Catecholamines:

Mediator of the Hypermetabolic Response to Thermal Injury

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Hypermetabolism characterizes the metabolic response to thermal injury and the extent of energy production is positively related to the rate of urinary catecholamine excretion. Alpha and beta adrenergic blockade decreased metabolism from 69.6 ± 5.3 Kcal/m²/hr to 57.4 ± 5.2 ($p < 0.01$), and infusion of 6 μgm epinephrine/minute in normal man significantly increased metabolic rate. Twenty noninfected burned adults with a mean burn size of 45% total body surface (range 7–84%) and four normal controls were studied in an environmental chamber at two or more temperatures between 19 and 33 C with vapor pressure constant at 11.88 mm Hg. All burn patients were hypermetabolic at all temperatures studied and their core and mean skin temperatures were significantly elevated above control values. Between 25 and 33 C ambient, metabolism was unchanged in controls and burns of less than 40% total body surface (48.9 ± 4.6 Kcal/m²/hr vs. 48.9 ± 4.5), but metabolic rate decreased in larger burns in the warmer environment (72.0 ± 1.9 vs. 65.8 ± 1.7, $p < 0.001$). At 21 C, metabolism and catecholamines increased, except in four nonsurvivors who became hypothermic with decreased catechol elaboration. Metabolic rate in ten patients with bacteremia was below predicted levels while catecholamines were markedly elevated suggesting interference with tissue uptake of the neurohormonal transmitters. Feeding burn patients or administering glucose and insulin improved nitrogen retention and altered substrate flow but did not significantly reduce urinary catecholamines or metabolic rate. Burned patients are internally warm, not externally cold, and catecholamines appear to mediate their increased heat production. Hypermetabolism may be modified by ambient temperature, infection, and pharmacologic means. Alterations in hypothalamic function due to injury, resulting in increased catecholamine elaboration, would explain the metabolic response to thermal injury.

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HYPERMETABOLISM characterizes the metabolic response to thermal injury, and the magnitude of this post-traumatic physiologic alteration is closely related to the extent of injury. Negative nitrogen balance, loss of other intracellular constituents, and a rapid decrease in body weight are consequences of the increase in metabolic activity, and extensive loss of protoplasmic mass may result in severe erosion of energy and protein stores essential to optimal body function. Similarities between the thermally injured and individuals with thyrotoxicosis prompted early metabolic and endocrine studies, but the increased oxygen consumption has not been related to abnormal thyroid function.[10] Increased evaporative water loss from the burn wound results in surface cooling, which could stimulate metabolic activity to maintain normal heat balance and core temperature. The purpose of this study was to define the relationship between surface cooling and hypermetabolism in a controlled ambient environment, to determine the mediator of the profound hypercatabolic response, and to assess the effect of nutritional support on the hypermetabolic response following thermal injury.

Materials and Methods

Patients

Twenty noninfected burn patients, between the ages of 14 and 49 years, were initially studied along with four normal individuals of approximately the same age. Burn patients were selected to represent a range in size of total body surface injury, all except one were

male, and none had significant pre-existing disease before thermal injury (Table 1). The patients were studied between the sixth and 33rd postburn days, with the mean day of study being the 11th day following injury. All patients in this initial group were stable following initial resuscitation and during the study period, and were alert and cooperative during the studies. These patients did not have systemic infection, as determined by stable body temperature, absence of clinical signs of infection, and negative blood cultures and endotoxin levels before, during, and after the study period.

The control individuals were healthy male subjects working on the Burn Unit, who were accustomed to the techniques and methodology of respiratory and metabolic testing. There was no history of chronic disease in this group, and all were vigorous, active individuals.

Place of Study

The studies took place in an environmental chamber on the Burn Ward. This rectangular room, previously described in detail,[51] can maintain a selected temperature and humidity between +15 C and +40 C (range ± 2%), limited by a −1.1 C and 35 C dewpoint. The maximum air velocity in the chamber is less than 50 feet per minute at the level of the bed, three feet above the floor. The room maintains good thermal stability with electronic equipment and three individuals present, and clinical monitoring, patient care, and burn wound treatment were continued while each patient was housed in the chamber.

Study Design

The four normals and the first nine patients were studied in the chamber for two consecutive 24-hour periods after entering the chamber at approximately 9:00 A.M. During one 24-hour interval, the environmental temperature was set at 25 C, vapor pressure at 11.88 mm Hg, and, during the other 24-hour study period, the environmental temperature was set at 33 C with the same vapor pressure. The order of the study periods was sequentially altered, and tests were made between the 18th and 24th hours of each study day.

TABLE 1. *Characteristics of Patients Studied at Two or More Ambient Temperatures*

Subjects	Age (Year)	Weight (Kg)	Body Surface Area (m^2)	Total Body Burn (Per Cent)	Per Cent Third Degree	Postburn Day Studied	Comment
Control							
1*	25	75.0	1.90	0	0		
2*	20	72.2	1.98	0	0		
3*	23	88.0	2.17	0	0		
4*	34	78.0	2.04	0	0		
Mean	26	78.3	2.02				
Range	20–34	72–88	1.90–2.17				
Patients							
1*	43	69.5	1.82	7	7	8–9	
2	14	59.0	1.72	10	0	7	
3*	28	63.0	1.79	15	2	7–8	
4	17	55.7	1.93	23	4	7	
5*	15	48.0	1.56	26	18	17–18	Associated head injury, tracheostomy.
6*	49	87.5	2.01	34.5	0	8–9	
7	18	70.0	1.79	39	12	8	
8*	24	87.0	2.09	40	14	8–9	
9	43	118.0	2.36	41	3	10	
10	32	50.0	1.48	46	17.5	6	Tracheostomy, female.
11	40	80.0	1.99	50	0	12	
12	38	113.0	2.15	51	22	7	
13*	26	65.9	1.78	52	8	10–11	
14	18	60.5	1.77	53	9.5	14	
15*	34	85.0	2.00	60	16.5	14–15	
16*	18	66.0	1.88	63.5	21.5	10–11	
17	19	96.0	2.23	66	25.5	14	
18	34	77.0	1.91	66.5	39.5	14	Tracheostomy
19	22	48.0	1.59	76	33.5	32–33	Tracheostomy
20*	25	68.0	1.85	84	76	8–9	Tracheostomy
Mean	28	73.4	1.88	45	16.5	11	
Range	14–49	48–118	1.48–2.36	7–84	0–76	6–33	

* Studied over two consecutive 24-hour periods.

As more patients were evaluated, shorter equilibration times were allowed, so that the final 11 patients were studied at two or more temperatures on the same day. These patients entered the chamber in the morning between 6 and 8 A.M., were allowed to rest 4–6 hours in the 33 C environment, and then studied. A new ambient temperature was then selected, a period of equilibration allowed, and additional measurements made. The ambient temperatures selected for this study were 33, 29, 25, 21, and 19 C, and all individuals were studied while in two or more ambient conditions. Vapor pressure was maintained at 11.88 mm Hg throughout the range of ambient temperatures. Patients who were studied in the cooler environments (less than 25 C) were evaluated in these ambient conditions as the final test in the series, and were exposed for only one to two hours to the cooler ambient conditions before the measurements were made. In all other instances, the equilibration period was four hours or more.

Study Methods

The methods of study have been previously described in detail.[51] In summary, all patients were treated by the open method with topical mafenide (Sulfamylon®) cream applied to the burn wounds. The individuals were maintained in the supine position, on a water-resistant mattress, several hours before each test. All patients were fasted three or more hours before and while measurements were made, but received water by the oral or parenteral routes if required to maintain a normal state of hydration. Expiratory gas was collected in two 200 L Douglas bags to determine oxygen consumption and carbon dioxide production. A mouth piece and nose clip or nose plugs were used as an interface with the patient except in those individuals with tracheostomies in whom a direct connection with the tracheostomy tube could be made. All patients were previously trained with the equipment, and application of topical anesthesia to the lips and nose was utilized in patients with facial burns to allow patient acceptance of the equipment by minimizing pain and discomfort. After a steady state was achieved, the expiratory gas was collected and analyzed and the metabolic rate calculated from the oxygen consumption corrected for the respiratory quotient and expressed in Kcal/m² body surface area/hour. Core temperature was continuously monitored from rectal and tympanic probes, and a small hand-held thermocouple was used to measure skin temperature. Between 20 and 50 skin temperatures were taken from areas not in contact with the mattress and the mean skin temperature calculated. These three basic measurements (metabolic rate, core temperature, and mean skin temperature) were carried out at each ambient condition after the period of equilibration.

