samples obtained within 24 hr of dopamine or glucocorticoid administration were discarded from analysis. In one assessment of the data, each variable was considered as the mean value of all measurements of that variable obtained during the PBD 3–26 period for each patient, but since major changes in most variables took place over this time, the time factor was accounted for in separate analyses using individual values of variables in a standard stepwise multiple linear regression program (BMDP, UCLA) performed on a PDP 1140 computer. To assess curvilinear dependent variability, independent variables TBS and PBD were also entered as TBS^2 and PBD^2 into the multiple regression analyses. Hormonal variables were added to these to determine if they would significantly ($p < 0.05$) reduce the residual dependent variances. To assess the impact of T_4 treatment or clinical sepsis, one of these was included as an independent variable by assigning its presence a value of 1 and its absence a value of 0.

In a separate study (see below), nine normal subjects aged 24 to 36 years (seven men and two women) and eight burned patients aged 19 to 60 years (six men and two women) were sampled every 2 hours through an indwelling venous catheter over a 24-hr period for serum cortisol determinations. The results were evaluated by individual cosinor curve fitting, as well as by comparison of estimates of group cosinor parameters (8).

TABLE I
Characteristics of patient groups

	N	%TBS (Mean)	%TBS (Range)	Final Sample (PBD)
CONT	8	4.5	2–7.5	5–26
SURV	10	44.3	18–82	33–88
NSURV	4	68.4	55–93	5–54
SURV-TX	10	45.3	28–75	31–73
NSURV-TX	4	72.9	62–85	12–19

TBS, total burn size as % body surface; PBD, postburn day; CONT, controls with small burns; SURV, placebo-treated survivors; NSURV, placebo-treated nonsurvivors; SURV-TX, T_4-treated survivors; NSURV-TX, T_4-treated nonsurvivors.

RESULTS

The more severely injured patients had higher cortisol concentrations than did CONT (Fig. 1). Multiple regression analysis showed no effect of T_4 treatment or the presence of clinical sepsis on cortisol beyond the variation accountable by TBS and PBD. Although cortisol was not related to ACTH in the T_4-untreated patients over PBD 3–26, consideration of all groups did allow inclusion of ACTH as a predictor of cortisol (Table II). The positive relationship between cortisol and TBS seen during this interval was beginning to develop by PBD 3 and PBD 5 (Fig. 2). The relationship of ACTH to cortisol was not discernible using mean values (Fig. 1), and ACTH was unrelated to TBS or PBD on multiple regression analyses. Cortisol was not correlated with days before death in nonsurviving patients. The final samples were taken within 48 hr of death in six of eight nonsurvivors and within 24 hr in three.

Multiple regression analyses did not demonstrate a significant effect of treatment with T_4 on MR, rectal temperature, or urinary catecholamine excretion. During the interval of PBD 3–26, MR was related to TBS and PBD (Fig. 3). Although cortisol was positively related to MR and to temperature, and both were related to TBS (Figs. 3 & 4), multiple regression analyses including all groups indicated that MR and temperature were not significantly correlated with cortisol nor with each other beyond their individual relationships to TBS and PBD. Excretion of total urinary catecholamine per gram of creatinine (UCA) was elevated in proportion to TBS, and MR and temperature were correlated with UCA (Fig. 5). Multiple regression analyses showed that after correlation with TBS and PBD, the residual variance of both MR and temperature was significantly ($p < 0.001$) reduced by including values of UCA. TBS and PBD accounted for 70 to 75% of the variation in MR, and UCA accounted for an additional 5 to 9% (Table II). Cortisol was not correlated with UCA beyond their individual relationships to TBS and PBD.

In the study of nine normal subjects and eight burned patients the cortisol rhythm mesor (fitted curve mean) was significantly elevated above normal in burned pa-

