OBJECTIVE EVALUATION OF CUTANEOUS THERMAL SENSITIVITY

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W. van Beaumont

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J.C. Strand

for
THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
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Department of Physiology

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Regional Sweating Responses to Contralateral Cooling

SYNOPSIS

Sensations of humans to changes in environmental temperature are difficult to express objectively in quantitative terms. Measurable effects of ambient thermal stress on heart rate and respiration, par example, require gross changes in intensity and time and are quite unreliable because of interference through uncontrollable mental excitation. The present investigation was undertaken to study the possibility of obtaining reliable and objective quantitative responses under conditions where presumably only temperature changes in localized cutaneous areas evoked measurable changes in remote sudomotor activity. The fact that in this investigation both male and female subjects were studied, provided a first opportunity to evaluate objectively whether a sex difference in thermal sensitivity exists.

Because of the innovative nature of this study, more questions arose than were answered. On the other hand, the feasibility to obtain valuable information of human thermal sensitivity became quite apparent. A continued effort with the present technique seems certain to provide more useful information for establishing comfort and safety limits for humans in different thermal environments under various conditions of stress.

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CHAPTER I

INTRODUCTION

The hypothalamus, the neural site for integration of thermosensory input, is generally considered to be the controller of thermal eccrine sweating. However, various peripheral events have been clearly demonstrated to influence the regulation of eccrine sweating. These peripheral modifiers have been increasingly scrutinized for the last 50 years.

Investigators have observed in man the effects of partial body heating and cooling in a hot environment, but the conclusions and assertions drawn from these studies are varied and often conflicting. Apparently, the contribution and importance of peripheral events to thermoregulatory control are not yet fully understood; specifically, the nature of the mechanism(s) causing sweat rate reduction as a result of cutaneous cooling has not been fully elucidated. The modifications in sweat rate, skin temperature, blood flow, receptor activation and other related factors produced by cutaneous cold stimulation are pertinent to understanding the nature of thermoregulatory control. This present study was designed and performed with the intent of more clearly describing the nature of the reflex sweating response to remote cutaneous cooling.

Historical Background

Filehne (1910) was the first to record that regional cutaneous cooling caused a generalized reduction of sweating. Because thermal sweating was diminished by placing the hands in cold water and no change in rectal temperature resulted from this action, he reasoned that cutaneous thermal receptors initiated a reflex mediated by the central thermoregulatory apparatus. In experiments designed to identify the mechanism involved, Hill (1921) observed that, by occluding the circulation to the arms before hand cooling, the reduction in sweating over the rest of the body did not occur. Hill maintained that the whole body sweat reduction during hand cooling must be due to blood cooling. Burch and Sodeman (1944) tested Hill's conclusions by cooling the forearm of subjects in a hot environment both before and during arterial occlusion of the cooled limb, and agreed that the effects produced by regional cooling must result mainly from changes in normal body temperature and not from any significant neural influences.

In challenge to Hill's assertions, Kuno (1956) occluded the circulation to a hand, immediately immersed that hand in water at 10^{o} C, and observed a marked suppression in whole body sweating for 5 minutes. When the occlusion was removed, but the hand still remained in the water, a gradual decrease in sweating was observed to last an additional 5 minutes. Further, inhibition of sweating lasted about 10 minutes after withdrawl of the hand from the cold water. Kuno considered the observed response to be a nervous reflex elicited by cold stimulation because the

initial inhibition of sweating was sudden and transitory in nature.

Since the response to regional cooling was to be regarded as a neural reflex, attempts were made to identify the pathways, both afferent and efferent. Because the response to regional cooling was a diminution of whole body sweat rate, the efferent neural pathway certainly involved an alteration in generalized sympathetic nervous discharge to the sweat glands. However, the afferent neural pathway remained elusive. Brebner and Kerslake (1961a), like Hill (1921) and Burch and Sodeman (1944), found that skin cooling of legs distal to circulatory occlusion resulted in no depression of forearm sweat rate. These investigators concluded that their results failed to demonstrate the existence of thermoreceptors in the skin of the legs, which contributed to the control of forearm sweat rate. However, later the same year Brebner and Kerslake (1961b) reported that cyclic heating of the trunk influenced the forearm sweat rate. Because of the 3.5 second or less time delay between each stimulus and response, they concluded that their findings demonstrated the existence of a neural pathway whereby thermoreceptors in the skin of the trunk could influence activity of the sweat glands in the forearm.

By examining three subjects, a normal man, a lumbar sympathectomized man and a paraplegic man (section at T-12), Rawson and Hardy (1967) observed changes in trunk sweating due to leg cooling, having previously arrested the circulation to the legs. Trunk sweating was depressed in the normal and lumbar sympathec-

tomized subjects, but not in the paraplegic subject whose sympathetic innervation was intact. They concluded that the reflex was primarily neurogenic, and that intact somatosensory nerves were essential if the reflex was to be observed. The identification of the somatosensory nerves responsible for the reflex response to regional cooling remains obscure. During the same year, Bullard, Banerjee and Mac Intyre (1967) performed regional cooling experiments on sweating subjects. Cooling the area distal to limb occlusion sharply diminished the sweat rates in other areas of the body. Contrary to Hill (1921), Bullard, Banerjee and Mac Intyre (1967) substantiated the neural reflex hypothesis. Subsequently, Banerjee, Elizondo and Bullard (1969) investigated the reflex response of human sweat glands to different rates of skin cooling. They ascertained that both the size of the skin area cooled and the rate of change in temperature applied to be important in determining the magnitude as well as the duration of the reflex response.

Statement of Purpose

The present study was designed to determine the regional variations in sweating responses to remote or contralateral cooling of small skin areas. Further, an attempt was made to correlate these responses with the period of latency to onset of whole body sweating by exposure to a hot environment. Specifically, the following hypotheses were formulated to be tested experimentally:

1. The immediate response of the eccrine sweat glands to

contralateral cutaneous cooling is mediated by a neural reflex.

2. The responses of the sweat glands in the skin of the forearm, calf and over the scapula are quantitatively similar, irrespective of the site of contralateral skin area cooled, when the size of the area cooled is constant.
3. The response of the sweat glands to contralateral skin cooling is quantitatively similar in men and women.
4. The response of the sweat glands to contralateral skin cooling in females is influenced by the menstrual cycle.
5. The threshold and latency to the onset of eccrine sweating produced by total body heating differs between men and women, and may be used to predict responsiveness to local skin cooling.

CHAPTER II

METHODS

Subjects

Four male and 4 female subjects participated in these experiments, each subject being studied on 6 different occasions. Prior to these experiments, the protocol was approved by the human research committee. Each subject was required (1) to submit to a physical examination by a physician, (2) to take and pass a standardized treadmill stress test designed to detect possible cardiovascular pathology, and (3) to sign a consent form giving permission to allow him- or herself to be used as a subject. In addition, subjects were requested to avoid all medication during the entire 2-3 month period when the experiments were being conducted. The age, physical characteristics and other biometric data of each subject are presented in Table 1.

Materials

During each experiment, sweat rates from the skin of the right lateral calf, right medial forearm and over the right scapula were measured continuously and simultaneously by resistance hygrometry (Bullard, 1962; van Beaumont, Bullard and Banerjee, 1966; van Beaumont, 1969). An additional sweat capsule was placed on the left medial forearm in all cases just

TABLE 1

AGE, PHYSICAL CHARACTERISTICS AND
BIOMETRIC DATA OF SUBJECTS

	Subject	Age (years)	Height (cm)	Weight (kg)	BSA[a] (m^2)	% of BSA cooled by thermode	% of BSA cooled by WHC[b]	Average T_A[c] (°C)
Male	R. W.	24	175	83	1.99	0.4	2.67	48.8
	N. B.	23	192	94	2.25	0.4	2.38	44.8
	J. D.	23	187	92	2.19	0.4	2.38	49.1
	J. K.	23	181	66	1.84	0.4	2.75	45.0
	mean	23.2	184	84	2.07	0.4	2.55	46.9
Female	M. M.	28	169	63	1.71	0.5	2.39	47.8
	E. S.	24	178	67	1.83	0.4	2.22	50.2
	M. S.	25	173	60	1.71	0.5	2.82	48.5
	G. T.	24	164	52	1.54	0.5	2.67	46.8
	mean	25.2	171	60	1.70	0.5	2.52	48.3

[a]Body Surface Area.

[b]Whole Hand Cooling.

[c]Average environmental temperature of 4 experiments for each subject.

prior to the left whole hand cooling procedures. Sweat capsules were held in place using standard ECG electrode rubber straps. Similarly, skin temperatures (T_S) of the right lateral calf, over the right scapula, right medial forearm, right medial thigh, right chest, and forehead were continuously measured by thermistors also held in place with rubber straps. Rectal temperature (T_R) of each subject was continuously measured during 1 of the 4 experiments by insertion of a thermistor 12 cm into the rectum of the subject. The T_R was continuously measured in all experiments where threshold of sweating was determined. Thermode temperature (T_T) was continuously measured by a thermistor taped with a light-weight adhesive material to the surface of the thermode in all experiments. Sweat rates, T_R, T_T and T_S were simultaneously recorded on a Honeywell visicorder.

The thermode used in this study was a rectangular-shaped copper box with 2 inlets and 1 outlet through which water was pumped to maintain any desired temperature. The surface area of the thermode which contacted the skin measured 81 cm^2. In two subjects, 1 male and 1 female, contact of the entire surface of the thermode with the scapular skin area was not complete because of body contour. In those cases the position of the thermode was adjusted to produce maximum skin contact, i.e., at least 75% of the surface of the thermode contacted the skin. Problems of this type were not encountered on the other two skin areas cooled by the thermode. Except during cooling intervals, the temperature of the thermode was maintained at the same temperature as the underlying skin. After initiation of a cutane-

ous cooling period, changes in thermode temperature were 75% complete by the end of 30 seconds, 95% complete by the end of the first minute and 100% complete by the end of 90 seconds in all cases.