The core to skin heat transfer coefficient was calculated by the following equation:

$$\text{Core-skin (Kcal/m}^2\text{/hr/C)} = \frac{\text{metabolic rate (Kcal/m}^2\text{/hr)}}{\text{core temp (C)} - \text{skin temp (C)}}$$

In selected patients, urine and/or plasma was collected for the determination of catecholamines, measured by an automated fluorimetric method.*[46] The urine was collected during the final hour of each ambient study condition, usually by an indwelling catheter which was present in most of these patients, the volume excreted per unit time recorded, the specimen acidified and frozen for analysis. Blood samples were immediately chilled and plasma immediately analyzed for catecholamine levels.

Adrenergic Blockade

Nine studies were performed in six patients (Table 2). The patients were placed in a warm environment in the early morning and allowed to rest and equilibrate with the ambient condition for several hours. Basal studies of pulse rate, blood pressure, respiratory rate, minute ventilation, metabolic rate, serum free fatty acids,

* Total catecholamines will be referred to throughout this paper, but the samples have been fractionated and norepinephrine represents the major (85–95%) catechol component.

TABLE 2. *Description of Patients Studied Following Alpha and Beta Adrenergic Blockade*

Patient	Age (Year)	Weight (Kg)	Body Surface Area (m²)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied
1	38	113.0	2.15	51	22	22, 24
2	34	77.0	1.91	66.5	39.5	13
3	18	70.0	1.92	55	18	24, 28, 34
4	22	48.0	1.59	76	33.5	37
5	21	77.7	2.05	28.5	4	9
6	14	52.9	1.54	57	27	27
Mean	24	73.1	1.86	55.5	24.0	24
Range	14–38	48.0–113.0	1.54–2.15	28.5–76	4–39.5	9–37

TABLE 3. *Characteristics of Patients With Bacteremia*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m^2)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied	Organism Cultured From Blood	Endotoxin
1	18	70.0	1.92	55	12	8	Staphylococcus aureus	*
2	38	70.5	1.88	56.5	56.5	10	Klebsiella	Positive
3	48	105.0	2.15	61	13	12	Staphylococcus aureus	*
4	39	78.0	2.00	73	49	4	Aeromonas liquefaciens	*
5	34	65.0	1.85	76	28	7	Providencia stuarti	*
6	22	84.0	2.02	82	49	5	E. coli	Positive
7	43	57.4	1.73	45	15	17	Klebsiella	*
8	63	73.6	1.87	31.5	25	17	Providencia stuarti	Negative
9	37	71.6	1.81	67	46	3	Bacillus species	*
10	64	95.2	2.20	49	44	10	Providencia stuarti	*
Mean	41	77.0	1.94	59.5	34	9		
Range	18–64	57.4–105	1.73–2.20	31.5–82.0	12–56.5	3–17		

* Not measured.

blood sugar, and insulin were performed. Blockade was effected by the intravenous administration of phentolamine (Regitine®), 75 mg (alpha blockade) or phentolamine, 75 mg and propanolol (Inderal®), 75 mg infused over 15 to 30 minutes (combined alpha and beta blockade). The adequacy of beta blockade was determined by the absence of response in heart rate or increase in serum free fatty acids following intravenous administration of 2 μgm isoproterenol (Isuprel®). Orthostatic hypotension and nasal stuffiness were present in patients following alpha blockade. After adequate blockade, the initial studies were repeated.

Septic Patients

Eighteen studies were performed in 10 septic individuals (Table 3), all with proven bacteremia demonstrated by a positive blood culture obtained at the time of study. All patients maintained an adequate urine output at the time of study and did not demonstrate hypotension or signs of cardiovascular instability. Metabolic rate, core and skin temperature, urine, and/or plasma catecholamines were measured in selected patients as previously described.

TABLE 4. *Characteristics of Normal Subjects Receiving Epinephrine Infusion*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m^2)	Comment
1	35	76.2	2.02	1a. Four days fasting 1b. Five days fasting (second fast) 1c. Fed
2	39	83.0	2.07	Five days fasting
3	22	72.0	1.95	3a. Four days fasting 3b. Ten days fasting (same fast)
4	18	76.3	1.96	Fed
5	41	107.2	2.19	Fed
6	32	74.9	1.94	Fed
7	26	69.0	1.87	Fed
Mean	30	79.8	2.00	
Range	18–41	69.0–107.2	1.87–2.19	

Epinephrine Infusion

Ten studies were performed in seven normal males who received intravenous epinephrine to evaluate the metabolic and respiratory response to catecholamine infusion. Five of the studies were performed following a 10-hour overnight fast and the remaining five studies were carried out in normals who were fasted and exercised for four to 10 days prior to study (Table 4). The infusion was performed in the environmental chamber which was maintained at 28 C, vapor pressure 11.88 mm Hg, and the subjects entered the study room in the late evening or early morning and slept in the supine position for at least four hours before study. At 7:00 A.M., a large forearm vein was cannulated under local anesthesia and an infusion of .04 M saline started and maintained at a constant rate by infusion pump. After one hour, expiratory gas was collected in Douglas bags as previously described and blood was drawn from the indwelling venous catheter for determination of glucose, blood urea nitrogen, creatinine, free fatty acids, glucagon, cortisol, human growth hormone, and plasma catecholamines. The urine formed during a carefully-timed two to three hour basal period was collected, the volume measured and the specimen processed for determination of urea, creatinine, and catecholamines. After baseline vital signs and electrocardiograms were obtained, the epinephrine infusion was started. The solution, composed as described by Porte,[39] was initially infused slowly, then gradually increased over 10 minutes to volumes comparable to the control and recovery periods, while maintaining an infused dose of 6 μgm epinephrine/minute. Expiratory gas was collected 20–30 and 50–60 minutes after the start of the infusion, and

blood and urine samples were obtained after 60 minutes of infusion. The Douglas bag measurements and blood and urine studies were repeated during recovery, one hour post-infusion, and for several consecutive hours in selected subjects.

Nutritional Support, Nitrogen Excretion, and Energy Expenditure Interaction

The effect of nutritional support on metabolic rate and nitrogen loss was evaluated in 43 studies in normal and injured men. The patients, with a mean burn size of 53 per cent of the body surface (Table 5), received a wide range of nutritional support administered by the enteral, parenteral, or enteral-parenteral routes. The normal individuals were studied the day before epinephrine infusion as previously described. Resting metabolic rate was determined in all subjects between 6:00 A.M. and 8:00 A.M. following at least three hours of restriction of *ad libitum* oral caloric intake. However, calories and nitrogen administered by the intravenous route were continued at a constant infusion rate during the measurement period. Blood was obtained for determination of glucose, urea, free fatty acids, insulin, human growth hormone, glucagon, cortisol, and catecholamines and a timed urine specimen was obtained for catecholamine determination. The caloric and nitrogen intake for the accompanying 24-hour period was determined from the composition as listed by the manufacturer, and food intake was determined by the dietitian from known lots of food prepared in the research

TABLE 5. *Characteristics of Subjects Studied*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m^2)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Mean Postburn Day Studied
Control						
1	23	55.8	1.66	0	0	—
Patient						
1	18	52	1.61	58	28.5	a. 25 b. 63
2	17	60.6	1.76	58	14.5	6
3	33	72.6	1.98	50.5	2.5	a. 12 b. 26
4	29	70.3	1.83	47.5	14	15
5	63	73.6	1.87	31.5	25	17
6	64	95.2	2.20	59	54	10
7	51	95.0	2.19	58	27.5	6
8	64	57.2	1.66	39	23	5
9	39	90.0	2.08	23*	10	9
10	29	50.0	1.59	47	0	18
11	60	67.3	1.84	62	53	42
12	25	54.3	1.64	78.5	11	31
13	41	53.0	1.65	60	8	a. 77 b. 85
14	19	77.0	1.98	33.5†	33.5	a. 255 b. 248
15	28	58.0	1.90	75.5	57	a. 49 b. 42
16	16	62.0	1.79	38	14	a. 24 b. 17
17	18	66.0	1.88	64	22	a. 17 b. 24
18	18	66.0	1.88	64	22	a. 32 b. 26
19	21	76.5	1.95	45	26	a. 20 b. 24
20	34	85.0	2.00	60	16.5	a. 24 b. 17
21	22	48.0	1.59	56.5	33.5	a. 44 b. 37
22	14	42.0	1.54	57	27	a. 36 b. 43
Mean	33	66.9	1.84	53	24	29‡
Range	14–64	42.0–95.2	1.54–2.20	23–78.5	0–57	6–255

* Multiple fracture.
† Initial injury 75 per cent; wound partially grafted before transfer.
‡ Excluding patient No. 14.