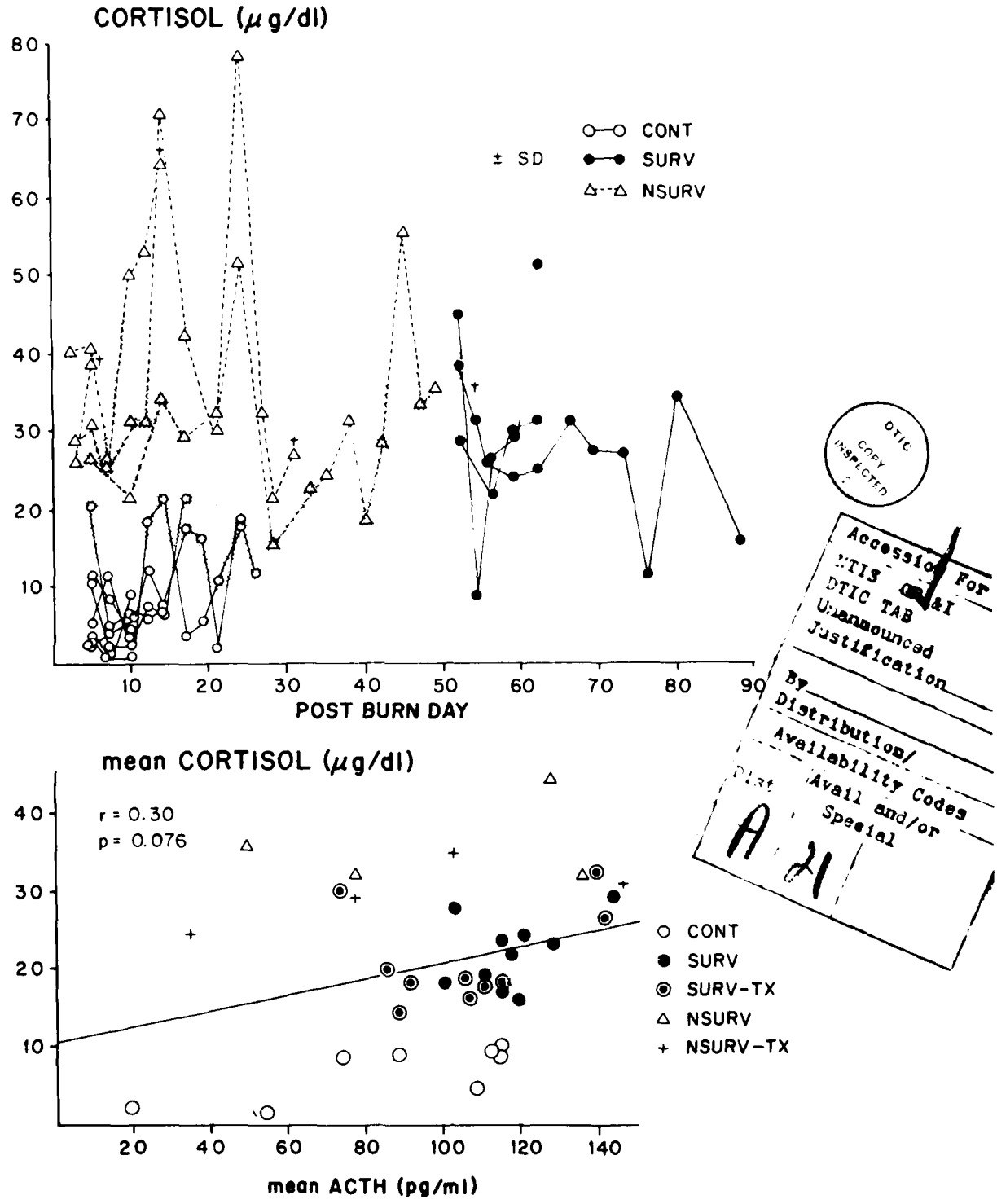

FIG. 1. Plasma cortisol concentration sampled serially on mornings following burn injury. The crosses nearest a final symbol for nonsurvivors indicate the day of death (top panel). Linear regression of mean cortisol and ACTH as the mean taken over postburn days 3–26 for each patient (bottom panel). For group designations in this and subsequent figures, see Table I.

tients ($p < 0.01$), and within the burn group the cortisol mesor was positively correlated with TBS ($p < 0.05$). The burn group rhythm was statistically significant (Fig. 6), and group rhythmicity was still evident ($p < 0.05$) after excluding the two patients with the smallest burns (TBS 5.5 and 13.8%, remaining TBS 36–67%). That cortisol rhymicity was reduced in burned patients is indicated by absence of a statistically detectable rhythm in

TABLE II
Predictive variables for cortisol and metabolic rate

Variables, intercept and coefficients	Including T-treated	Samples (N)	r
Cortisol = 8.6 + 0.31 TBS	–	148	0.39
Cortisol = −10.1 + 0.32 TBS + 2.7 PBD − 0.1 PBD^2 + 0.05 ACTH	+	264	0.47
MR* = 42.4 + 0.44 TBS − 0.68 PBD	–	38	0.70
MR = 38.1 + 0.33 TBS − 0.59 PBD + 0.062 UCA	–	38	0.79
MR* = 44.4 + 0.495 TBS − 0.853 PBD	+	64	0.75
MR = 39.3 + 0.42 TBS − 0.71 PBD + 0.05 UCA	+	64	0.80

* UCA values omitted from regression; TBS, total burn size; PBD, postburn day; MR, resting metabolic rate; UCA, urinary catecholamine

all individual patients (but present in eight of nine normal individuals) and a group amplitude-acrophase point significantly ($p < 0.05$) different from normal with an amplitude reduced by one half. The timing of the rhythm appeared normal in the patients.

DISCUSSION

Cortisol concentrations (Fig. 1) in the patients with very small burns were lower than usual morning normal values (8–25 μg/dl), possibly because the morning samples taken in this study would have represented a time 8 hr earlier (evening) in their preinjury location. In the new location and before possible rhythm re-entrainment, which was not identified by nyctohemeral sampling in this population, cortisol would be expected to be near the nadir of its daily cycle at the time of sampling.

The single time point morning samples did allow observation of elevated plasma cortisol in proportion to burn size in the first 4 weeks after injury in adults. This confirms a similar relationship reported in a study of both children and adults during the first 2 weeks postburn (32) and in children during the first 4 weeks (23). In addition, we found cortisol concentration to be related to burn size as early as PBD 3 or 5. This elevation of plasma cortisol concentration is reflected in elevated values for the entire 24-hr period in proportion to burn size. Molteni et al. (22) found no rhythmicity in cortisol during the first 4 postburn days, with a trend toward the normal rhythm apparent by the fifth day. Rhymicity was present at the time our nyctohemeral samples were taken (PBD 7–29). The suppression of rhythm amplitude that we observed may represent another expression of injury-induced alteration of hypothalamic function, which also includes elevated core temperature, an elevated ambient temperature of optimal comfort, suppressed growth hormone response to hypoglycemia (30), and excess sympathetic tone and hypermetabolism (28).

A recent report (20) suggests that reduced urinary excretion of cortisol plus cortisone is associated with increased mortality. Such data are difficult to interpret, because it has been suggested that conversion of cortisol to cortisone is positively influenced by body temperature and negatively by elevated cortisol secretion (10), and the relative hepatic and renal extractions of these compounds in traumatized patients are not known. We found no fall in plasma cortisol associated with death, in agreement with similar findings in other studies of urinary corticoid excretion and plasma cortisol levels (22). Cortisol is reportedly elevated in bacterial sepsis (24). However, in our injured patients with already elevated cortisol, we did not see further elevation of cortisol levels during clinical sepsis.

The physiologic significance of elevated cortisol might be diminished if there were a sufficient elevation in plasma binding to prevent an elevation of free cortisol in burned patients. However, this appears not to be the case, since Mortensen et al. (21) found a decrease, roughly proportional to burn size, in cortisol binding by human postburn sera. More dramatically, Wise et al. (32) showed that the decreased serum-binding capacity in burned patients was associated with a two- to sevenfold rise in the free portion of total serum cortisol compared to that in normal volunteers. Thus the vigorous postburn response is even more robust for free than for total cortisol levels.