Mean skin temperature ($\overline{T}_S$) was calculated as the sum of the six skin temperatures weighted according to the fraction of total skin surface each area represented (Hardy and Du Bois, 1938a). The following formula was applied:

$$\overline{T}_S = 0.07T_1 + 0.19T_2 + 0.175T_3 + 0.175T_4 + 0.20T_5 + 0.19T_6$$

T_1 through T_6 represented skin temperatures of the forehead, arm, chest, back, lower leg and thigh, respectively. Mean body temperature ($\overline{T}_B$) was calculated as follows:

$$\overline{T}_B = 0.8T_R + 0.2\overline{T}_S$$

In this formula, the rectal (core) temperature and mean skin temperature were weighted by the corresponding coefficients according to the influence each temperature contributed to $\overline{T}_B$ (Hardy and Du Bois, 1938b).

Hand area was determined by covering the left hand with transparent surgical adhesive. After the adhesive was cut away from the hand and mounted on a flat surface, the surface area was measured using a compensating polar planimeter.

Sweat rates were quantitated by measuring the area between the baseline and cyclic sweat rate tracing in 1-minute intervals using a compensating polar planimeter. The area measured was equated to a sweat rate and recorded as milligrams of sweat per square centimeter of skin surface per minute ($mg/cm^2/min$).

Sweat rate data were evaluated statistically using analy-

sis of variance (Sokal and Rohlf, 1969). Sweat rates during thermode-induced cutaneous or whole hand cooling were individually compared to the mean of three successive 1-minute control values just prior to cooling. Compared to their respective controls, the responses were considered to be statistically significant at the 0.05 level of confidence. The analysis of variance cited above may be considered not strong since only three values comprised the control sample in each case. In the threshold of sweating experiments, the data for women from days 1 and 15 of the menstrual cycle were compared using a 2-tailed Student's T-test for paired observations. The data from the men were compared to each of the two groups of women using a 2-tailed Student's T-test for unpaired observations (Steel and Torrie, 1960). To compare the latency to threshold for whole body sweating with responsiveness to thermode cooling, the standard correlation coefficient for paired data was employed (Steel and Torrie, 1960).

Protocol

The subjects participated in two different but related sets of experiments. In the first set, each subject was studied 4 times at approximately 2-week intervals. The women were tested twice on the first day of menses (day 1) and twice on the 15th day ± 2 days (midcycle). No effort was made to determine if ovulation had or had not occurred by the time of the midcycle test. Scheduling of experiments at the same time of day for each subject was not possible. During the experiments, men wore lightweight cotton shorts and women wore 2-piece bathing suits. The

ambient temperature (T_A) was held constant during each experiment to produce moderate sweat rates in the subject (0.2-0.6 mg/cm^2/min) from those areas where sweat output was measured. However, a different T_A (range = 43-52^o C dry bulb) was necessarily selected for each subject, because the same T_A produced sweat rates which were dramatically different among all subjects. Relative humidity was 30 ± 5% and turbulent wind velocity, measured by anemometer, was 0.12 ± 0.02 m/sec.

Within 5 minutes after the subject entered the hot room and sat on a wooden chair, the sweat capsules and thermistors were strapped to the various skin surfaces. The thermode was strapped to the left medial thigh, i.e., contralateral to the sweat capsules and thermistors. Prior to the experimental procedure, the subject was allowed a minimum of 30 minutes in the heat to permit stabilization of sweat rates. Following the intervals of thigh cooling, the thermode was moved to the scapula in two experiments and to the medial forearm in the other two experiments. For the duration of the cutaneous cooling experiment (2-3 hours), each subject sat quietly in the heat.

The experimental protocol consisted of 3 sequential thermode cooling periods of 5 minutes duration on each of two skin areas. The temperature of the thermode was progressively reduced during the 3 exposures in any one area, although the temperature was held constant during each separate cooling episode. A mild (26-29^o C), moderate (17-22^o C) or severe (9-13^o C) thermal stimulus was applied to the skin via the thermode. Each cooling period was separated by at least 5 minutes of non-cooling by

circulating water through the thermode so that skin temperature was maintained at the same level as that measured prior to the cooling period. Control thermode temperature was determined by the temperature of the skin contralateral to the thermode; e.g., control T_T applied to the thigh was determined by the T_S of the contralateral thigh. The seventh and last cooling period of each experiment, left whole hand cooling, was accomplished by having the subject submerse his hand to the wrist in a basin of water for 5 minutes at 32-33° C or 27-28° C which was 5 or 10° C, respectively, below hand surface temperature. When the hand was removed from the basin, a towel was quickly wrapped around the wet limb to prevent evaporative cooling. In 2 of the 4 experiments with 2 male subjects, arterial occlusion of the left arm was initiated and maintained for 12 minutes prior to and 3 minutes during whole hand cooling. In an additional experiment with the same 2 male subjects, occlusion alone was maintained for 15 minutes. Arterial occlusion was performed by inflating a blood pressure cuff to 180 mm Hg on the left upper arm. Although the radial artery was not palpated for pulsations, this method of arterial occlusion was judged to be effective because the area distal to the pressure cuff appeared cyanotic; each subject reported the absence of pain and venous distension concomitant with an increasing numbness distal to the cuff as the occlusion progressed.

In the second set of experiments, the latency period to the threshold of sweating was determined for each of the 4 men and for 3 of the 4 women. Two experiments were performed on

each subject at 2-week intervals; both experiments on each subject were performed at the same time of day. In the case of the women, one experiment was performed on day 1 of menstruation and the other experiment during midcycle. Sweat rates and skin and rectal temperatures were measured as previously described. Wind velocity and relative humidity were similar to the previous set of experiments. The subjects, dressed in shorts (men) or bathing suits (women), entered the environmental chamber and sat quietly for 15 minutes (T_A = 22-23° C dry bulb). The T_A was gradually increased until sweating was initiated; threshold of sweating (whole body) was arbitrarily determined to be the initial detection of cyclic sweat gland activity from any one of the three skin areas monitored by sweat capsules.

CHAPTER III

RESULTS

Sweat Rate Responses to Contralateral Cooling

Cutaneous cooling, produced both with the thermode and with whole hand cooling, often resulted in an immediate diminution of sweat rates in remote skin areas (Figures 1, 2 and 3). Since the distance between the sweat capsules and humidity sensors caused a delay of 7 seconds for any change in sweat rate to be recorded, and since the recorded response following the initiation of cutaneous cooling occurred within 10 seconds, the reduction of sweat rates occurred within 3 seconds following the stimulus. Therefore, a positive response was defined as any reduction in sweat rate which occurred within 10 recorded seconds following the initiation of contralateral cutaneous cooling, induced either by thermode or by whole hand cooling. When a positive response did occur, an initial depression in cyclic sweat gland activity was most often observed.

Tables 2 and 3 show the significance of positive sweat rate responses due to thermode and whole hand cooling in 4 men and 4 women, respectively. Sweat rate depression did not always occur in response to thermode cooling (0.4% of body surface area); when a response did occur, the duration varied from 1 to 5 minutes. Following the local cooling, the recovery period allowed the sweat

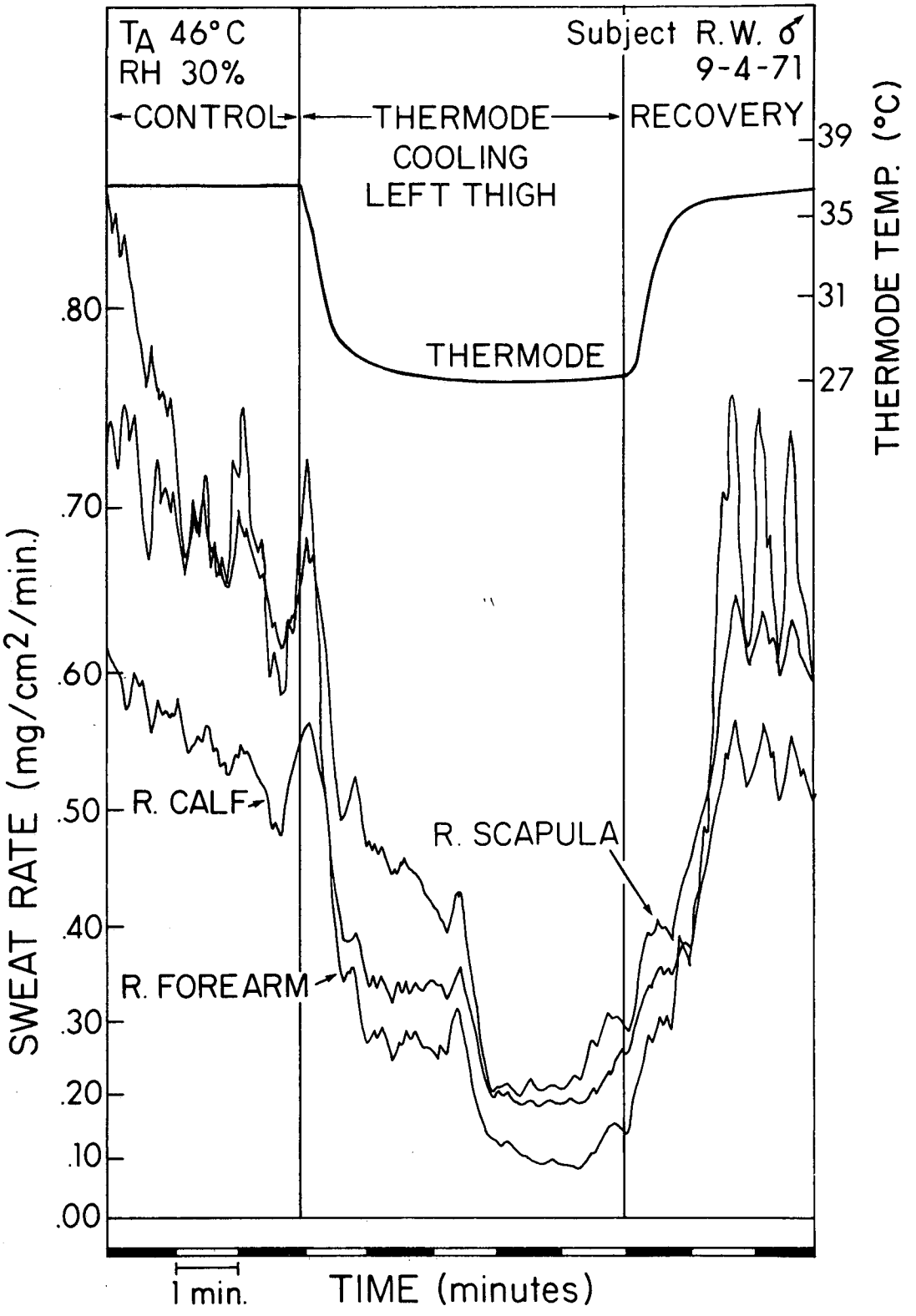

Figure 1. Changes in sweat gland activity due to thermode cooling on the medial left thigh of male subject.