TABLE 6. *Metabolic Rate, Body and Skin Temperatures, and Heat Transfer Coefficient at Different Temperatures*

Subject	Metabolic Rate (Kcal/m²/hr)	Core Temperature (°C)	Skin Temperature (°C)	Core-Skin Heat Transfer Coefficient (Kcal/m²/hr/°C)
Measurements at 33C				
Control				
1	39.8	36.7	33.6	12.8
2	34.5	36.9	34.8	16.4
3	37.9	36.9	34.5	15.8
4	33.0	36.9	33.8	10.6
Patients				
1	37.7	38.7	35.6	12.2
2	42.2			
3	43.6	37.5	35.1	14.4
4	60.0			
5	69.4	39.0	37.0	34.7
6	71.0	40.1	37.3	25.4
7	68.8	38.1	36.7	49.1
8	64.9	38.5	36.5	32.4
9	69.4	37.8	36.0	38.5
10	57.5	37.5	36.3	47.9
11	55.0	38.3	36.0	29.3
12	71.7	38.2	34.4	18.8
13	55.6	37.4	35.8	34.7
14	68.0	37.0	34.7	29.6
15	74.8	39.7	36.8	25.8
16	63.6	38.7	36.1	24.2
17	65.8	37.4	35.5	34.6
18	65.2	37.2	35.1	31.0
19a	67.0	38.6		
19b	71.7			
20	71.6	36.9	35.0	37.7
Measurements at 29 C				
Patients				
12	76.8			
16	75.8			
18	70.2	37.6	34.6	23.4
19a	68.3	38.7		
19b	66.3			
Measurements at 25 C				
Control				
1	37.8	36.7	31.4	7.13
2	31.8	36.7	31.3	5.89
3	40.1	37.3	32.0	7.57
4	32.7	36.5	31.0	5.95
Patients				
1	36.9	38.5	31.5	5.27
2	43.0			
3	49.1	38.4	32.5	8.32
4	65.1			
5	62.0	39.5	33.9	11.1
6	72.3	38.8	33.8	14.5
7	67.5	39.7	34.6	13.2
8	58.2	38.5	33.3	11.2
9	69.2	39.0	33.7	13.0
10	70.1	38.5	33.5	14.0
11	62.8	38.4	33.1	11.8
12	78.8	37.5	31.4	12.9
13	61.8	38.5	32.8	10.8
14	76.8	37.9	32.0	13.0

metabolic kitchen. Urine was collected in 24 hour pools and concentrations of sodium, potassium, creatinine, urea, and total nitrogen determined. Generous estimates of stool losses (2–3 g nitrogen/day) were made for the few patients receiving enteral residue-containing diets. Wound loss was not measured. Insulin was administered as required to those patients with elevated blood or urine glucose and human growth hormone, 10 international units, was given daily by intramuscular injection to nine subjects to evaluate the effect of endogenous reset of insulin output.[52] The mean values of all measurements obtained over three to seven days in the patients were computer-processed with the control data to determine the interaction and effect of caloric and nitrogen support and metabolic rate on nitrogen excretion.

Results

Body Temperature and Heat Transfer

Core temperature did not change significantly between the ambient conditions at 25 and 33 C, but skin

TABLE 6. (*Continued*)

Subject	Metabolic Rate (Kcal/m²/hr)	Core Temperature (°C)	Skin Temperature (°C)	Core-Skin Heat Transfer Coefficient (Kcal/m²/hr/°C)
Measurements at 25 C				
Patients				
15	80.0	38.3	34.8	22.9
16	69.9	37.5	33.0	15.5
17	71.6	37.4	33.8	19.9
18	71.4	37.1	32.5	15.5
19a	79.3	38.8		
19b	78.2			
20	79.8	38.2	32.0	12.9
Measurements at 21 C				
Control				
1	41.7	36.7	30.2	6.4
3	40.3	37.0		
4	41.6	36.5	29.8	6.2
Patients				
4	75.8			
5	90.3	38.0	32.2	15.6
7	74.7	39.2	32.2	10.7
9	74.1	39.3	32.3	10.6
10	79.2	38.8	32.2	12.0
14	89.1	37.1	31.4	15.6
15	94.2	37.1		
16	91.9	37.3		
19a	84.0	38.1		
Measurements at 19 C				
Control				
1	48.9	37.0	28.8	6.0
3	49.8	37.0		
4	46.2	36.5		
Patients				
5	89.2			
10	82.7	38.7	32.1	12.5

temperature was altered and moved in the direction of the environmental temperature. However, a marked difference was noted in the core and skin temperatures when comparing normal individuals with burn patients; the average core and skin temperatures were consistently 1–2 C higher in the injured patients when compared with controls (Table 6, 7). This difference was present at all ambient conditions studied between 33 and 25 C, and was also found at the cooler temperature in those patients who were able to increase their metabolic rates in the 21 and 19 C environments. Heat transfer coefficients demonstrated a two-fold increase in core to skin conductance of heat in the burn patients when compared with control individuals, and this two-fold increase was present at all temperatures studied.

Effect of Burn Size and Ambient Temperature on Metabolic Rate

Metabolic rate increased with burn size. The relationship appeared curvilinear, metabolism approaching 70–75 Kcal/m²/hr when measured in the 33 and 25 C environment as burn size exceeded 50% total body surface (Table 8). In the controls and patients with smaller burns (less than 40% total body surface), there was no change in mean metabolic rate between 33–25 C (48.9 ± 4.6 Kcal/m²/hr at 33° vs. 48.9 ± 4.5, mean ± S.E.M.). However, it appeared that a consistent decrease in caloric expenditure occurred in patients with larger burn injuries in the warmer environment when compared with 25 C. Mean metabolic rate at 25 C was 72.0 ± 1.9 Kcal/m²/hr, which decreased to 65.8 ± 1.7 Kcal/m²/hr at 33 C ($p < 0.001$ by paired t test). As the ambient temperature decreased below 25 C, metabolism increased in both the controls and those patients who eventually survived. However, oxygen consumption rarely exceeded two and one-half times basal levels (Fig. 1). In contrast, four patients with more extensive burns became hypothermic at 21 C, with decreased metabolic rate and a marked fall in core and skin temperature.

TABLE 7. *Measurements From Four Normals and 20 Patients at Two Ambient Temperatures* (Mean ± S.E.)