Although Dolecek et al. (12) found a rough correlation of ACTH with burn size, they state that quite normal or only slightly elevated ACTH levels were found in some patients after major burns and that ACTH levels were unpredictable and exhibited a wide range of values. Our results are similar, except that we also found no correlation of ACTH with burn size or time after injury. Using mean values over PBD 3–26, cortisol also was not significantly correlated with ACTH (Fig. 1), although mean cortisol was closely correlated with burn size (Fig. 2). Such observations suggest that factors other than plasma ACTH concentration are at least partially responsible for the large postburn cortisol response. Excessive adrenal responsiveness to ACTH is unlikely, in that Bane et al. (7) found no response of plasma cortisol after ACTH injection in either of two burned patients tested. The afferent portion of the adrenocortical response to injury appears to be neurally mediated (29). Possible efferent control of adrenocortical function that does not involve ACTH is also suggested by previous reports. Spinal cord section blocks circadian rhythmicity of corticosterone in rats (4), normal human subjects exhibit nocturnal pulses of cortisol that do not appear associated with pulses of ACTH (3), and hemorrhage in dogs provokes a rise in plasma cortisol without a preceding rise in ACTH (16). However, ACTH may play some role, perhaps a permis-

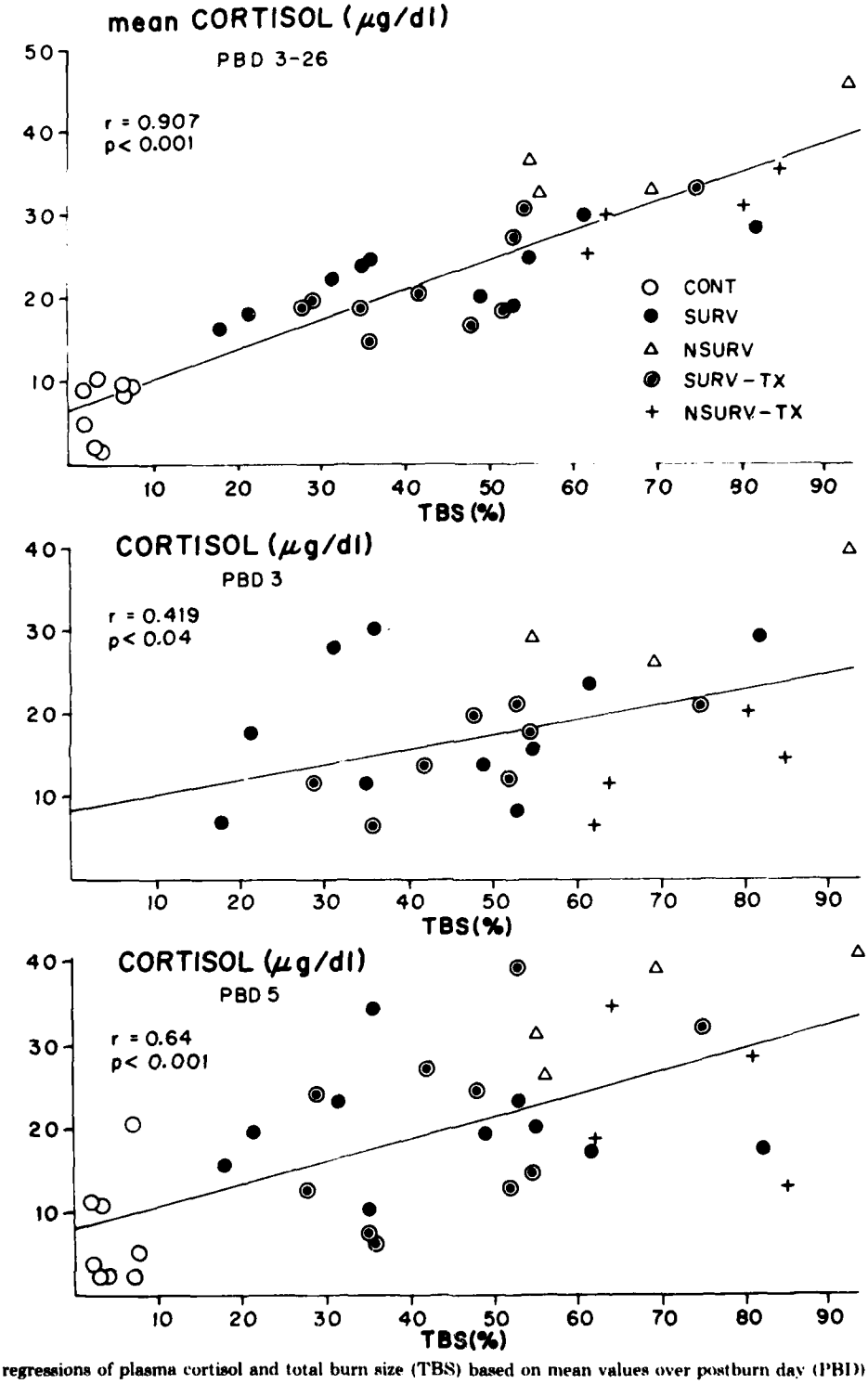

FIG. 2. Linear regressions of plasma cortisol and total burn size (TBS) based on mean values over postburn day (PBD) 3-26, or values for PBD 3 or PBD 5.

sive one, in maintaining cortisol levels in burned patients. In analyses with larger numbers of samples, unrestricted according to group, ACTH concentration was found to be related to that of cortisol (Table II).