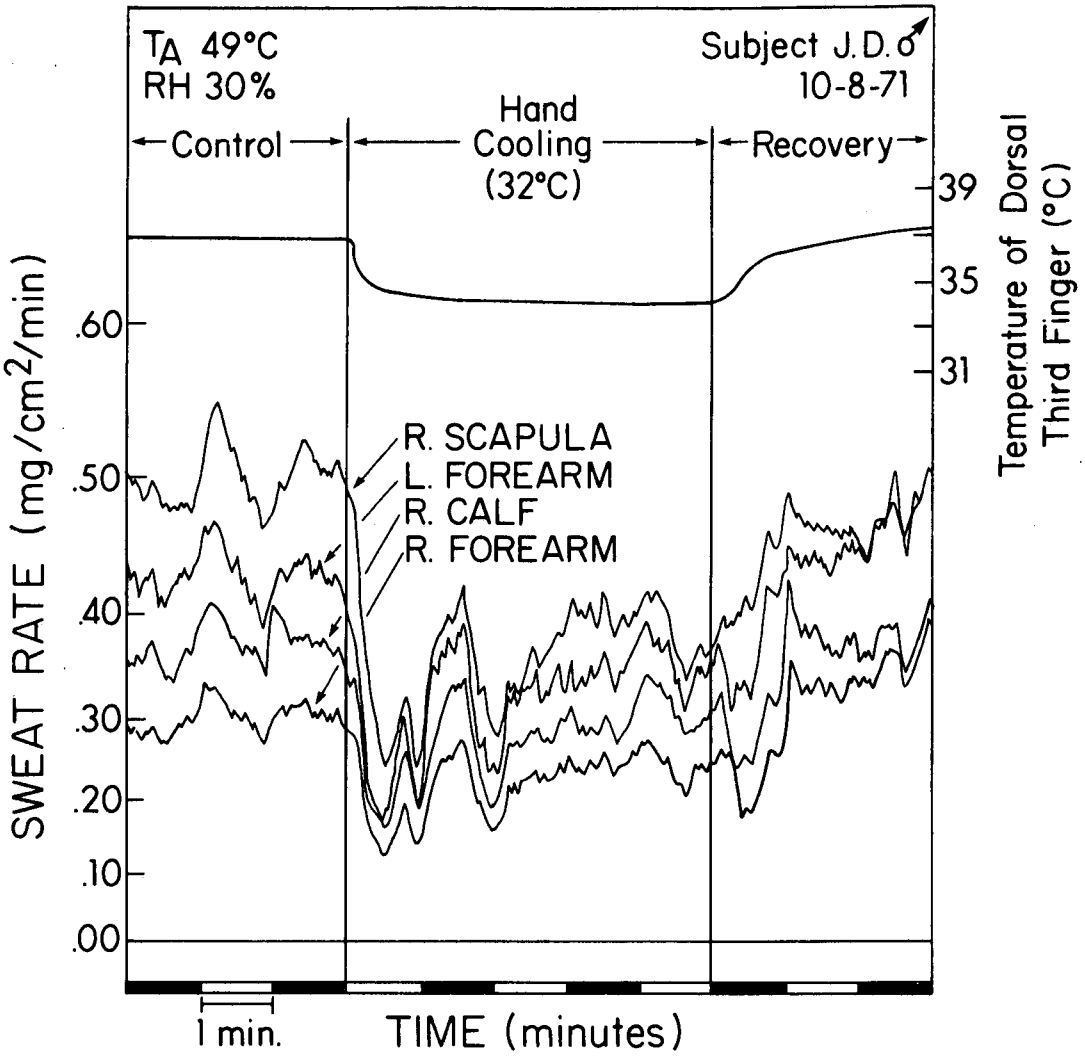

Figure 2. Changes in sweat gland activity due to whole left hand cooling at 32°C in a male subject.

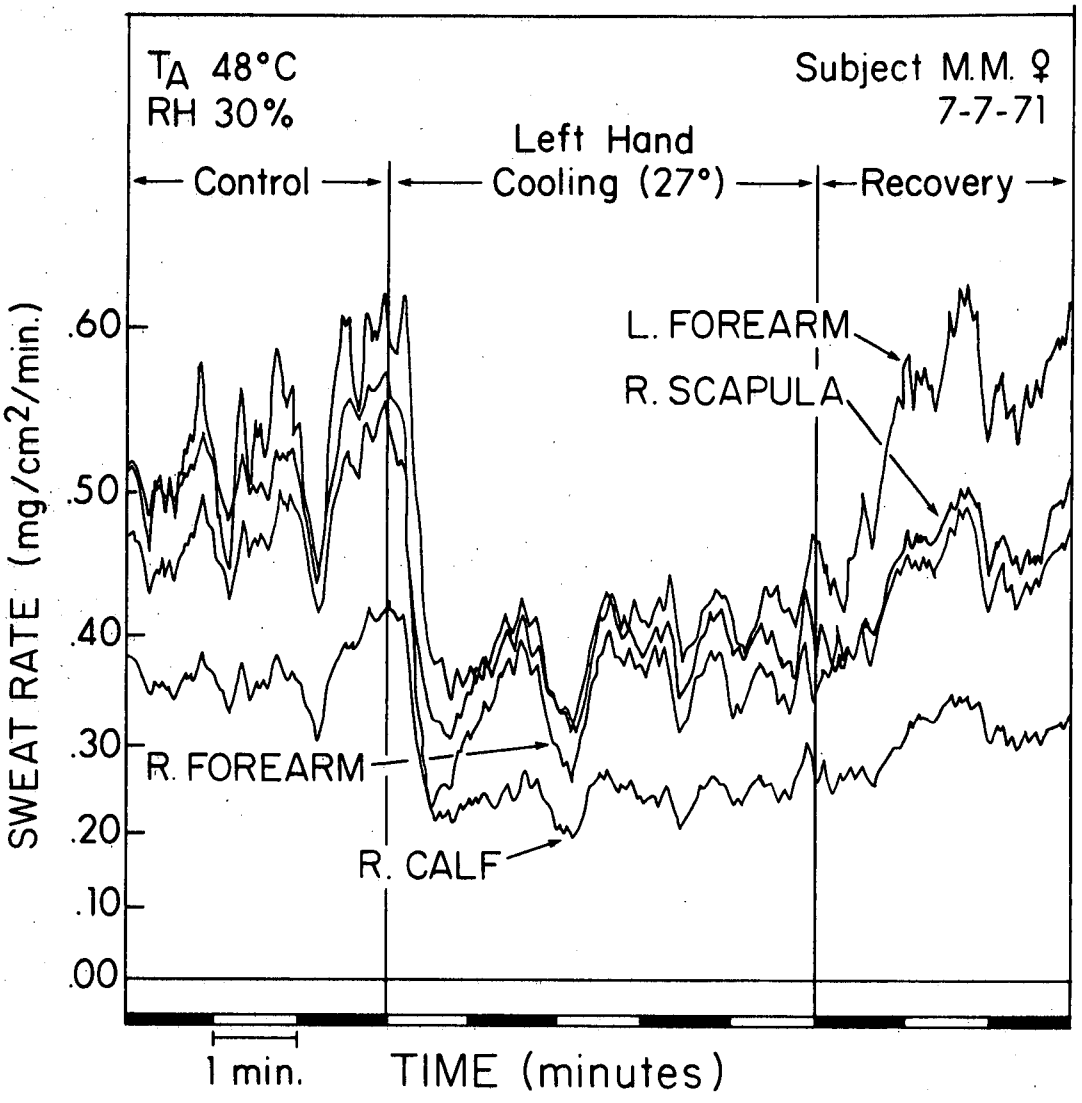

Figure 3. Changes in sweat gland activity due to whole left hand cooling at 27°C in a female subject.

TABLE 2

MEAN AND RANGE OF P VALUES FOR POSITIVE RESPONSES DUE TO CONTRALATERAL CUTANEOUS COOLING IN 4 MEN

Effect of left thigh cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance		
		R. Calf	R. Scapula	R. Forearm
R. W.	26	NS	NS	NS
R. W.	26	NS	NS	NS
R. W.	27	0.01 (0.005-0.05)	0.0005 (0.0005)	0.0025 (0.0025-0.01)
R. W.	25	NS	NS	NS
N. B.	26	NS	NS	NS
N. B.	26	NS	0.005 (0.0025-0.025)	NS
J. D.	26	NS	NS	0.005 (0.0025-0.01)
J. D.	26	NS	NS	NS
J. K.	19	NS	NS	NS
R. W.	19	NS	NS	NS
R. W.	19	NS	NS	NS
R. W.	20	0.025 (0.0125-0.025)	0.01 (0.025-0.01)	0.0125 (0.01-0.025)
R. W.	17	0.0125 (0.0025-0.025)	0.0125 (0.005-0.05)	NS
N. B.	20	0.01 (0.005-0.0125)	0.025 (0.0125-0.05)	NS
N. B.	20	0.05 (0.01-NS)	0.05 (0.01-NS)	NS
N. B.	20	0.01 (0.01-NS)	0.005 (0.0025-NS)	0.05 (0.05-NS)
J. D.	21	0.05 (0.025-NS)	0.05 (0.05-NS)	NS
J. D.	21	NS	NS	NS
J. D.	18	NS	0.01 (0.01-0.05)	NS
J. K.	21	NS	NS	NS
R. W.	9	0.025 (0.025-NS)	0.0125 (0.0125-NS)	0.025 (0.025-NS)
R. W.	11	NS	NS	NS
R. W.	10	NS	NS	NS
J. D.	12	NS	0.05 (0.05-NS)	0.05 (0.05-NS)
J. K.	12	0.01 (0.0025-0.025)	NS	NS
J. K.	11	0.025 (0.0125-0.05)	0.025 (0.01-0.05)	0.0125 (0.01-0.025)