	Normal	Burns	p
25 C			
Metabolic rate (Kcal/m²/hr)	35.6 ± 2.0	66.8 ± 2.6	<0.001
Core temperature (°C)	36.7 ± 0.2	38.4 ± 0.2	<0.001
Skin temperature (°C)	31.4 ± 0.2	33.1 ± 0.2	<0.001
Core skin heat transfer coefficient (Kcal/m²/hr/°C)	6.6 ± 0.4	13.3 ± 1.0	<0.001
33 C			
Metabolic rate (Kcal/m²/hr)	36.3 ± 1.6	62.6 ± 2.3	<0.001
Core temperature (°C)	36.9 ± 0.1	38.1 ± 0.2	<0.001
Skin temperature (°C)	34.2 ± 0.3	35.9 ± 0.2	<0.01
Core-skin heat transfer coefficient (Kcal/m²/hr/°C)	13.9 ± 1.4	30.6 ± 2.5	<0.001

TABLE 8. *Relationship Between Metabolic and Per Cent Total Body Surface Burn at Varying Temperatures*

Ambient Temperature (°C)	Relationship	r^2
21	$y = 42.70 + 1.539x - 0.01290x^2$	0.877
25	$y = 35.50 + 1.050x - 0.006698x^2$	0.889
33	$y = 36.15 + 1.001x - 0.007694x^2$	0.795
T*	$y = 188.8 + 1.211x - 10.38T - 0.009274x^2 + 0.1701T^2$	0.849

y = Metabolic rate in Kcal/m²/hr
x = Per cent body surface burn
T = Ambient temperature °C (T 19–33)
$p < 0.05$ for all equations
* Based on 72 measurements of metabolic rate at five different temperatures; hypothermic patients not included.

Relationship Between Metabolic Rate and Catecholamines

The urinary excretion of catecholamines per unit time was related to metabolic rate measured during the same time period. The relationship appeared linear until metabolic rate approached two times basal levels, then increased excretion in urinary catecholamine was associated with only a slight increase in metabolic rate, with the predicted metabolic response never exceeding two and one-half times basal levels for normal man (Fig. 2). The ability to generate additional heat in a cool environment was variable in patients with burns greater than 40% total body surface (Table 9). In four patients with an average burn size of 57% (range 41–76), there was a marked accentuation of hypermetabolism, and this compensatory increase in heat production maintained core temperature and was accompanied by an increase in excretion of urinary catecholamines. However, four patients with a mean burn size of 65% (range 51–84) studied in a cool ambient temperature failed to maintain heat balance and became hypothermic. These "nonresponders" had a sudden decrease in their catecholamine excretions during exposure to the cooler ambient temperature (Fig. 3).

Effect of Adrenergic Blockade

No consistent change in metabolic rate was seen with alpha blockade alone, and the mean basal metabolic rate was 70.7 ± 7.9 Kcal/m²/hr before blockade and 68.1 ± 4.6 Kcal/m²/hr following blockade (n = 3). However, there was a significant decrease in metabolic rate associated with combined alpha and beta blockade (Table 10) or beta blockade alone, and this response was associated with a decrease in pulse rate, blood pressure, minute ventilation, and free fatty acids. The

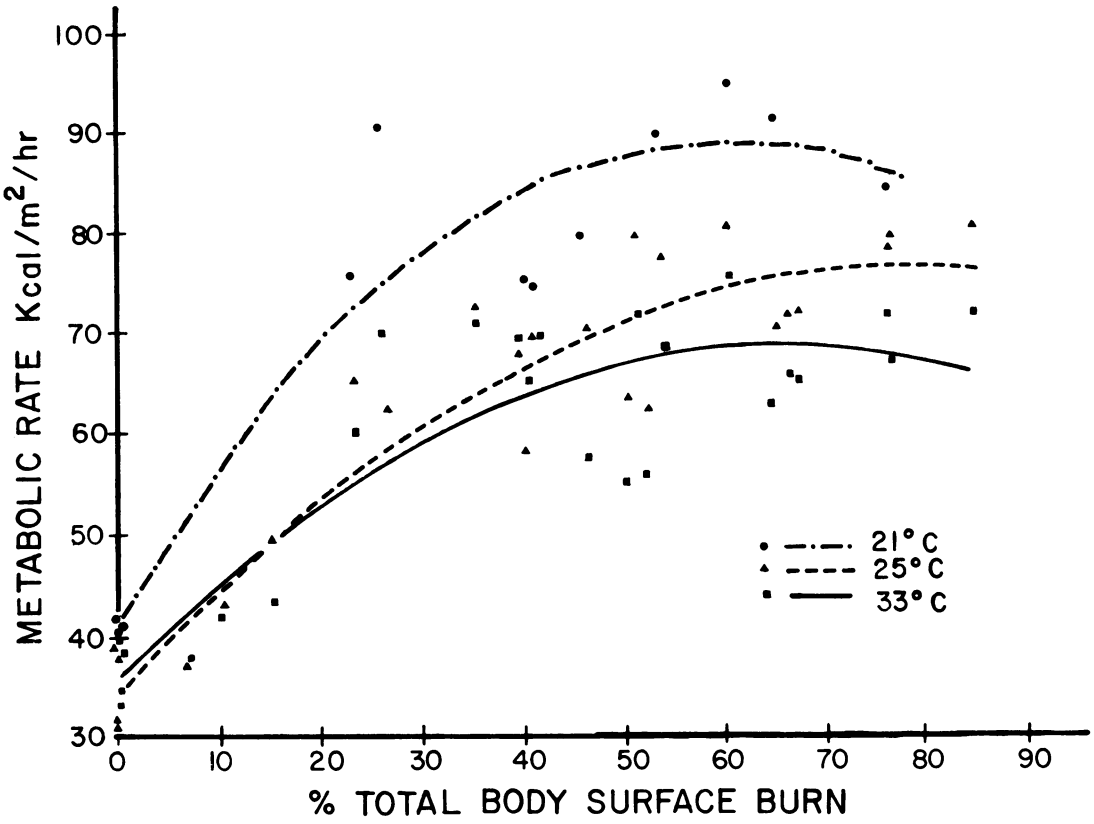

FIG. 1. The relationship between metabolic rate and environmental temperature is demonstrated by the individual regression curves derived for 21, 25, and 33 C ambient (from data listed in Table 6, as calculated from individual equations in Table 8). Both normal men and burn patients increased metabolic rate at 21 C when compared with 25 and 33 C. Only a small decrease in metabolism occurred in patients with large thermal injury studied at 25 and 33 C, and the reduction was in the order of 5–8 Kcal/m²/hr. Metabolic rate did not return to normal when the patients were studied in a warm environment.

dose of propanolol required for competitive blockade of the beta receptor system in these hypermetabolic burn patients was greater than the dose required for normal man, and a persistent sympathetic break-through occurred with the administration of smaller doses of the drug per unit time. Metabolic activity returned to its preblockade level within two to three hours following drug administration.

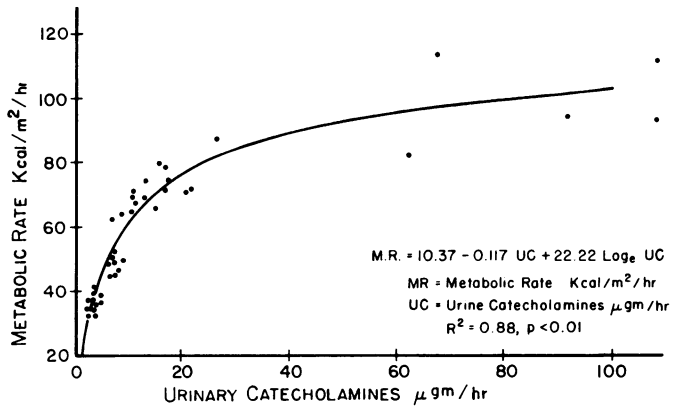

FIG. 2. Relationship between metabolic rate and urinary catecholamines. The response curve to a dose of catecholamine or to nerve stimulation has the shape of a rectangular hyperbole, with a large quantitative difference in response elicited by a small change in dose. As the catecholamines increase, a plateau is reached and increasing doses exert little effect on metabolic rate. Our data expressed as a hyperbolic function is:

$$MR = 100.93 - \frac{580.56}{UC} + \frac{1{,}584.58}{UC^2} - \frac{1351.64}{UC^3}$$

$$n = 55,\ r^2 = 0.84,\ p < 0.05.$$

Septic Patients

Metabolic rate was significantly decreased in 10 septic patients studied. The mean metabolic rate was 50.3 ± 2.2 Kcal/m²/hr compared with predicted or measured rates during nonseptic intervals which averaged 73.0 ± 1.2 Kcal/m²/hr (Table 11). Urinary catecholamines were markedly elevated in these patients, averaging 910.8 ± 406 μgm/hr, and this level of catecholamine excretion was inappropriately high for the metabolic response measured (Fig. 2).