Metabolic rate (Fig. 3) and body core temperature (Fig. 4) are both elevated as a function of burn size. This has already been reported for metabolic rate (28). These relationships support the thesis that the elevated thermogenesis in burned patients results not from attempts to restore heat content lost excessively to the environ-

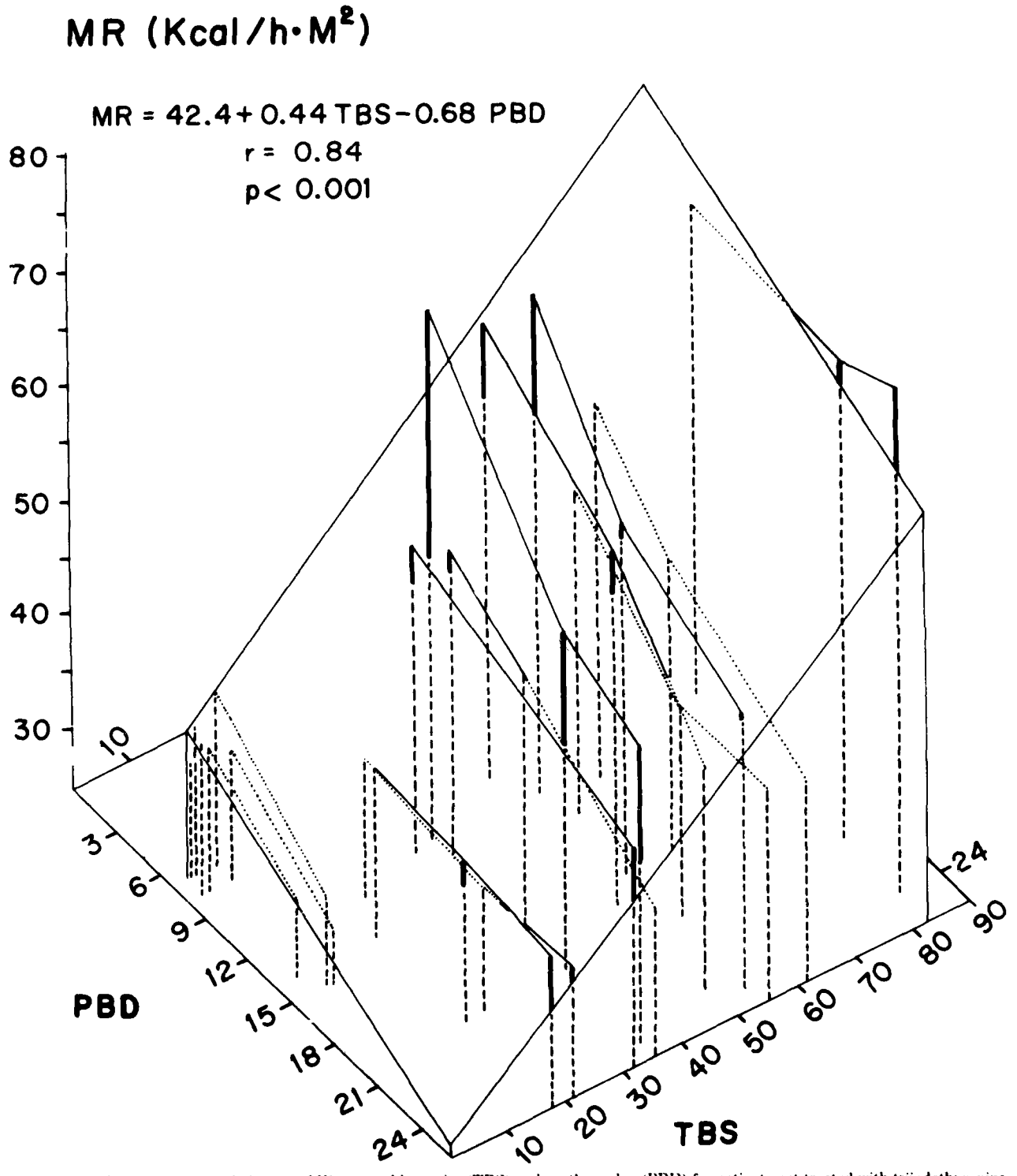

FIG. 3. Relationship of metabolic rate (MR) to total burn size (TBS) and postburn day (PBD) for patients not treated with triiodothyronine (T_3). The equation for the plane of best fit is indicated.

ment ('externally cold') but rather from an altered setting of neural centers that results in heat production sufficient to raise core temperature to a higher level ('internally warm') (28). The correlations of cortisol with temperature and metabolic rate (Fig. 4) could suggest either an interaction between cortisol and thermogenesis or independent responses of cortisol and thermogenesis to severe injury. The former possibility should be considered,