TABLE 2--Continued

Effect of left scapula cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance		
		R. Calf	R. Scapula	R. Forearm
R. W.	27	0.05 (0.025-NS)	0.025 (0.025-NS)	0.05 (0.025-NS)
J. D.	27	0.01 (0.01-NS)	0.05 (0.05-NS)	0.05 (0.05-NS)
J. K.	27	0.05 (0.05-NS)	0.05 (0.05-NS)	NS
R. W.	20	NS	NS	NS
J. D.	21	0.01 (0.005-NS)	0.01 (0.005-0.05)	0.01 (0.01-NS)
R. W.	10	0.0125 (0.0125-NS)	0.0125 (0.0125-NS)	0.025 (0.0025-NS)
Effect of left forearm cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance		
		R. Calf	R. Scapula	R. Forearm
J. K.	24	NS	NS	0.05 (0.05)
R. W.	21	0.005 (0.005-0.0125)	0.01 (0.01-0.05)	0.05 (0.025-NS)
R. W.	22	NS	NS	NS
R. W.	17	NS	0.01 (0.01)	NS
J. K.	18	NS	NS	NS
R. W.	12	0.0025 (0.0005-0.01)	0.005 (0.0025-0.005)	0.005 (0.0025-0.01)
N. B.	11	NS	--	NS
J. D.	11	NS	0.01 (0.005-0.01)	NS
J. K.	10	NS	NS	NS

TABLE 2--Continued

Effect of left whole hand cooling on remote sweat rates					
Subject	Water Temperature (°C)	Significance			
		R. Calf	R. Scapula	R. Forearm	L. Forearm
R. W.	26	0.05 (0.01-0.05)	0.0005 (0.0005)	0.01 (0.005-0.025)	0.0125 (0.0125-NS)
R. W.	27	NS	NS	NS	NS
N. B.	27	NS	NS	NS	NS
N. B.	26	NS	NS	NS	NS
J. D.	27	0.0025 (0.0025-0.005)	0.0025 (0.0025-0.005)	0.0025 (0.0025)	0.0005 (0.0005-0.0025)
J. D.	27	0.01 (0.01-0.05)	0.025 (0.0125-0.05)	0.025 (0.025-NS)	0.025 (0.01-0.05)
J. K.	26	0.01 (0.01-0.05)	0.0005 (0.0005)	0.025 (0.01-0.025)	0.05 (0.025-0.05)
J. K.	26	0.05 (0.05-NS)	0.05 (0.05-NS)	NS	NS
J. D.	32	0.01 (0.005-0.01)	0.01 (0.005-0.0125)	0.01 (0.005-0.025)	0.0025 (0.0025-0.005)
J. D.	32	NS	0.05 (0.05-NS)	0.025 (0.025-NS)	0.0125 (0.0125-0.05)
J. K.	32	0.025 (0.025-NS)	0.05 (0.05-NS)	0.05 (0.05-NS)	0.05 (0.05-NS)
J. K.	32	0.025 (0.025-NS)	NS	NS	0.025 (0.025-NS)

TABLE 2--Continued

Effect of left whole hand cooling during and after left arm occlusion on remote sweat rates					
Subject	Water Temperature (°C)	Significance			
		R. Calf	R. Scapula	R. Forearm	L. Forearm
R. W.	26 DO[a]	0.05 (0.05-NS)	NS	0.05 (0.05-NS)	0.05 (0.05)
	AO[b]	NS	NS	NS	NS
R. W.	27 DO	0.05 (0.05-NS)	NS	0.05 (0.05-NS)	0.005 (0.005-0.025)
	AO	0.05 (0.0125-0.05)	0.005 (0.0025-0.0125)	NS	NS
N. B.	26 DO	NS	0.05 (0.025-0.05)	NS	NS
	AO	NS	NS	NS	NS
N. B.	26 DO	NS	NS	NS	0.025 (0.01-0.05)
	AO	NS	NS	0.05 (0.05)	NS

[a]During occlusion

[b]After occlusion

When statistical significance is lost by minute 2 of the cooling period, the significance for minute 1 with the range of values are given. When statistical significance is lost by minute 3 of the cooling period, the most significant value from minutes 1 and 2 with the range of values are given. When statistical significance is lost by minute 4 or 5 of the cooling period, the most frequently occurring value with the range of values are given.

Ranges of significant values are given within parentheses.

TABLE 3

MEAN AND RANGE OF P VALUES FOR POSITIVE RESPONSES DUE TO CONTRALATERAL CUTANEOUS COOLING IN 4 WOMEN DURING DAYS 1 AND 15 OF THE MENSTRUAL CYCLE

Effect of left thigh cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance-day 1		
		R. Calf	R. Scapula	R. Forearm
G. T.	25	0.01 (0.005-NS)	0.01 (0.005-NS)	0.0125 (0.0125-NS)
G. T.	20	NS	NS	NS
M. M.	20	NS	NS	NS
M. M.	21	NS	NS	NS
G. T.	11	0.05 (0.05)	0.01 (0.01-0.025)	0.025 (0.025-0.05)
G. T.	13	0.01 (0.01-NS)	0.01 (0.01-NS)	0.01 (0.01-NS)
M. M.	11	NS	NS	NS
M. S.	10	0.01 (0.005-0.025)	0.01 (0.01-0.025)	0.05 (0.025-0.05)
Effect of left scapula cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance-day 1		
		R. Calf	R. Scapula	R. Forearm
M. M.	26	NS	NS	0.025 (0.025-NS)
M. S.	26	NS	NS	NS
M. M.	22	0.05 (0.05-NS)	0.05 (0.05-NS)	0.0125 (0.0125-NS)
G. T.	10	NS	NS	0.0125 (0.0125-NS)
M. M.	11	0.05 (0.025-NS)	0.01 (0.01-NS)	0.05 (0.05-NS)
Effect of left forearm cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance-day 1		
		R. Calf	R. Scapula	R. Forearm
E. S.	25	NS	NS	NS
M. M.	19	NS	NS	NS
E. S.	17	NS	NS	NS
M. S.	20	NS	0.05 (0.025-NS)	NS
G. T.	13	NS	NS	NS
M. M.	10	NS	NS	NS

TABLE 3--Continued

Effect of left thigh cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance-day 15		
		R. Calf	R. Scapula	R. Forearm
M. M.	27	0.005 (0.0025-0.025)	0.0125 (0.0125-NS)	0.025 (0.025-NS)
G. T.	22	--	NS	NS
M. M.	21	NS	NS	NS
E. S.	21	0.01 (0.01-NS)	0.05 (0.05-NS)	NS
M. M.	12	NS	NS	NS
M. S.	13	NS	NS	NS
Effect of left forearm cooling on contralateral sweat rates				
Subject	Thermode Temperature (°C)	Significance-day 15		
		R. Calf	R. Scapula	R. Forearm
M. M.	25	NS	NS	NS
E. S.	26	0.025 (0.025-NS)	0.025 (0.025-NS)	0.025 (0.01-0.05)
G. T.	21	NS	NS	NS
M. M.	19	NS	NS	NS
E. S.	19	NS	NS	NS
M. S.	20	NS	NS	NS
G. T.	12	NS	0.025 (0.025-NS)	0.05 (0.05-NS)
M. M.	11	NS	NS	NS
E. S.	12	NS	0.005 (0.0025-0.05)	NS

TABLE 3--Continued

Effect of left whole hand cooling on remote sweat rates					
Subject	Water Temperature (°C)	Significance-day 1			
		R. Calf	R. Scapula	R. Forearm	L. Forearm
G. T.	27	NS	NS	NS	NS
G. T.	27	NS	0.025 (0.025-NS)	0.025 (0.025-NS)	0.025 (0.0125-0.05)
M. M.	27	0.005 (0.005-0.025)	0.005 (0.005)	0.025 (0.025)	0.025 (0.0125-0.05)
M. M.	26	0.0125 (0.01-0.05)	0.025 (0.01-0.05)	0.05 (0.0025-0.01)	0.005 (0.005-0.025)
E. S.	28	NS	0.05 (0.025-0.05)	0.025 (0.01-0.025)	NS
E. S.	27	NS	NS	NS	0.01 (0.005-0.05)
M. S.	27	0.01 (0.005-NS)	0.0025 (0.0005-0.01)	0.005 (0.0025-NS)	0.01 (0.01-0.025)
M. S.	28	0.025 (0.01-0.05)	0.025 (0.0125-0.025)	0.0125 (0.01-0.025)	0.01 (0.01-0.05)
		Significance-day 15			
G. T.	27	0.01 (0.005-0.01)	0.01 (0.005-0.01)	0.005 (0.005-0.01)	0.01 (0.01)
G. T.	27	NS	NS	NS	NS
M. M.	27	0.05 (0.0125-NS)	0.025 (0.01-NS)	0.025 (0.0125-NS)	--
M. M.	26	NS	NS	NS	NS
E. S.	27	0.05 (0.0125-0.05)	0.005 (0.0025-0.025)	0.005 (0.0025-0.01)	NS
E. S.	27	0.01 (0.005-0.025)	0.005 (0.0025-0.005)	0.05 (0.025-NS)	0.01 (0.005-0.0125)
M. S.	27	0.05 (0.05-NS)	0.025 (0.01-NS)	0.025 (0.0125-NS)	0.025 (0.01-NS)
M. S.	27	0.025 (0.01-NS)	0.0025 (0.0025-0.01)	0.0025 (0.0025-0.01)	0.0125 (0.01-0.05)

See Table 2 for explanation of notation.

rates to recover to pre-cooling values. Sweat rate depression consistently occurred in response to whole hand cooling (2.5% of body surface area). In most cases, the depression was significantly sustained below control levels throughout the whole hand cooling period. Following cessation of the stimulus, the depression of sweat rates continued from 1 to 8 minutes. Individual variation in response to similar stimuli between subjects was quite noticeable.

Comparison of Sweat Rate Responses Between Men and Women to Contralateral Cooling

Table 4 divides the results of the cutaneous cooling experiments into 2 groups according to sex. The thermode cooling results are treated both by (1) pooling the sweat rate data from the 3 different skin areas monitored during contralateral cutaneous cooling of 1 skin area (horizontal tabulation), and (2) by pooling the sweat rate data monitored from 1 skin area during contralateral cutaneous cooling of 3 different skin areas (vertical tabulation).