Epinephrine Infusion

Metabolic rate increased with the infusion of 6 μgm epinephrine/minute in normal man when compared with the basal period (Table 12). The hypermetabolism was accompanied by an increase in respiratory rate and minute ventilation, and these alterations in metabolic and respiratory function returned toward normal following infusion. Blood glucose, free fatty acid, and glucagon increased, growth hormone fell, and insulin and glucocorticoids remained unchanged during catecholamine infusions, alterations consistent with pre-

TABLE 9. *Variable Response of Patients With Large Thermal Injury to Decreasing Environmental Temperature*

	Metaboic Rate (Kcal/m²/hr)					Urinary Catechols (μgm/hr)					Skin Temperature (C)					Tympanic Temperature (C)				
Patient	33	29	25	21	19	33	29	25	21	19	33	29	25	21	19	33	29	25	21	19
1	69.4		69.2	74.0		13.5		12.0	13.5		36.0		33.7	32.3		37.8		39.0	39.3	
2	57.6		70.0	79.2	82.7	8.4		28.0	91.0		36.3		33.5	32.2	32.1	37.5		38.5	38.8	38.7
3	63.6		69.9	91.9		15.3		18.5	34.2		36.1		33.0			38.7		37.5		
4	67.0	66.3	79.3	84.0		6.6	8.2	16.2	96.0							38.6	38.7	38.8	38.1	
5	63.5	52.6	50.8			9.2	11.8	10.2			34.8	33.6	32.3			37.2	36.8	36.2		
6	71.7		78.7	69.3		22		17.5	10.8		34.4		31.4	29.5		38.2		37.5	37.9	
7	84.0		83.2	57.6							34.6		32.1	30.4		36.3		35.4	35.9	
8	80.2	87.0	81.5			22.5	27.6	12.5			34.5	33.3	31.5			37.3	37.0	36.5		
9	65.2	72.3	71.4	68.4		16.8		17.6	7.6		35.1	34.6	32.5	30.9		37.2	36.9	37.1	36.7	
10	71.4		79.7	67.0							35.0		32.0	29.3		37.0		38.2	38.0	

viously reported observations.[17,27,36,39] Excretion of urea nitrogen was not altered throughout the study in the fed patients (52.6 ± 10.6 mg urea nitrogen/hr pre-infusion, 48.5 ± 9.7 during infusion, and 46.3 ± 12.0 post-infusion), but nitrogen loss increased with infusion in the fasting subjects (44.0 ± 5.8 mg/hr pre-infusion, 60.6 ± 7.2 during infusion, 48.6 ± 6.0 post-infusion, $p < 0.05$ difference between infusion period and pre-infusion and post-infusion period). No significant alteration in blood urea nitrogen occurred during the study.

Nutritional Support, Nitrogen Excretion, and Energy Expenditure Interaction

Increased nitrogen excretion was associated with hypermetabolism and/or with increased dietary protein intake. Nitrogen excretion decreased with administration of nonprotein calories and/or an increase in plasma insulin (Table 13, 14). Metabolic rate was related to urinary catecholamines as previously described, and a positive correlation also existed between glucagon levels and catecholamine excretion. Each of these three variables relates in similar fashion to protein metabolism, with a positive correlation existing between urinary catecholamines, metabolic rate, or glucagon and nitrogen excretion. Metabolic rate and catecholamine excretion were not reduced by calorie and nitrogen administration, confirming previous studies,[53] but the protein-wasting resulting from the hypermetabolism was diminished or reversed with nonprotein calorie intake, nitrogen administration, and/or maneuvers which increased basal insulin levels (Table 14).

TABLE 9A. *Description of Patients Studied: Multiple Temperatures*

Patient	Age	Weight (Kg)	Body Surface Area (m²)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied
1	43	118.0	2.36	41	3	10
2	32	50.0	1.48	46	17.5	6
3	18	66.0	1.88	63.5	21.5	10–11
4	22	48.0	1.59	76	33.5	33
5	74	66.4	1.71	46	27	6
6	38	113.0	2.15	51	22	7
7	22	64.0	1.86	57.5	19.5	7
8	60	67.3	1.84	62	53	11
9	34	77.0	1.91	66.5	39.5	14
10	25	68.0	1.85	84	76	8–9

Discussion

Hypermetabolism characterizes the metabolic response following thermal injury, and this alteration in metabolic activity correlates well with increased evaporative water loss from the burn wound.[28] Decreasing wet or dry heat loss in small animals has been reported to return metabolic rate towards normal.[6,37] Burn patients treated in a warm environment (32 C) demonstrate lower metabolic rates than when treated in a cool environment (22 C),[1] and this evidence has been interpreted to support the thesis that hypermetabolism in the burn patient is a response to increased surface cooling due to increased evaporative water loss. In contrast, however, Zawacki and associates covered burn wounds with a water-impermeable membrane and thus blocked evaporative water loss, but found no consistent alterations in metabolic rate in burn patients at approximately 25 C ambient temperature.[56]

In this study, the average core temperature of the burn patients was elevated above normal, and the mean skin temperature was increased in all nonhypothermic patients at all ambient conditions studied when compared with normal man, demonstrating that the burn patients are internally warm and not externally cold. The usual response of normal man to a cold environment involves both vasoconstriction to achieve core insulation and decreased sweat secretion. Further cooling results in hypermetabolism, which occurs in an individual with a normal or slightly decreased core temperature and a cool dry skin. Our patients, however, were hypermetabolic in a warm environment, with elevated core and skin temperatures, and, when equili-