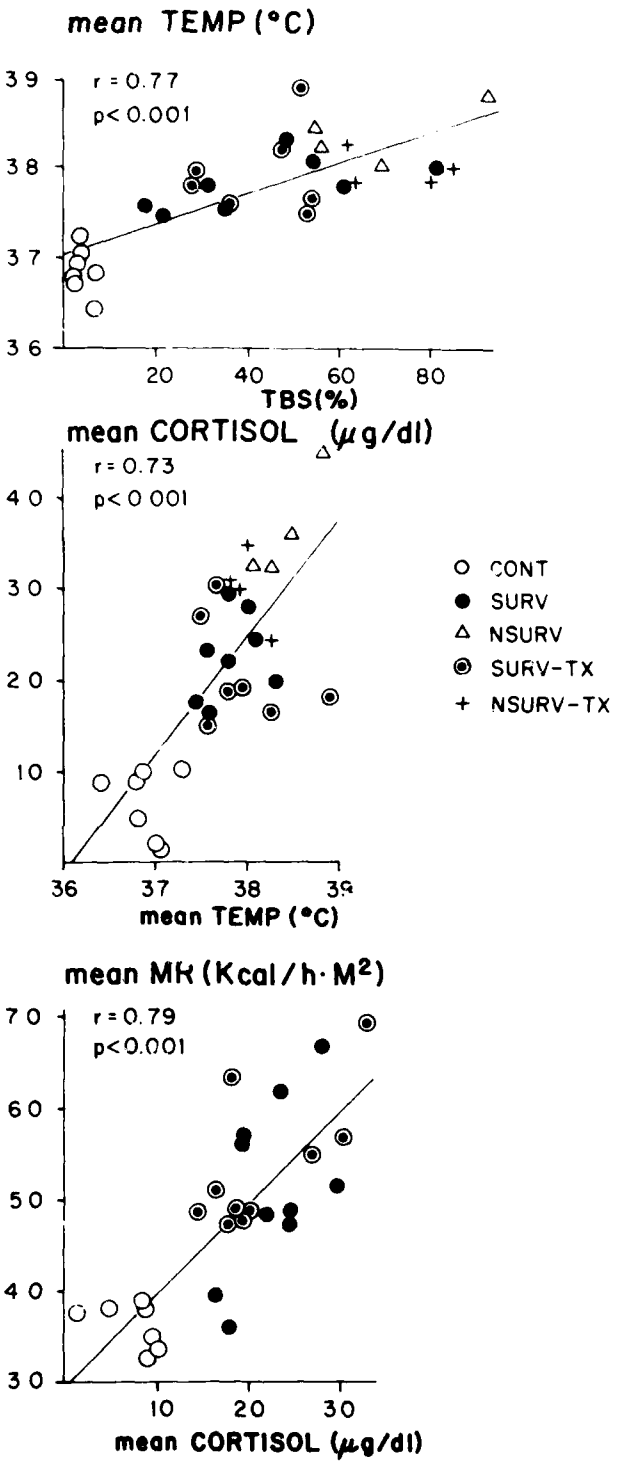

FIG. 4. Linear regressions between rectal temperature (TEMP) and total burn size (TBS), and between TEMP or metabolic rate (MR) and plasma cortisol, based on mean values for each patient over postburn days 3–26.

because in normal human subjects induced hypothermia lowers plasma cortisol (18), and hyperthermia raises it (10). In a study of prolonged swimming at various water temperatures, serum cortisol rose only in experiments in which body temperature increased (15). In addition, hypothermic patients had reduced responsiveness to injected ACTH (14), and elevated serum cortisol paralleled the degree of hyperthermia in several febrile illnesses (19). The interaction between temperature and cortisol seems likely for the direction of an influence of temperature on cortisol levels, and it is thus possible that hyperthermia may account at least in part for the elevated cortisol in burned patients.

The function of glucocorticoids in thermogenesis of experimetal animals has been reviewed by Deavers and Musacchia (11). The results show that whereas glucocorticoid is necessary for animals to restore body temperature following induced hypothermia, there is no effect of glucocorticoid in thermogenesis in animals not exposed to cold. However, in burned patients, thermogenesis is reset around a higher core temperature, allowing the possibility that otherwise usual environmental temperatures may be sensed as cold (28). In this condition, cortisol might be envisioned as a potential mediator of hypermetabolism. Plasma cortisol has been linked to some of the metabolic substrates or intermediates in burned patients, the presence of which is thought to be related to hypermetabolism. Volenec et al. (27) found cortisol level correlated with plasma glucose level. Alberti et al. (1) noted correlations of cortisol with alanine, lactate, free fatty acid, ketone, and urea levels in burned patients. By raising cortisol in normal subjects using ACTH injections, they produced a rise in circulating glucose, lactate, and alanine. Those authors concluded that cortisol plays the major role in the catabolic response to injury.

However, there are several limits on interpretation of those data (1). Although in Alberti's study the known gluconeogenic and catabolic nature of cortisol was evident in the normal subjects, the relationship of this hormone to the metabolic response of burned patients was not assessed in a manner which would establish that cortisol bore a better relationship to metabolic response than did extent of injury, or determine whether variation of metabolic response was more closely related to variation in other gluconeogenic hormones after accounting for the extent of injury. These authors mentioned that plasma glucagon levels and excretion of metanephrine were elevated. Their results were essentially limited to the first 5 postburn days. Finally, the metabolic variables reported are elements of biochemical pathways in energy metabolism and are indirect and restricted reflections of the elevated resting metabolic rate that occurs after burn injury. Although we have found that cortisol level was closely correlated with both metabolic rate and temperature, this appears to reflect the general relationship of metabolic rate and temperature to burn size and postburn day, and no specific connection between cortisol and thermogenesis was identified. That cortisol may contribute to hypermetabolism is not excluded by these results. However, consideration of urinary catecholamine excretion reduced the residual variance of both metabolic rate