In the men, scapular skin cooling (60 observations) produced 30.0% positive responses, which was slightly more than one-half the percentage of positive responses produced by cooling either the thigh (141 observations, 55.3% responses) or the forearm (56 observations, 46.4% responses). However, the percentage of significant responses was slightly greater during scapular skin cooling (23.3%) than during either thigh or forearm cooling (20.6% and 16.1%, respectively). The percentage of positive sweat rate responses from each area was quantitatively similar (47.1-

TABLE 4

TOTAL, POSITIVE AND SIGNIFICANT SWEAT RATE RESPONSES DUE TO CONTRALATERAL CUTANEOUS COOLING IN 4 MEN AND 4 WOMEN

Area Cooled	Frequencies: R. Calf	R. Scapula	R. Forearm	L. Forearm	Totals	% positive responses of total observations	% significant responses of: positive responses	% significant responses of: total observations
MEN								
Thigh (47)[a]	47/26/10	47/26/12	47/26/ 7		141/78/29	55.3	37.2	20.6
Scapula (20)	20/ 6/ 5	20/ 6/ 5	20/ 6/ 4		60/18/14	30.0	77.8	23.3
Forearm (19)	19/ 9/ 2	18/ 8/ 4	19/ 9/ 3		56/26/ 9	46.4	34.6	16.1
Total	86/41/17	85/40/21	86/41/14		257/122/52	47.5	42.6	20.2
% positive responses of total observations	47.7	47.1	47.7					
% significant responses of: (a) positive responses	41.5	52.5	34.2					
% significant responses of: (b) total observations	19.8	24.7	16.3					
WHC (26-27° C)	8/ 8/ 5	8/ 8/ 5	8/ 8/ 4	8/ 8/ 4	32/32/18	100	56.2	56.2
WHC (32° C)	4/ 4/ 3	4/ 4/ 3	4/ 4/ 3	4/ 4/ 4	16/16/13	100	81.2	81.2
WHC-occ.[b] (26-27° C)	4/ 4/ 2	4/ 4/ 1	4/ 4/ 2	4/ 4/ 3	16/16/ 8	100	50.0	50.0
WOMEN								
Thigh (48)	47/13/ 6	48/14/ 6	48/14/ 6		143/41/18	28.7	43.9	12.6
Scapula (22)	22/ 5/ 2	22/ 5/ 2	22/ 5/ 4		66/15/ 8	22.7	53.3	12.1
Forearm (22)	22/15/ 1	22/15/ 4	22/15/ 2		66/45/ 7	68.2	15.6	10.6
Total	91/33/ 9	92/34/12	92/34/12		275/101/33	36.7	32.7	12.0
% positive responses of total observations	36.3	37.0	37.0					
% significant responses of: (a) positive responses	27.3	35.3	35.3					
% significant responses of: (b) total observations	9.9	13.0	13.0					
WHC (26-28° C)	16/16/10	16/16/12	16/16/12	15/15/10	63/63/44	100	69.8	69.8

[a] Parentheses indicate number of cooling periods unless otherwise indicated.

[b] Occlusion.

Notation example of the form 20/10/5 is as follows: first value (20) indicates total number of experiments performed; second value (10) indicates the number of positive responses; and the third value (5) indicates the number of significant responses.

47.7%) regardless of the contralateral location which was cooled. Significant reductions in sweat rate from the scapular skin during thermode cooling occurred slightly more often (24.7%) than did reductions in sweat rate of the right calf (19.8%) or of the right forearm (16.3%). In brief, thermode cooling of the scapular skin produced the highest percentage of significant sweat rate reductions, and the sweat rate of the same area produced the highest percentage of significant reductions regardless of the area cooled.

In women, thermode cooling of the forearm produced a greater percentage of positive responses (68.2%) than did cooling either the thigh or the scapular area (28.7% and 22.7%, respectively). However, the significant responses of the sweat rates to thermode cooling in all 3 areas were essentially similar, i.e., no one area responded differently from any other area. Therefore, no one area cooled generated more significant responses than any other area cooled and, likewise, no one area responded predominantly.

In summary, for 86 thermode cooling periods in 4 men, 257 sweat rates yielded 122 positive responses (47.5%) of which 52 were significant (20.2%). For 92 thermode cooling periods in 4 women, 275 sweat rates yielded 101 positive responses (36.7%) of which 33 were significant (12.0%).

Positive responses were consistently observed during whole hand cooling in all subjects. In 8 experiments on 4 men where the water temperature was 10^{o} less than hand temperature, 56.2% of 32 sweat rates were significantly reduced. In a total of 4 experiments on 2 of the 4 men, where the water temperature was 5^{o} C

less than hand temperature, 81.2% of 16 sweat rates responded significantly. The large difference in significant responses between whole hand cooling at 10^{o} C less than hand temperature and at 5^{o} C less than hand temperature may be attributed to the smaller number of observations of the latter. Therefore, more or less significant responses would more greatly influence the final result in the case of whole hand cooling at 5^{o} C less than hand temperature. In 16 whole hand cooling experiments on 4 women where the water temperature was 10^{o} C less than hand temperature, 69.8% of 63 sweat rates were significantly reduced.

In a total of 4 experiments on 2 men during arterial occlusion of the left arm, which was maintained 12 minutes prior to whole hand cooling, all sweat rates except that of the occluded limb were observed to increase (Figure 4). When the occlusion was maintained and whole hand cooling initiated, 50.0% of 16 sweat rates decreased significantly. When the occlusion was removed but the hand remained in the water for an additional 3 minutes, 18.8% of the 16 sweat rates were significantly diminished below those observed during occlusion. Figure 5 illustrates the effect of 15 minutes of left arm arterial occlusion on remote sweat rates. All sweat rates, except that of the occluded limb, increased during arterial occlusion but subsided to pre-occlusion values when the occlusion was released.

Skin (T_S) and rectal (T_R) temperatures were not perceptively altered during thermode or whole hand cooling. However, local cooling could have affected temperature changes which were imperceptible to the thermal sensors used. Small variations in the

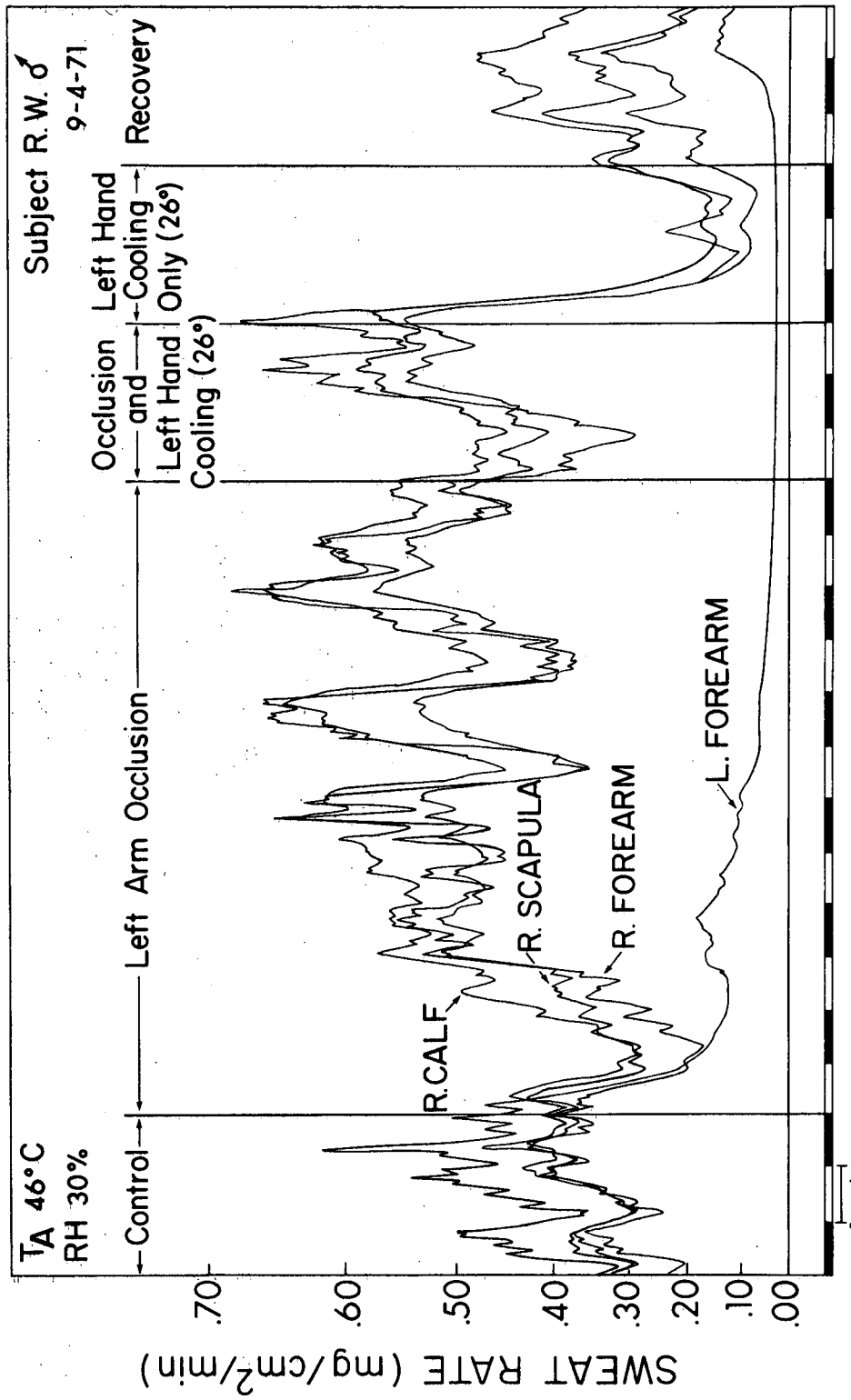

Figure 4. Changes in sweat gland activity due to left arm occlusion and left whole hand cooling in a male.