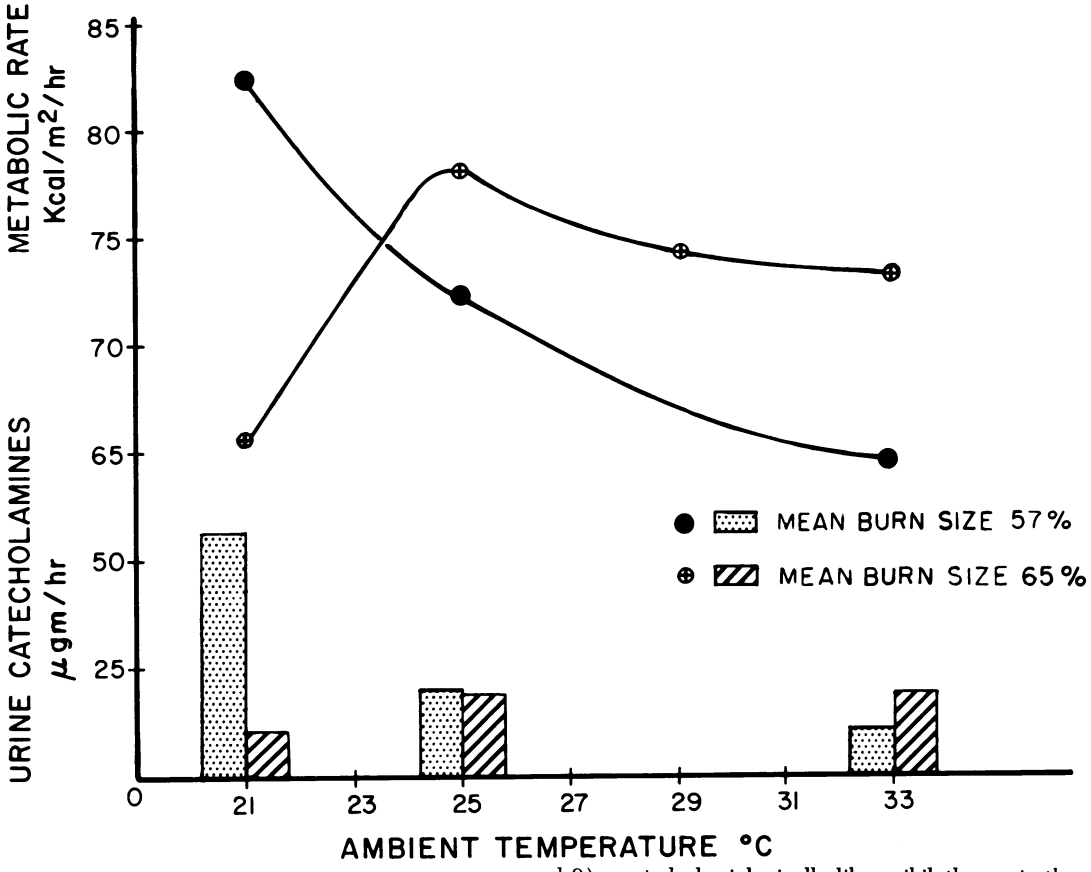

FIG. 3. Failure to respond to cooling in patients with large thermal injury. The ability to generate additional heat to cold stress is variable in patients with large thermal injury, but appears to depend primarily on burn size. Individuals with smaller injuries and available metabolic reserve (mean values from Patients 1–4, Table 9) respond to cooling by increasing metabolic rate and this response is associated with increased urinary catecholamines (solid dots, stippled bars), while others (Patients 6, 7, 9, 10) lack catechol or tissue reserves, fail to maintain heat balance, and become hypothermic (crossed dots). These "nonresponders" are apparently at maximal rates of energy production and cannot respond appropriately to catechol mediated stress, such as cooling, infection, and hemorrhage. Two elderly patients studied (No. 5 and 8) reacted physiologically like poikilotherms in the varying ambient temperatures.

brated with a cooler environment, continued or slightly increased their hypermetabolism while their core and skin temperature remained higher than those of the normal controls. Evaporative water loss and surface cooling in the burn patient is not the primary stimulus for the hypermetabolic state but rather the hypermetabolic response is related to an endogenous reset in metabolic activity. Vaporizational heat loss serves as a convenient route for transfer of this large heat load from the body.

TABLE 10. *Effect of Alpha and Beta Blockade on Hypermetabolism Following Thermal Injury*

	Pulse (Beats/Min)		Blood Pressure (mmHg)		Respiratory Rate (Breaths/Min)		Minute Ventilation (L/Min)		Metabolic Rate (Kcal/m²/Hr)		Free Fatty Acids (mEq/L)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Alpha Blockade												
1a	120	110			29.0	32.9	38.2	29.1	80.2	76.8	2.0	8.0
1b	126	118			25.6	24.9	24.3	19.7	76.8	66.7	1.3	3.5
3	100	84	142/70	120/50	12.0	12.5	12.1	16.1	55.0	60.9		
Mean*	115	104			22.2	23.4	24.9	21.6	70.7	68.1	1.6	5.8
S.E.	8	10			5.2	5.9	7.5	3.9	7.9	4.6	0.4	2.2
Alpha and Beta Blockade												
2	118	84	116/72	88/52	40.0	38.0	35.4	32.2	68.0	59.9	4.0	1.7
3a	96	88	160/82	124/68	16.0	19.5	18.0	9.4	66.8	44.9	4.6	2.3
3b	98	84	128/80	100/70	22.7	24.0	12.0	10.1	46.9	42.4	5.0	3.5
4	120	96	120/100	90/—	17.7	14.0	22.6	19.0	78.7	64.7		
5	120	84	118/80	80/60	19.4	17.5	19.4	17.5	72.0	55.8	4.9	3.6
6	144	96	115/80	86/—	17.7	14.6	20.5	17.2	85.1	76.6	2.2	1.3
Mean	116	89	126/82	95/63	22.2	21.3	21.3	17.6	69.6	57.4	4.1	2.5
S.E.	7	2	7/4	6/4	3.7	3.7	3.2	3.4	5.3	5.2	0.5	0.5
p	<0.01		<0.001/<0.01		>0.10		<0.02		<0.01		<0.01	

* Effect not different by paired t test.

TABLE 11. *Metabolic Requirements in Patients With Bacteremia*

Patient	Ambient Temperature	Metabolic Rate (Kcal/m²/Hr) Predicted*	Metabolic Rate (Kcal/m²/Hr) Measured	Urinary Catecholamines (μgm/Hr)
1	21	84.5	66.2	668
	25	74.3	51.7	195
	33	70.2	58.8	22.8
2	25	74.5	40.6	
	29	69.8	35.6	
3	33	71.0	60.4	
4	25	74.7	54.5	
5	21	84.4	51.3	
	25	74.2	53.8	
	29	69.4	48.2	
	33	70.1	45.5	
6	25	72.7	35.9	
	29	67.9	35.9	
7	25	71.4	44.4	930
	25	71.4	54.0	1,391
8	25	64.7	54.7	264
9	25	75.2	52.0	3,498
10	25	72.8	62.3	318

* Based on regression equation (Table 8), measurements in five patients before septic episode are comparable to the predicted values.

The inability of the burn patient to return metabolic rate to normal levels in a warm environment is comparable to reports by Swedish investigators, who found a decrease of metabolic rate between 22 and 32 C, but failed to demonstrate a return of metabolism to basal levels in patients in warm dry air.[1] As noted in the present study, hypermetabolism occurs in normal man at 21 C, and other reports suggest that the critical temperature for man is approximately 24–25 C (range 22–27).[12,50] Exposure to ambient conditions below this temperature results in hypermetabolism. Increased heat production, accentuated nitrogen excretion, and weight loss occur in fasted normal man,[33] burn patients,[4] and individuals with fractures[11] when studied below critical temperature, and this is a normal physiologic response to cold exposure. We interpret our data and the other clinical reports as indicating that warm environments do not abate the metabolic response to injury but rather that cold environments accentuate or augment the post-traumatic metabolic response to injury.

What is the mediator for the increased energy production following thermal injury? Hormonal stimulation of heat production occurs with the elaboration of thyroid hormones or catecholamines.[31] Thyroid function has been carefully studied and hyperthyroidism does not appear to cause the increased oxygen consumption following burn trauma.[10] Catecholamines are elevated following thermal injury,[18] and adrenergic activity, as measured by urinary excretion of catecholamines,[47] is related to the extent of stress or severity of injury and to the oxygen consumption of the patient.[29] With wound healing, catecholamines and metabolic rate return to normal.

Cannon demonstrated the importance of the sympathetic nervous system to the maintenance of body homeostasis following a wide variety of stresses, and suggested that increased heat production, which characteristically occurs with sympathoadrenal discharge, may be one of the most important physiologic effects of these hormones.[7] Catecholamines infused into animals increase metabolic rate, and epinephrine or norepinephrine[42] infusions in normal man produce hypermetabolism. Rats in which adrenergic function is completely blocked die in three hours when exposed to 4 C ambient environment, while normal animals

TABLE 12*A*. *Measurements Before, During, and After Epinephrine Infusion in Normal Man*

	Basal					Infusion*				
Subject	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)
Fasting										
1a	5.22	4.8	1.08	0.68	32.0	7.53	6.2	1.25	0.66	45.8
1b	6.05	4.3	1.42	0.67	34.8	9.32	14.2	0.66	0.64	45.3
2	6.06	8.6	0.71	0.70	34.3	9.33	9.9	0.94	0.68	52.0
3a	6.28	11.9	0.52	0.70	38.3	8.06	11.7	0.69	0.69	48.4
3b	4.68	9.5	0.49	0.70	31.5	7.08	11.9	0.59	0.58	42.6
Fed										
1c	4.88	4.8	1.04	0.72	31.9	7.01	5.0	1.45	0.70	44.3
4	4.29	4.3	1.00	0.68	33.3	7.90	9.1	0.90	0.76	49.0
5	8.70	12.8	0.68	0.68	36.3	11.31	15.4	0.74	0.69	48.5
6	5.26	5.9	0.89	0.71	34.3	7.44	8.4	0.89	0.67	44.0
7	5.33	8.2	0.64	0.78	31.4	6.42	6.6	0.97	0.77	41.7
Mean	5.68	7.51	0.85	0.70	33.8	8.14	9.8	0.91	0.68	46.2
S.E.	0.39	1.00	0.09	0.01	0.7	0.46	1.1	0.09	0.02	1.0
						p† <0.001	<0.05	>0.50	>0.10	<0.001

* Mean measurements from four Douglas bag collections.
† Paired t-test compared with basal.