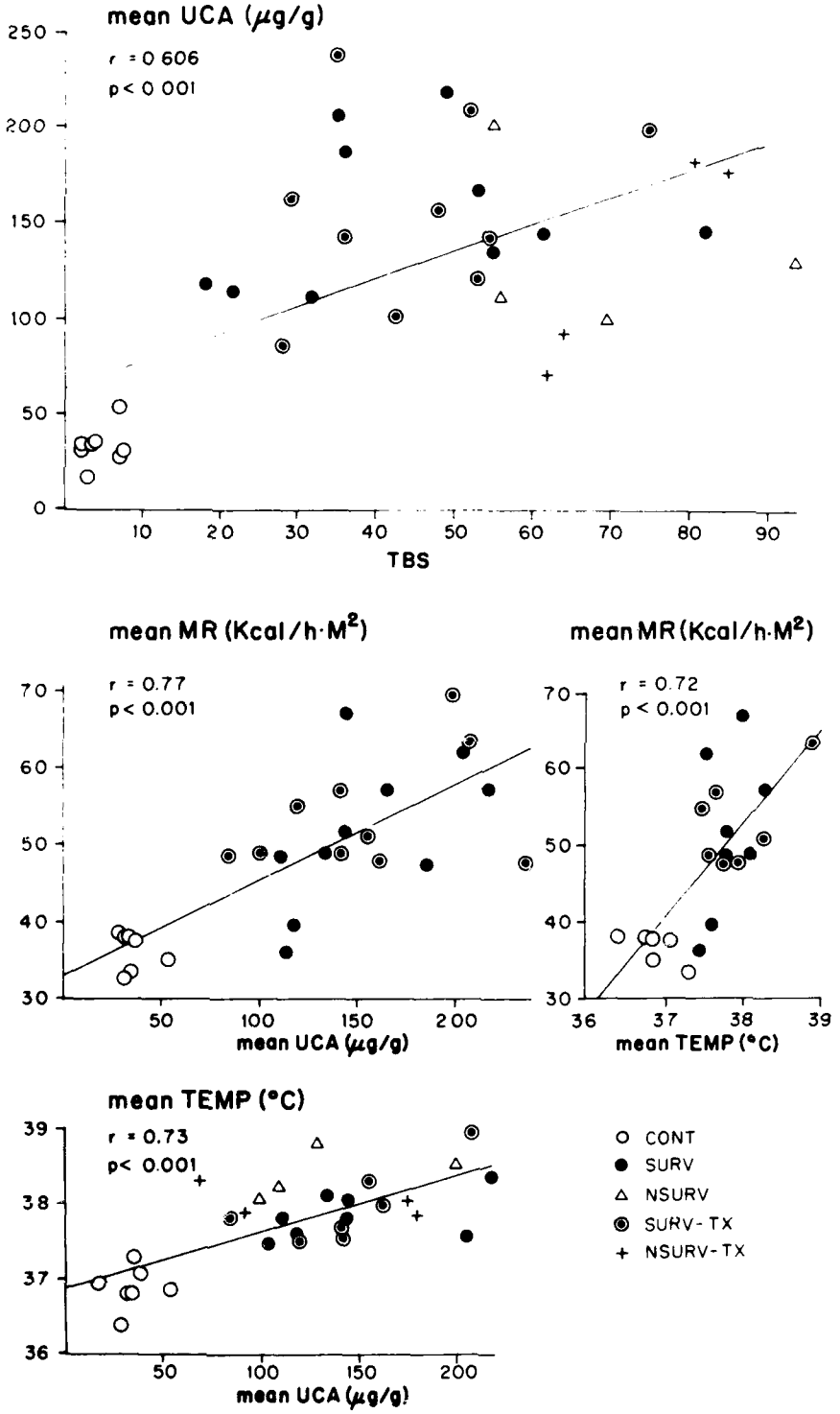

FIG. 5. Linear regressions between excretion of total urinary catecholamines (UCA, μg/gm creatinine) and total burn size (TBS), metabolic rate (MR), or rectal temperature (TEMP), and between MR and TEMP, based on the mean values for each patient over postburn days 3–26.

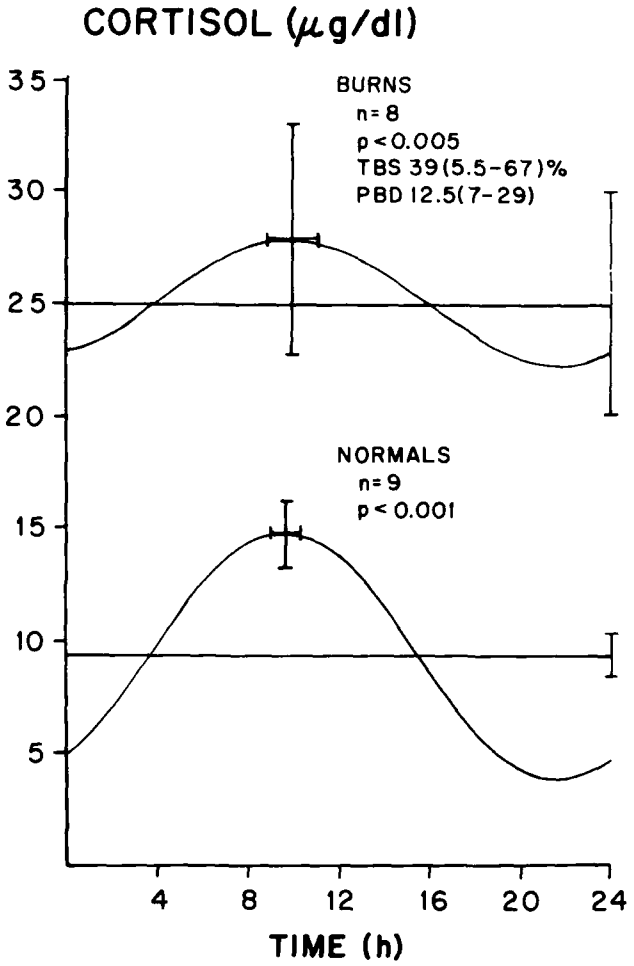

FIG. 6. Best-fit group cosinor curves for plasma cortisol based on samples taken at 2-hr intervals for a 24-hr period and their individual best-fit curves. The error bars are SEM for curve peaks (mesor plus amplitude) and peak times (acrophases), and for curve means (horizontal lines). TBS, total burn size. PBD, postburn day.

and temperature after accounting for variation associated with burn size and time since injury. These findings corroborate a role of catecholamines and suggest less importance of cortisol in postburn hypermetabolism.

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DISCUSSION

DR. DOUGLAS W. WILMORE (Brigham and Women's Hospital, Boston, MA 02115): My congratulations to the authors for their somewhat global and yet integrative undertaking which correlated stress hormones with degree of injury, time following injury, and the hypermetabolic response to injury. This paper should cause us all to reflect for just a moment on the contributions of David Hume in this area.

Doctor Hume in the late 1940's and early 1950's, when he was still a surgical resident, embarked on a series of very careful and now classic studies which described ACTH and cortisol response to stress and delineated the afferent nervous and hypothalamic pathways for this response. His contributions to surgery, surgical biology, and care of the critically ill patient are multiple, and when we see work such as this that extends his original observations, we must be mindful and thankful for his contributions to our field.

The authors have reported that blood cortisol concentrations roughly correlate with burn size and time postinjury and when all patients are considered with ACTH levels. They found there was no correlation between ACTH and cortisol concentration. Moreover, ACTH concentration did not relate to burn size, although cortisol concentrations did.

[Slide] How can we explain this discrepancy? First of all, realize that there are a variety of afferent stimuli, both nervous and circulating factors, that bombard the central nervous system following injury. These signals arise from pain, fear, or anxiety or come from circulating factors such as toxins and pyrogens. These signals are perceived in the hypothalamus, which stimulates the pituitary gland to elaborate ACTH. ACTH signals the adrenal gland to release cortisol.