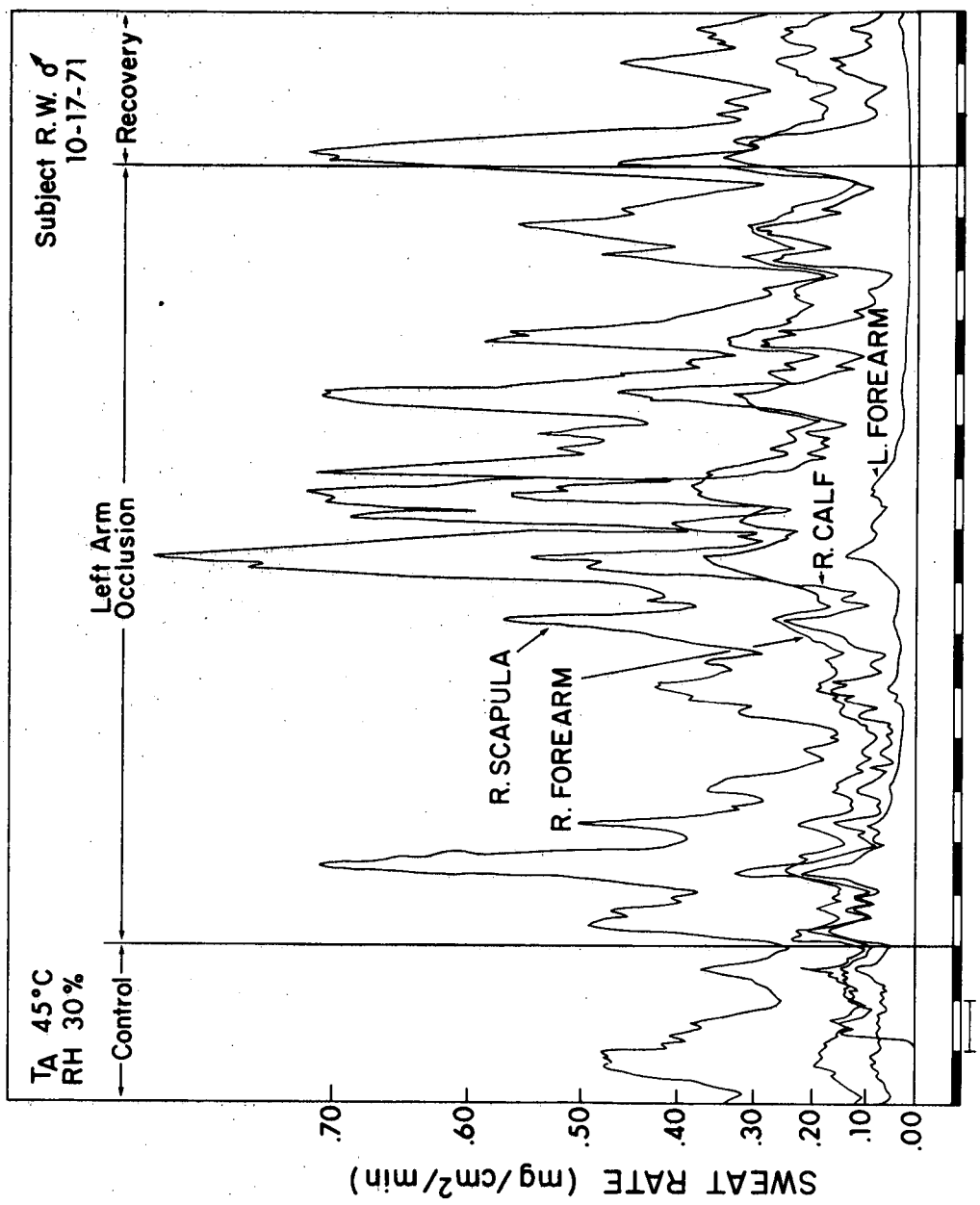

Figure 5. Changes in sweat gland activity due to left arm occlusion.

six T_S occasionally occurred (± 0.2° C) during each experiment, but they were not necessarily related to any experimental intervention. Further, these changes were never reflected in all six T_S simultaneously. During the time each subject spent in the hot room (2-3 hours), T_R gradually increased 0.10-0.32° C above a relatively stable temperature established during the initial 30 minutes of heat exposure.

Influence of the Menstrual Cycle on the Sweat Rate Responses to Contralateral Cooling

Table 5, which is constructed in the same manner as is Table 4, presents the results of 16 experiments in 4 women performed on days 1 and 15 of their menstrual cycle and grouped accordingly. As previously stated, forearm cooling gave the largest percentage of positive responses, and this was true regardless of the time during the menstrual cycle when the experiments were performed. However, the results indicate that on day 1 the scapular skin yielded a higher percentage of responses than did either of the other two areas tested. Similarly, on day 15 the forearm yielded a higher percentage of significant responses than did either of the other two areas tested. Thermode cooling of the scapular skin area produced no positive responses on day 15. The sweat rates of the forearm showed a slightly larger number of significant responses to thermode cooling than did either of the other areas tested on day 1. Likewise, on day 15 the sweat rates of the scapular skin produced a larger number of significant changes to thermode cooling than did the other areas tested.

In summary, then, 138 sweat rate observations from 46 ther-

TABLE 5

TOTAL, POSITIVE AND SIGNIFICANT SWEAT RATE RESPONSES DUE TO CONTRALATERAL CUTANEOUS COOLING ON DAYS 1 AND 15 OF THE MENSTRUAL CYCLE

Area Cooled	Frequencies				Totals	% positive responses of total observations	% significant responses of	
	R. Calf	R. Scapula	R. Forearm	L. Forearm			positive responses	total observations
					DAY 1			
Thigh (24)	24/ 8/ 4	24/ 8/ 4	24/ 8/ 4		72/24/12	33.3	50.0	16.7
Scapula (11)	11/ 5/ 2	11/ 5/ 2	11/ 5/ 4		33/15/ 8	45.4	53.3	24.2
Forearm (11)	11/ 6/ 0	11/ 6/ 1	11/ 6/ 0		33/18/ 1	54.6	5.6	3.0
Total	46/19/ 6	46/19/ 7	46/19/ 8		138/57/21	41.3	36.8	15.2
% positive responses of total observations	41.3	41.3	41.3					
% significant responses of:								
(a) positive responses	31.6	36.8	41.3					
(b) total observations	13.0	15.2	17.4					
WHC (26-28° C)	8/ 8/ 4	8/ 8/ 6	8/ 8/ 6	8/ 8/ 6	32/32/22	100	68.8	68.8
					DAY 15			
Thigh (24)	23/ 5/ 2	24/ 6/ 2	24/ 6/ 2		71/17/ 6	23.9	35.3	8.4
Scapula (11)	11/ 0/ 0	11/ 0/ 0	11/ 0/ 0		33/ 0/ 0	0.0	----	0.0
Forearm (11)	11/ 9/ 1	11/ 9/ 3	11/ 9/ 2		33/27/ 6	81.8	22.2	18.2
Total	45/14/ 3	46/15/ 5	46/15/ 4		137/44/12	32.1	27.3	8.8
% positive responses of total observations	31.1	32.6	32.6					
% significant responses of:								
(a) positive responses	21.4	33.3	26.7					
(b) total observations	6.7	10.9	8.7					
WHC (26-28° C)	8/ 8/ 6	8/ 8/ 6	8/ 8/ 6	7/ 7/ 4	31/31/22	100	71.0	71.0

See Table 4 for explanation of notation.

mode cooling periods involving 3 different skin areas were made on day 1 of menstruation. Of those observations, 57 (41.3%) positive responses occurred of which 21 (15.2%) were significant. On day 15 after the onset of menstruation, 137 sweat rate observations from 46 thermode cooling periods of 3 different skin areas produced 44 (32.1%) positive responses of which 12 (8.8%) were significant. The number of significant sweat rate responses on day 1 was nearly twice as large as those on day 15. The significant sweat rate responses to whole hand cooling on day 1 and day 15 were 68.8% and 71.0%, respectively.

Comparison of Threshold of Sweating Responses Between Men and Women

Table 6 presents the results of the threshold of sweating experiments to total body heating for 4 male and 3 female subjects. The results were divided into 3 groups; (1) women on day 1, (2) women on day 15, and (3) men at a 2-week interval. Figures 6 and 7 show that the increases in T_A during the 2 experiments on any one subject were similar.

As a group the women displayed a significantly longer period to sweating onset (latency = 67 minutes on day 1 and 87 minutes on day 15) than did the men (latency = 32 minutes), but there was no significant difference between day 1 of menses and day 15 following onset of menses, primarily due to the large variation in latency times and the small number of observations. T_A at onset of sweating was significantly higher for the women on day 1 ($P < 0.005$) and day 15 ($P < 0.001$) as compared to the men. The change (Δ) in $\overline{T}_S$, derived as the difference between initial or

TABLE 6

TIME TO ONSET OF SWEATING WITH CONCOMITANT VALUES FOR MEAN SKIN ($\bar{T}_S$), RECTAL (T_R), MEAN BODY ($\bar{T}_B$), AND ENVIRONMENTAL TEMPERATURES (T_A)