TABLE 12B. *Measurements Before, During, and After Epinephrine Infusion in Normal Man*

	One-Hour Postinfusion					Two-Hour Postinfusion				
Subject	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)
Fasting										
1a	6.68	4.8	1.38	0.70	41.6					
1b	6.71	4.4	1.52	0.69	37.3	6.35	4.0	1.55	0.70	36.4
2	6.89	6.8	1.01	0.70	41.8					
3a	6.46	11.2	0.58	0.71	39.0	5.07	10.8	0.47	0.70	37.7
3b	6.36	11.0	0.58	0.68	36.1					
Fed										
1c	4.80	3.0	1.59	0.70	34.1	5.44	2.9	1.90	0.70	34.6
4	5.41	8.1	0.67	0.71	35.0					
5	12.62	14.2	0.89	0.77	43.6					
6	5.87	4.7	1.25	0.72	35.6					
7	4.84	7.4	0.66	0.72	32.7					
Mean	6.66	7.6	1.01	0.71	37.7					
S.E.	0.70	1.1	0.13	0.008	1.2					

adjust to the temperature by increasing their metabolic rate.[5] Totally sympathectomized cats can be maintained in a carefully controlled laboratory environment, yet are unable to defend against hypoxia, fluid restriction, stresses of environmental temperature, hemorrhage, and exercise.[8] The importance of the adrenergic beta receptors in mediating calorigenesis was demonstrated by Estler and Ammon,[13] and was confirmed in our patient studies. Alpha blockade did not affect heat production in the burn patients, while combined alpha and beta blockade and beta blockade alone significantly reduced metabolic rate. Thus, the increased heat production appears to be mediated by catecholamines, which have a direct effect on cellular calorigenic activity. However, the increase in sympathetic activity and catecholamine elaboration in the burn patients is not the immediate effect of cold stimulation of peripheral or central nervous system receptors.

Other factors interact with the basic reset in internal metabolic activity to alter the final sympathetic-mediated physiologic response. First, ambient temperature affects the basic reset to increase metabolic rate as environmental temperature falls below 25 C. Moreover, patients with burns greater than 40% of the total body surface demonstrate a slight reduction in heat production between 25 and 33 C. This response is due to the inability of patients with large thermal injury to achieve adequate core to skin insulation and reduce surface temperature in response to cooling,[51] as demonstrated in this study by the increased core-skin heat conduction in the burn patients as compared to controls. One explanation for the impairment in insulative function and inability to regulate skin temperature and limit heat loss is that tissue injury results in increased blood flow to the skin, apparently to aid oxygenation and improve nutrient supply to insure wound healing. This thesis is supported by studies in burns demonstrating a hyperdynamic circulatory state, increased cutaneous blood flow, and peripheral shunting, associated with normal visceral flow and oxygen extraction.[26]

Secondly, the ability to respond to a stimulus requiring catecholamine-mediated calorigenesis depends upon the availability of catecholamine reserves and the ability of tissue to respond to increased catechol stimuli. Goodall and Haynes[19] reported that patients with large thermal injury may show depletion of adrenal medullary catecholamines, and Goodall and Moncrief[20] demonstrated that severe thermal injury could deplete monoamine stores in the sympathetic nerve endings and sympathetic ganglia. Labelled dopamine administered to patients with large thermal injury demonstrated an increased turnover compared with normals, and there was a marked shift of this precursor toward noradrenaline synthesis and utilization.[21] The turnover and excretion of dopamine was so rapid that Goodall suggested precursors be administered to burn patients to insure adequate adrenergic stores. These study patients with burns of more than 40% of the body surface appear to maintain maximal or near maximal rates of catechol synthesis and utilization. Exposing these patients to a cool environment (21 C) results in a mild cold stress, ordinarily a stimulus for the elaboration of additional catecholamines. Patients who eventually survived responded by increasing heat production as a result of increased elaboration of catecholamines. In contrast, the patients who lacked catecholamine reserve or tissue responsiveness to these mediators failed to generate additional heat to maintain heat balance in the 21 C environment and became hypothermic, with the decrease in catecholamine excretion reflecting a predictable hormonal response during hypothermia. All of these nonresponding patients subsequently died from complica-

TABLE 13. *Metabolic Rate, Caloric and Nitrogen Intake, Nitrogen Excretion, and Basal Insulin in Normal and Injured Man*

Subject	Nitrogen Excretion (gm/m²/Day)	Metabolic Rate (Kcal/m²/Day)	Nitrogen Intake (gm/m²/Day)	Non-Protein Caloric Intake (Kcal/m²/Day)	Insulin (μU/ml)
Controls-Fed					
1	7.90	888	9.00	1196	20.7
1c*	8.06	769	9.12	810	17.5
4*	7.52	808	9.00	1014	13.8
5*	8.23	871	10.10	1104	14.0
6*	7.70	889	8.71	1133	9.4
7*	8.52	835	10.50	990	17.0
Controls-Fasting					
1b*	5.33	750	0	0	9.5
2*	4.33	823	0	0	11.0
3b*	8.93	919	0	0	12.5
Patients					
1a	8.79	2030	6.52	2258	6.0
1b	11.42	1545	20.20	2468	24
2	11.52	1718	5.68	1392	9.5
3a	14.0	2244	12.38	1436	17.5
3b	10.1	1404	13.00	1893	13.0
4	13.10	1524	15.84	1654	14.5
5	10.40	1312	9.51	1187	24
6	7.92	1495	0	913	37
7	12.44	1680	0	548	19.5
8	7.99	1022	4.34	850	13.5
9	15.74	1608	0	515	36
10	10.48	2200	8.01	2460	40
11	9.9	1526	8.50	1280	61
12	7.5	2026	7.75	2006	25
13a	8.6	1375	12.2	2009	17
13b	4.4	1375	12.2	2009	31
14a	6.0	1207	15.8	2055	23
14b	4.7	1207	15.8	2055	80
15a	9.7	1716	13.6	1934	24
15b	6.5	1716	13.6	1934	49
16a	12.8	1658	17.1	1907	17.5
16b	9.9	1658	17.1	1907	23.7
17a	15.1	1616	16.1	1466	10.7
17b	10.7	1666	16.1	1466	20.1
18a	9.1	906	13.5	1458	26
18b	7.3	906	13.5	1458	42
19a	15.6	1440	17.5	1733	9.2
19b	12.5	1440	17.5	1733	28
20a	15.0	1894	13.8	1560	12.0
20b	16.0	1894	13.8	1560	15.5
21a	12.7	1878	22.0	2450	30
21b	9.5	1878	22.0	2450	46
22a	12.6	1794	14.0	1841	16.8
22b	8.0	1794	14.0	1841	45.6

* Subjects described in Table 4.

tions of their injury. Like Cannon's sympathectomized cats, the nonresponders lacked homeostatic reserve, for injury had reset their rate of energy production at a maximum level. Additional sympathetic nervous system reserve was unavailable for catecholamine-mediated responses to cooling, infection, or hemorrhage.

The third factor which interacts with the internal post-traumatic reset in metabolic activity is associated injuries and infection. Burn patients with associated injuries, such as fractures, head injuries, or visceral trauma, have metabolic rates which exceed values predicted for their burn wound size. This, however, only occurs if the burn injury is smaller than 40% of the total body surface and their metabolic activity is not at maximal levels. Associated injuries in patients with large burns exert little or no additional metabolic effect, for the thermal injury has already caused a maximal stress response.