What is the interaction between ACTH and the adrenal gland? Realize that a hormone interacts with a receptor on the cell surface. This receptor serves to amplify the very low concentrations of a particular hormone. After this amplification, the signal causes a whole cascade of intracellular events to occur, in this case the elaboration of cortisol.

Short-term hormonal stimulation is quite different from prolonged stimulation. Prolonged stimulation causes a modification of both cell surface receptors and the affinity of those receptors for a hormone. In the case of the adrenal gland there is a process referred to as up-regulation; that is, the long-term stimulation by ACTH causes more and more receptors to appear on the cell, and in fact we know that this up-regulation may cause cell hypertrophy and, in the case of Cushing's syndrome marked swelling and enlargement of the adrenal gland. Because of increased long-term stimulation, it is not surprising that a direct correlation between ACTH and cortisol does not occur over a long period of time in the severely injured patients.

Doctor Vaughan did not mention the variety of treatments that these patients received. Because ACTH output is modified by morphine, sedatives, tranquilizers, infusion of glucose and amino acids, anesthesia and operative procedures, and blood transfusions, these factors may have influenced output of ACTH and modified its interaction with cortisol.

Finally, a whole variety of nervous afferent pathways stimulate adrenal medullary output of epinephrine and norepinephrine, and these agents seem to interact with cortisol output. Hence, in these critically ill patients, a wide variety of factors may disassociate ACTH from cortisol output.

How then can clinical investigators disassociate these multiple stimuli? Three things are possible. One is to give epidural anesthetic to these severely ill patients and disassociate the relationship between afferent nervous stimuli and pain from other factors. Second, pharmacologic agents can be utilized to 'turn off' the hypothalamus and pituitary gland. Third, the burn wound, which appears to initiate the response and correlates closely with ACTH output, can be excised. Such excisional treatment will eliminate the initiation of stress response and allow the neurohormonal response to return to normal.

DR. DONALD S. GANN (Rhode Island Hospital, Providence, RI 02902): I too enjoyed the study very much, and would like to compliment the authors on the conduct of a really arduous piece of clinical investigation.

There is at least one factor on the horizon which Doctor Wilmore didn't mention and which has been evolving in my own laboratory and that of Doctor Dallman in San Francisco over the past several years. Namely, there is at least one determinant of adrenal sensitivity to ACTH which is not ACTH itself. We have evidence that with respect to the time of day or the history of previous stimulation, such a factor can be turned on in the absence of any change in ACTH.

This factor is clearly stimulated by at least three physiologic stimuli—small hemorrhage, pain, and a decrease in circulating cortisol secretion—so that in most respects it behaves like the stimuli which we associate with ACTH release, but it isn't ACTH. I think Doctor Vaughan and his colleagues have at least given us a reason to want to examine the possibility that such a factor may obtain in the clinical situation as well.

Also, their data recalled to my mind a paper by Eigler and his colleagues, published in the *Journal of Clinical Investigation* about 2 years ago, in which they examined the effects of epinephrine, glucagon, and cortisol alone and in combination on glucose production and utilization. They found, somewhat to their surprise but consistent with the observations that we have just heard, that cortisol has no effect on glucose metabolism by itself. In contrast, it potentiated the effects of both epinephrine and glucagon on glucose production. Thus it is entirely possible that it is a synergism which the authors have found in their current studies. I would like to hear Doctor Vaughan's comment on this.

DR. CHARLES HARTFORD (Crozer-Chester Medical Center, Upland, Chester, PA 19013): I would like to compliment the authors on helping to fit together another piece of the puzzle of steroid metabolism in burn patients.

We approached this problem by studying 24-hour urine cortisone and cortisol excretion using the high-speed liquid chromatography technique, and found that total steroid production related logarithmically to increasing burn size up to about 80%, where it then fell off, for what reasons we are not quite clear, and that total steroid production was elevated during the postburn period with increased production under the influence of stress of surgical procedures and during periods of sepsis. We also found that the highest levels occurred during the first 3 days. That piece of information is missing in this paper, and I wonder if it should be looked into.

The second point is that in the abstract they indicated that the peak levels were attained during the period of 7 to 14 days. Since this is the period of high likelihood of sepsis, I wonder whether the increased production doesn't reflect the stress of infection.

I would also like to ask the authors to comment on the clinical implications of their study.

DR. FRED T. CALDWELL (University of Arkansas Medical Center, Little Rock, AK 72205): I enjoyed Doctor Vaughan's presentation very much. I would like to make one comment and ask a question.

In studying the metabolic response to thermal trauma in children from 2 to 21 years old, we were unable to demonstrate

any correlation between plasma adrenalin levels and the metabolic rate, whether the patients were with or without a dressing. Plasma adrenalin is the calorigenic amine. Noradrenalin has essentially no, or at most 10%, effect on the metabolic rate in man. In burned patients, the major portion of the increase in the catecholamines is noradrenalin, not adrenalin.

As far as I know, without cold adaptation noradrenalin has almost no effect on the metabolic rate. So, if indeed Doctor Vaughan made the statement that catecholamines drive this response, how does he explain this disparity?