Subject	$\bar{T}_{S_i}$ (°C)	$\bar{T}_{S_f}$ (°C)	$\Delta\bar{T}_S$ (°C)	T_{R_i} (°C)	T_{R_f} (°C)	ΔT_R (°C)	$\bar{T}_{B_i}$ (°C)	$\bar{T}_{B_f}$ (°C)	$\Delta\bar{T}_B$ (°C)	Time to onset (min)	T_A at onset (°C)
1. Women - day 1											
E. S.	32.37	36.18	+3.81	37.68	37.29	-0.39	36.61	37.07	+0.46	79	43.0
G. T.	31.99	35.21	+3.22	37.95	37.60	-0.35	36.76	37.12	+0.36	61	41.1
M. S.	32.93	36.19	+3.26	37.80	37.44	-0.36	36.83	37.19	+0.36	61	41.7
$\bar{X}$	32.43	35.86	+3.43	37.81	37.44	-0.37	36.73	37.13	+0.39	67	41.9
±se	0.27	0.32	0.19	0.08	0.09	0.01	0.06	0.03	0.03	6	0.6
2. Women - day 15											
E. S.	32.31	36.88	+4.57	37.56	37.39	-0.17	36.50	37.29	+0.79	95	45.0
G. T.	31.40	36.02	+4.62	37.15	37.38	+0.23	36.00	37.10	+1.10	72	43.7
M. S.	31.86	37.67	+5.81	37.65	37.30	-0.35	36.49	37.37	+0.88	95	48.5
$\bar{X}$	31.86	36.86	+5.00	37.45	37.36	-0.10	36.33	37.25	+0.92	87	45.7
±se	0.26	0.47	0.41	0.15	0.02	0.17	0.17	0.08	0.09	8	1.4
3. Men											
R. W.	33.15	34.80	+1.65	37.97	37.92	-0.05	37.01	37.30	+0.29	28	36.4
	32.19	34.31	+2.12	37.69	37.50	-0.19	36.59	36.86	+0.27	31	36.8
N. B.	31.86	33.78	+1.92	37.64	37.58	-0.06	36.48	36.82	+0.34	30	34.0
	32.18	34.97	+2.79	37.73	37.76	+0.03	36.62	37.20	+0.58	34	35.2
J. D.	32.54	35.34	+2.80	38.00	37.84	-0.16	36.91	37.34	+0.43	40	37.5
	32.85	35.53	+2.68	38.10	37.84	-0.26	37.05	37.39	+0.34	52	38.4
J. K.	33.08	34.05	+0.97	37.88	37.91	+0.03	36.92	37.14	+0.22	17	31.1
	32.77	34.37	+1.60	37.56	37.38	-0.18	36.60	36.77	+0.17	27	34.2
$\bar{X}$	32.58	34.64	+2.06	37.82	37.72	-0.10	36.77	37.10	+0.33	32	35.4
±se	0.16	0.22	0.22	0.07	0.07	0.04	0.08	0.09	0.05	4	0.8
P <	NS	0.02 (1)(3)	0.01 (1)(3)	0.05 (2)(3)	0.02 (2)(3)	0.005 (1)(3)	0.025 (2)(3)	NS	0.05 (1)(2)	0.001 (1&2)(3)	0.005 (1)(3)
P <		0.001 (2)(3)	0.001 (2)(3)						0.001 (2)(3)		0.001 (2)(3)

Significant differences are indicated by the numbers in parentheses. Numbers within each pair of parentheses are not significantly different from each other. (1) indicates women - day 1; (2) indicates women - day 15; and (3) indicates men. ΔValues were calculated from the value at sweating onset (threshold) minus the 0-minute value at T_A 22-23° C. Subscripts (i) and (f) indicate initial and final values, respectively.

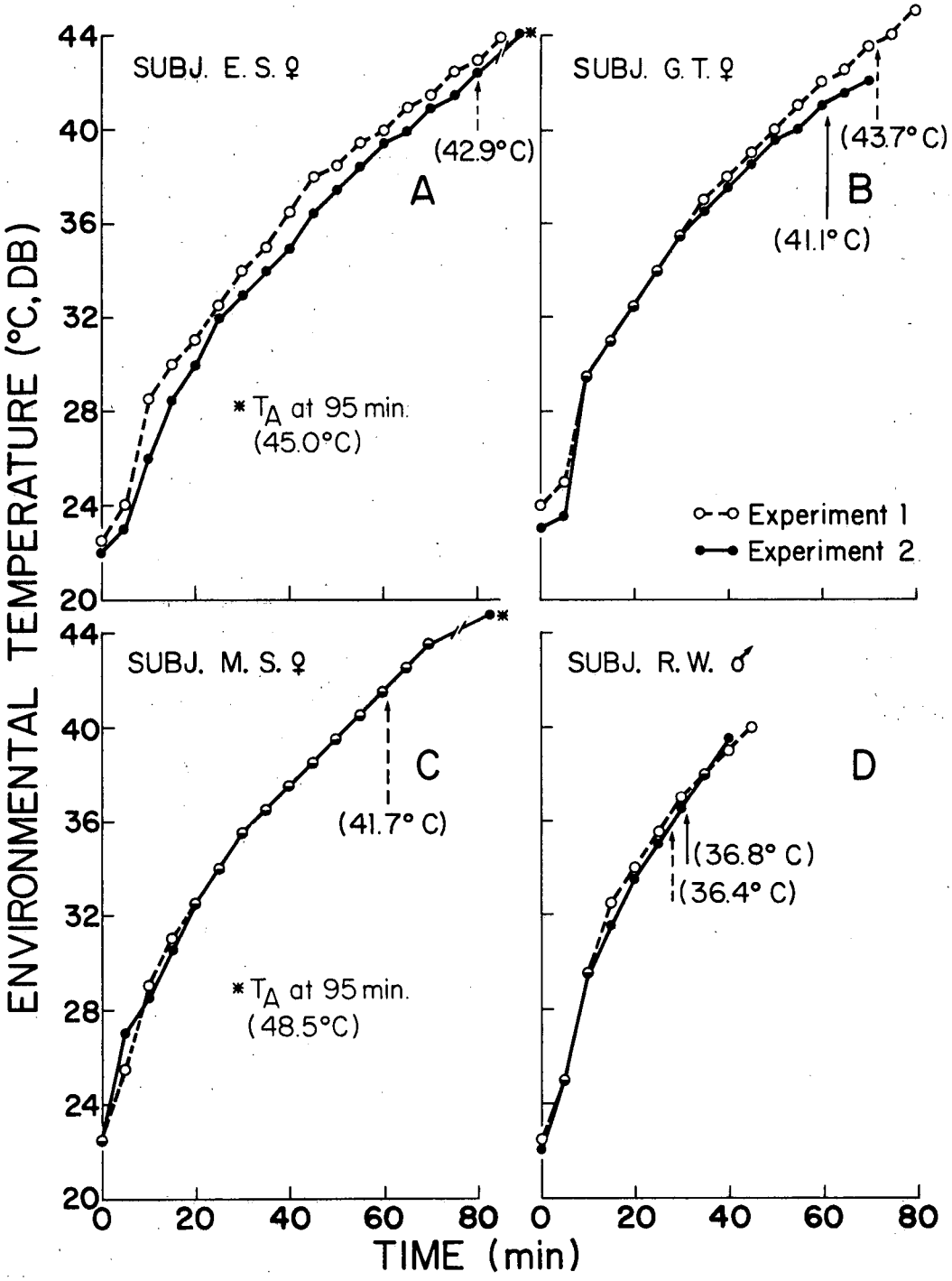

Figure 6. Rate of environmental temperature change during the determination of the threshold for whole body sweating. Graphs A through D represent 8 experiments with 4 subjects. Temperatures indicate onset of sweating.

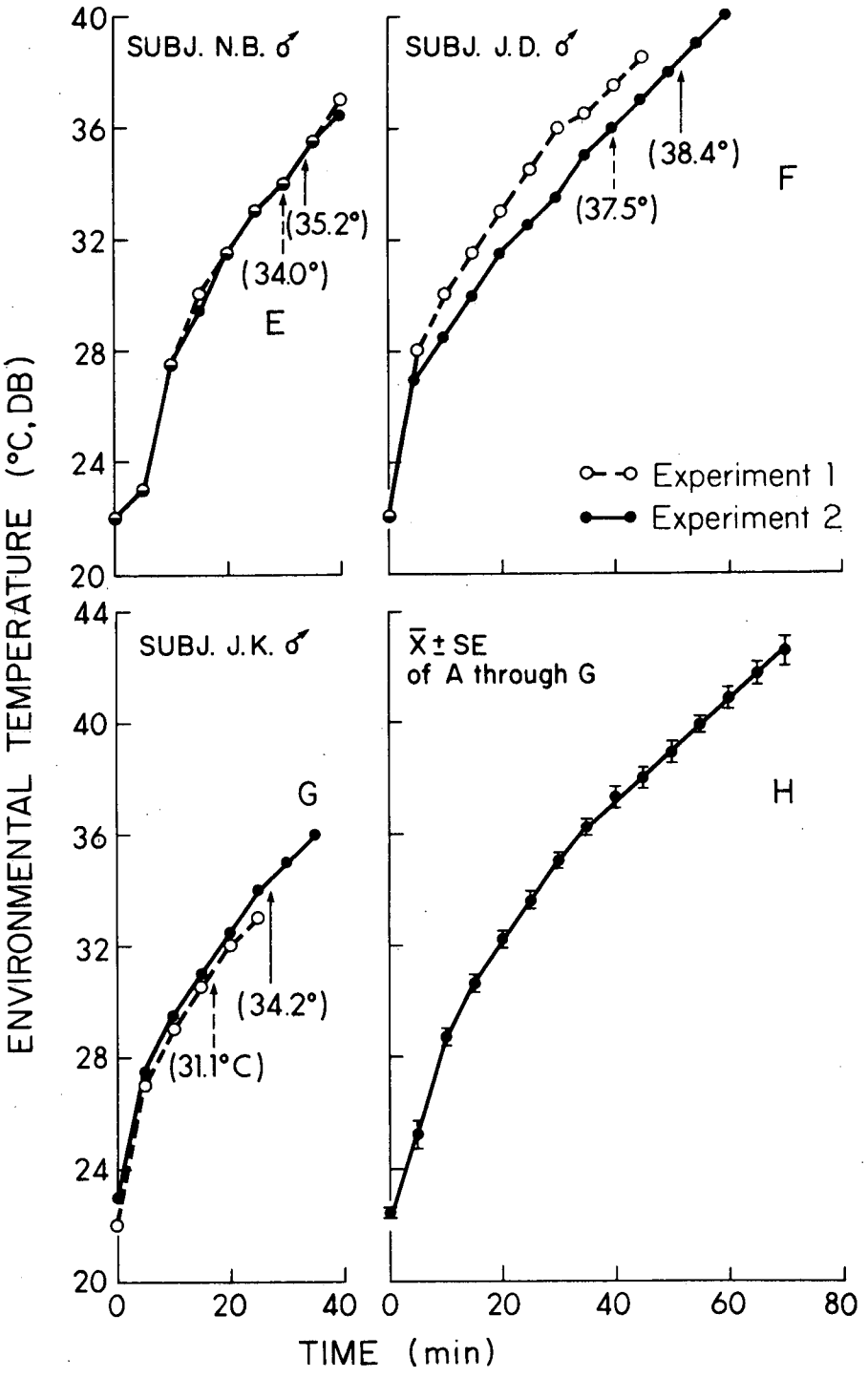

Figure 7. Rate of environmental temperature change during the determination of the threshold for whole body sweating. Graphs E through G represent 6 experiments with 3 subjects. Graph H is a composite of graphs A through G. Temperatures indicate the onset of sweating.

starting temperature and final or threshold temperature, was significantly larger in both groups of women than the change produced in the men. The ΔT_R was significantly greater in women on day 1 ($P < 0.005$) as compared to the men. Change in mean body temperature ($\overline{T}_B$), which is a function of $\overline{T}_S$ and T_R, was significantly greater in women on day 15 as compared to both the women on day 1 ($P < 0.05$) and the men ($P < 0.001$). Although initial skin temperatures for all 3 groups were not different, which reflects the influence of T_A on the skin, initial T_R values were lower in women on day 15 as compared to the other 2 groups.