Infection is commonly associated with a febrile response and an increase in metabolic rate.[9] This is true in patients with small burns who have "calorigenic reserve," for infection will cause an additional expenditure of energy which abates as the septic process is controlled. Sepsis evokes a sympathoadrenal response,[14,24,25] but the

TABLE 14. *Mathematical Relationships Between Energy Production, Food Intake, Nitrogen Excretion, and Basal Insulin*

N_{IN} = Nitrogen Intake (gm/m²/Day)
N_{EXC} = Nitrogen Excretion (gm/m²/Day)
N_{BAL} = Nitrogen Balance [$N_{IN} - N_{EXC}$] (gm/m²/Day)
MR = Metabolic Rate (Kcal/m²/Day)
NPC = Non-Protein Caloric Intake (Kcal/m²/Day)
BI = Basal Insulin (μU/ml)
$p < 0.05$, Factors listed on order of F-Ratio

$$N_{EXC} = -1.398 + 0.4153\ N_{IN} - 0.004530\ NPC - 0.07746\ BI + 0.01696\ MR - 0.000004\ MR^2$$

n = 35 (Eight values with error > 25 per cent were eliminated from Table 13)
$r^2 = 0.8246$

$$N_{BAL} = -3.830 + 0.6072\ N_{IN} - 0.006599\ MR + 0.004376\ NPC + 0.05570\ BI$$

n = 43
r = 0.9001
(All data listed in Table 13)

physiologic effects of the catecholamines appear to be blunted as a consequence of the infection in patients with large thermal injury, a response similar to pharmacologic competitive adrenergic blockade. The marked increase in catecholamines in the blood and urine of our septic patients was accompanied by an inappropriately low physiologic response to these neurohumoral mediators, resulting in inadequate heat production, increased skin blood flow, and progressive hypothermia. While these high levels of catecholamines may represent a massive response of the sympathetic nervous system to infection associated with tissue refractoriness, these infected patients are similar to others with large thermal injury with limited catecholamine stores and minimal homeostatic reserve. This large increase in excretion of urinary catecholamines is observed when the tissue inactivation process is inhibited, as seen with receptor blockade, which results in transmitter overflow[34] and a diminution of the end-organ physiologic response. We have not observed in nonseptic burn patients the very high plasma and urine concentrations of catecholamines measured in the infected patients.

Associated with the hypermetabolic response following injury is the negative nitrogen balance and loss of intracellular constituents. Like the post-traumatic hypermetabolism, the magnitude of the negative nitrogen balance is related to the extent of injury.[35] Studies in burn patients suggest that increased sympathetic activiy may result in a hormonal environment which favors proteolysis, gluconeogenesis, and ureagenesis.[54] Catecholamines stimulate glucagon elaboration[17] and suppress insulin release,[39] a hormonal setting which favors hepatic glucose production and ureagenesis.[44] Sympathetic activity returns to normal with closure of the burn wound, and at that time a normal relationship between insulin, catecholamines, and glucagon is re-established, associated with weight stabilization and weight gain.

Those factors which affect protein metabolism in injured man can be identified by inspection or analysis of our data. First, the influence of dietary factors: protein intake increases excretion of urinary nitrogen, and nonprotein calorie intake decreases nitrogen excretion. The nitrogen conserving effect of calorie intake is in part mediated by insulin stimulation, and a variety of metabolic studies confirm the positive correlation between protein sparing and insulin during calorie administration following injury. On the other hand, our data indicate that metabolic rate describes an effect on protein metabolism which is antagonistic to the anabolic activity of insulin. Nitrogen metabolism appears to be determined by the interaction between insulin (the dominant anabolic hormone) and sympathetic activity, as measured or expressed by catecholamine excretion rate, metabolic rate, or glucagon. Thus, a specific relationship between nitrogen balance and nitrogen and nonprotein calorie intake exists in injured man, if an adjustment is made for the various factors which alter insulin levels (such as the proportion of fat and carbohydrate in the nonprotein component of the diet, the route of food administration, and the exogenous administration of insulin) and the level of sympathetic activity in the patient. Finally, protein and calorie intake does not diminish the hypermetabolic response to injury, but feeding the patient minimizes or prevents severe protein wasting which may impair organ function.

Increased sympathetic activity occurs following burn injury but is also characteristic of major trauma,[15] cold exposure,[31] severe exercise,[48] infection,[25] shock,[49] hypoxia,[40] anxiety,[43] and other stresses.[45] The sympathetic nervous system directs the mobilization of substrate from tissue stores to provide specific body fuels by having direct effects on body tissues, by altering circulation, and by interacting with other hormones to regulate substrate flow.[30,41] In addition, catecholamines stimulate calorigenesis by a direct effect on cellular metabolic activity to increase heat production.[23] As the stress decreases, sympathetic activity falls to normal, and, with parasympathetic activity, substrate is directed into tissue synthesis and energy storage. Early physiologists recognized this interaction and characterized the sympathetic nervous activity as catabolic, directing the expenditure of energy, and the parasympathetic activity as anabolic, conserving and restoring body fuel.[2]

What then directs and regulates the sympathetic response following thermal injury? The reflex arc is composed of nervous and/or humoral afferent stimuli to the hypothalamus, which in turn initiate responses along sympathetic and motor efferent pathways.[22,32] Stimulation of the ventral medial nucleus of the hypothalamus in animals produces increased sympathetic activity associated with hyperthermia, hyperglycemia, hyperglucagonemia, and insulinopenia.[16] This and other related hypothalamic nuclei integrate the function of the auto-

nomic nervous system and regulate body temperature, the flow of energy substrates, metabolic rate, and other endocrine functions in a coordinated manner. The metabolic control center of the hypothalamus is closely integrated with the activity of the thermal regulatory centers, specifically with the posterior area described by Isenschmidt and Krehl, which regulates the cold response, and some authors have suggested that this thermal regulatory area and the sympathetic center are the same.[3]

Burn patients appear to have reset their thermal regulatory set-point upward, thus increasing the discharge of sympathetic impulses to stimulate heat production and substrate mobilization in order to maintain a new and elevated core temperature. Burn patients increase metabolic rate in a cool environment at core and skin temperatures above the set points recorded for normal man.[51] If burn patients are allowed to control the ambient temperature, they select "comfort" environments between 28 and 35 C and maintain elevated core and skin temperatures while subjectively comfortable.[55] Fasting blood glucose is above normal levels following injury, and the hyperglycemia is related to the extent of the injury and the increased catecholamine excretion rate. Fasting levels of growth hormone are also elevated above control values in spite of hyperglycemia.[38] Afferent neural or hormonal stimuli from the injury appear to influence hypothalamic centers to elevate central temperature (and possibly metabolic) set point, increasing sympathetic nervous system activity, and resulting in the hypermetabolism characteristic of thermal injury.

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Discussion

Dr. Timothy S. Harrison (Ann Arbor, Michigan): I would like to emphasize two aspects of their data which I consider particularly important.

The first deals with the observation that beta adrenergic receptor blockade eliminates the hypermetabolism of burned patients. This establishes that the hypermetabolic response to the burn injury is, in fact, mediated by the catecholamines, something which has been strongly suggested but not conclusively proved up until this time.

The second point of emphasis is that in burn patients in whom catecholamines are exhausted, there is insufficient precursor, these formerly hypermetabolic patients will, in fact, die. This is a definable source of burn mortality, and one which can be influenced favorably as Goodall and more recently, Dr. Wilmore have shown, by the administration of the appropriate precursor, dopamine or its equivalent.

If I may, I will show one slide briefly, (slide) which is a photomicrograph of the myocardium, and shows here a focal necrosis. This type of lesion can be produced by catecholamines in any species in which it is attempted.

This lesion also, interestingly enough, has been found in pheochromocytoma patients in a recent study from the Mayo Clinic. This particular section represents none of these situations, however, but, in fact, is the myocardium of a hypermetabolic burn patient with prolonged catecholamine hypersecretion. This patient died! These lesions were described, about 20 years ago, by Dr. Carl Moyer before this Association. He felt confident that this was a source of major burn mortality about which very little could be done. We feel the catecholamine hypersecretion was implicated strongly in this patient's death. Therefore, with a hyperreactive adrenergic nervous system one can define another source of burn mortality about which very little has been done therapeutically.

In the past 20 years nothing has altered the mortality from major thermal burns. I think insights such as those provided by the work described this afternoon will enable us to be more effective toward these patients than we have been up until now.