DR. GEORGE M. VAUGHAN (Closing): I would like to thank the discussants for raising key issues. While the last comments are fresh in mind, I am a little surprised at the noncorrelation of plasma epinephrine levels with metabolic rate in Doctor Caldwell's patients. Certainly we have found resting plasma norepinephrine concentrations (not reported in this paper) quite elevated in burned patients in proportion to burn size, and norepinephrine levels were more closely correlated with resting metabolic rate than were epinephrine levels in plasma (Becker, R. A., Vaughan, G. M., Ziegler, M. G., et al., in preparation). These results are in conformity with those in the literature. Although the thermogenic effect of epinephrine is well known, some authors (Hsieh, A. C. L., Carlson, L. D., Gray, G.: *Am. J. Physiol.*, **190:** 247–251, 1957; Brodie, B. B., Davies, J. I., Hynie, S., et al.: *Pharmacol. Rev.*, **18** (Part 1): 273–289, 1966; Horwitz, B. A.: *Fed. Proc.*, **38:** 2170–2176, 1979; Jessen, K.: *Acta Anaesth. Scand.*, **24:** 138–143, 1980) imply that norepinephrine is more important than epinephrine for calorigenesis in physiologic experiments. Thus, injection of norepinephrine is used to test nonshivering thermogenesis in rodents (Lynch, G. R., Epstein, A. L.: *Comp. Biochem. Physiol.*, **53-C:** 67–68, 1976; Heldmeier, G., Steinlechner, S., Rafael, J., et al.: *Science*, **212:** 917–919, 1981). Similarly, infusion of norepinephrine provokes hypermetabolism in normal humans (Stone, D. J., Keltz, H., Sarkar, T. K., et al.: *J. Appl. Physiol.*, **34:** 619–623, 1973; Jung, R. T., Shetty, P. S., James, W. P. T., et al.: *Nature*, **279:** 322–323, 1979). Finally, the acute hypermetabolic response of normal human subjects either fed a glucose load (Welle, S., Lilavivathana, U., Campbell, R. G.: *Metabolism*, **29:** 806–809, 1980) or exposed to cold (Jessen, K.: *Acta Anaesth. Scand.*, **24:** 138–143, 1980) was accompanied by an elevation of plasma norepinephrine without a rise in epinephrine. Since the burned patients had elevated concentrations of both hormones, it is possible that both contributed to their hypermetabolic response. The injury-related stimulus to prolonged catecholamine secretion is not yet understood but operates in the absence of recent caloric intake and at warm environmental temperatures (30°C).

Doctor Hartford's comment about lack of measurements in the first 3 days is correct. We didn't receive the patients until the second postburn day, and when we have examined other patients on days 1, 2, and 3 it was our impression that on day 1 some of the highest levels were obtained, although there is great variability in that regard. The apparent rise in plasma cortisol on postburn days 7 to 10 seemed to occur in both the T_3-treated and the placebo groups. When we added clinical sepsis (that is, obtundation or ileus) into the multiple regression analysis, we didn't find evidence that sepsis, whenever it occurred, increased the already high plasma cortisol levels. One clinical implication of this study is that adrenal insufficiency or exhaustion must not be an ordinary sequela of burn injury even in clinical decompensation.

Doctor Gann mentions evidence that cortisol may have no effect as a sole stimulus for gluconeogenesis in dogs but may interact with other hormones in this regard (Eigler and Sherwin: *J. Clin. Invest.*, **63:** 114–123, 1979). This idea, while in conformity with the known propensity of cortisol to generate amino acid substrate and of glucagon and catecholamines to stimulate conversion to glucose, seems at variance with the formulation of Alberti, but supports our findings of little correlation between cortisol and metabolic rate. Additionally, the effects of catechols on fat metabolism may have diluted any dependence of metabolic rate on glucose flow, in that burn injury was associated with lower RQ (burn size vs. RQ, $p < 0.02$ for rectilinear regression). I think it is too early to tell if our ACTH results are interpretable in the same way as are Doctor Gann's. His group has shown that acute ACTH elevation is not necessary for the increased plasma cortisol secretory rate following hemorrhage in dogs and that a previous hemorrhage, but not a previous injection of ACTH, increases the adrenal sensitivity to ACTH (Engeland, W. C., Byrnes, G. J., Presnell, K., et al.: *Endocrinology*, **108:** 2149–2153, 1981).

I think at this stage we are not able to choose ween a non-ACTH-dependent mechanism of elevated cor ersus Doctor Wilmore's kind of explanation, namely, th e adrenals would be more sensitive to ACTH because of l g been stimulated by ACTH for some days or weeks. A ist this latter and still attractive possibility are that we d not identify a fall of ACTH with time that might be d if sensitivity to it were increasing and resulting in ne ed-back from the cortisol and if the stimulus to ACTH e also resolving as the injuries healed, and that we have not seen adrenocortical hyperplasia at autopsy. With reference to the question of the variety of treatments the patients underwent, they were treated in the standard fashion at our institution, including vigorous fluid and nutritional support, an ambient temperature of 30°C, alternating topical mafenide acetate and silver sulfadiazine (morning and evening, respectively), excision and grafting when indicated, antibiotics for sepsis, and opiates for pain. All the potential stress elements could not be controlled, cortisol was elevated before the time when surgical procedures were performed, and cortisol and ACTH were sampled simultaneously in the morning before procedures performed during the day were initiated. Nevertheless, in the setting of burn injury, cortisol bore little relationship to ACTH. In addition, cortisol was not correlated with catecholamine excretion beyond the interrelationships with burn size and postburn day.

Doctor Wilmore proposes several possible ways to separate the cortisol response or link it to ACTH. An epidural anesthetic might help if the already nonelevated ACTH would fall, or if cortisol would fall with no change in ACTH. But interpretation might be difficult if, as expected, there were a large element of pulsatile secretion or if a lengthy time course for the effect of such neuronal blockade would be necessary. One might first repeat some of Hume's early studies using a chronic, rather than acute, burn in a dog model with mechanical nerve interruption. Dexamethasone suppression of ACTH is a relatively safe and simple experiment and may reveal some ACTH dependence of cortisol. In considering possible alternate stimulators of cortisol, angiotensin II has been found to be markedly elevated after burns (Dolocek, Adamkova, Sotornikova, et al.: *Scand. J. Plast. Reconstr. Surg.*, **13:** 9–16, 1979). Bartter's group (Slater, Barbour, Henderson, et al.: *J. Clin Invest.*, **42:** 1504–1520, 1963) showed that infusion of angiotensin II stimulated as big a response in secretory rate of cortisol as of aldosterone in hypophysectomized, nephrectomized dogs. This may also point to a fruitful area of investigation in the future.