Correlation of Latency to Threshold for Whole Body Sweating with Sweat Rate Responses to Thermode Cooling

When the latency period to the threshold for whole body sweating was correlated with the percentage of positive responses due to thermode cooling for each male and female subject, the result was a correlation coefficient (r) of -.63 (Figure 8). Although r was approaching the 0.05 level of confidence, the correlation was not statistically significant, primarily because of the small number of observations and large individual variations in responses. A negative relationship might exist, suggesting that the latency period to threshold of whole body sweating could be inversely related to the responsiveness of the sweat glands due to thermode cooling.

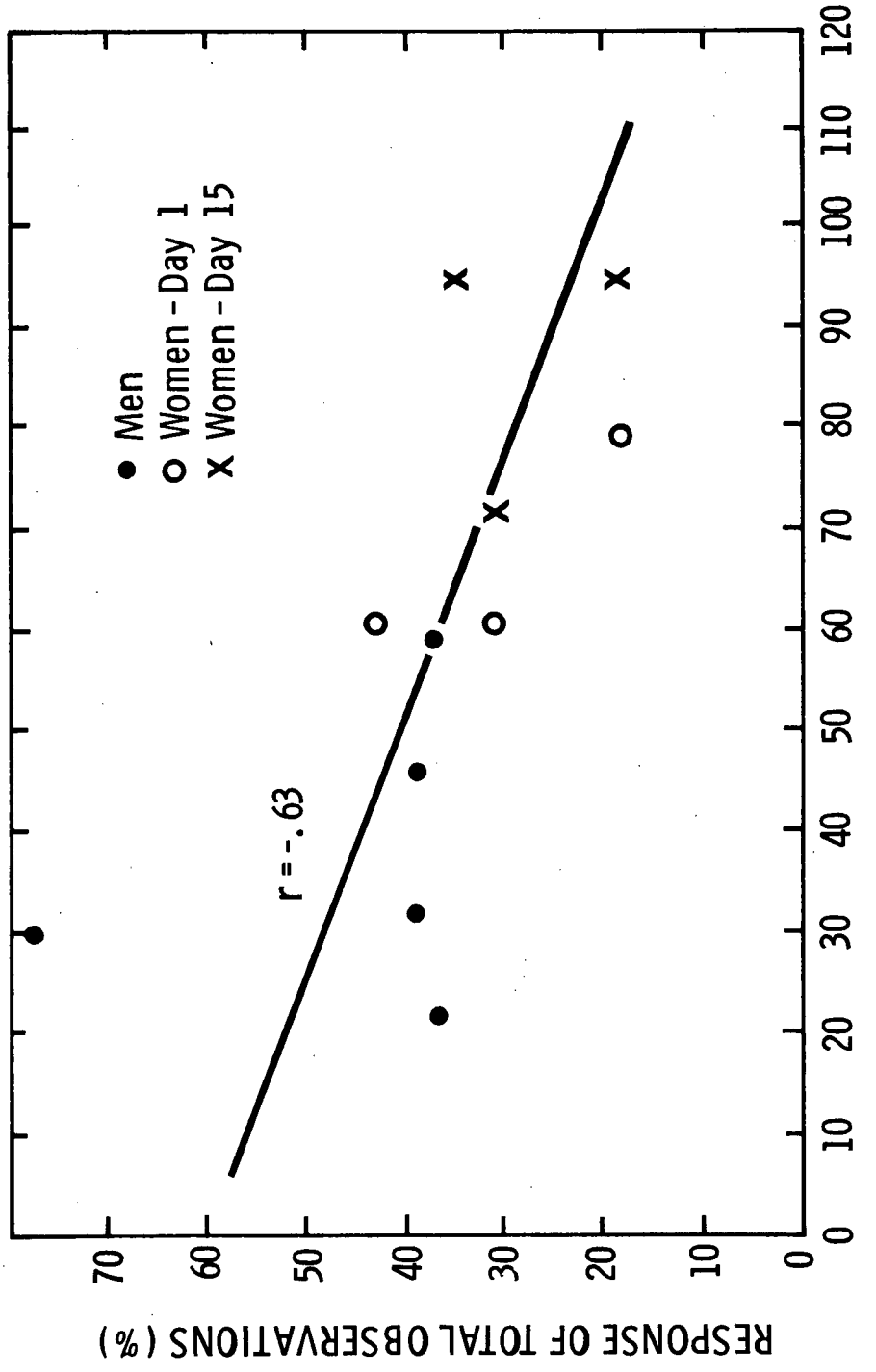

Figure 8. Correlation of frequency of responses with latency to threshold for whole body sweating.

CHAPTER IV

DISCUSSION

The sweat rate response to cutaneous cooling appears to be mediated by a neural reflex, since the interval between the cold stimulus and the sweat rate reduction was 3 seconds or less. No hormonal or cardiovascular mechanism could account for the brief interval observed between local stimulus and generalized response. Continuous monitoring of sweat rates by resistance hygrometry, with its sensitivity to small instantaneous changes in dynamic sudomotor activity, allows this conclusion to be drawn. These results strongly support the findings of Kuno (1956), Brebner and Kerslake (1961b), Rawson and Hardy (1967), Bullard, Banerjee and Mac Intyre (1967), and Banerjee, Elizondo and Bullard (1969) that the immediate diminution in sweat rate due to application of a cutaneous cold stimulus is mediated by a neural reflex.

The interpretation that the response to cutaneous cooling is neurally mediated is strengthened by eliciting sweat rate reductions in areas remote to the cooled limb which had its circulation occluded (Kuno, 1956; Bullard, Banerjee and Mac Intyre, 1967; Banerjee, Elizondo and Bullard, 1969). Figure 4 demonstrates the same result, but, more importantly, the response was markedly augmented when the occlusion was released. The statistical

treatment, however, does not reveal the true nature of the responses during and following release of the occlusion and is, in fact, misleading. The actual diminution of sweat rates was much greater during whole hand cooling following the release of the occlusion than before the release (Figure 4). This point was statistically concealed due to the large variation in sweat rates during whole hand cooling plus occlusion from which values were extracted and used as the control for whole hand cooling without occlusion.

During ischemia of the arm, the temperature of the occluded limb certainly increased due to the cessation of circulatory heat exchange and the marked attenuation in evaporative cooling. Bullard, Banerjee and Mac Intyre (1967) showed that when blood flow to the thigh was occluded, heating an area of skin distal to the occlusion presumably stimulated peripheral warm receptors which increased the sweat rates proximal to the occlusion. Concomitant with increased sweat rates proximal to the occlusion (Figure 4), the sweat rate distal to the occlusion was depressed, due partly to a loss of responsiveness of the sweat glands to neurotransmitter (Collins, Sargent and Weiner, 1959). The anoxic situation produced by occlusion reduces metabolic processes of the sweat glands, presumably rendering them less sensitive to sudomotor activity. However, 35 to 40 minutes of ischemia produced by occlusion of the upper arm apparently does not reduce sympathetic vasomotor and pilomotor activity distal to the occlusion (Lewis, Pickering and Rothschild, 1931). Similarly, sudomotor nerves of the same C fiber class, to which vasomotor

and pilomotor nerves belong, might be expected to resist the anoxic condition and attempt to maintain their function during occlusion. The reflex sweat rate response observed after release of the limb occlusion while whole hand cooling was continued, then, can be ascribed to increased afferent activity which was affected by the occlusion. Hensel (1953) observed that within a few minutes following ischemia of the cat tongue, the steady discharge of cold fibers from the ischemic area was abolished. When the occlusion was released, the discharge was restored to initial levels within 15 to 30 seconds. In view of these observations, the inability of Hill (1921) to see a neurally mediated sweat rate reduction, by occluding the circulation to the arms before hand cooling, is more understandable, particularly when the crude method of measuring sweat rate is considered. Burch and Sodeman (1944) and Brebner and Kerslake (1961a) failed in their attempts to elicit neurally mediated sweat rate responses from areas proximal to ischemic limbs which were cooled distal to the occlusion, because of effects produced by the occlusion and poor techniques used to measure sweat rates. The rapid and transient nature of the reflex sweat rate response, especially during cooling of an occluded limb, dictates a continuous measurement of cutaneous water loss, e.g., resistance hygrometry, for accurate measurements to be made and confident conclusions to be drawn.

When the blood supply to an arm was occluded for 15 minutes with no additional experimental intervention (Figure 5), increases in sweat rates to areas proximal to the occlusion were observed to occur concomitantly with a reduced sweat rate distal

to the occlusion. Restoration of blood flow to the limb resulted in re-establishment of pre-occlusion sweat rates. The mechanical act of occluding a limb was determined to be uninfluential in eliciting reflex responses to cutaneous whole hand cooling.

Men responded 8-11% more often to cutaneous cooling than did women (Table 4). In addition, the magnitude of the responses was significantly larger for the men (Tables 2 and 3). At least three possibilities could explain these differences. (1) The density of cold receptors could be less in the women. (2) Cutaneous cold receptors may be influenced by hormones. (3) Women, who have a greater skinfold thickness than do men, may have cutaneous or subcutaneous adipose tissue which could influence conductance of the cold stimulus to temperature sensitive receptors.

As of this time, no histological evidence has been presented to suggest that women have any fewer thermal receptors than do men. In fact, the inability to confidently define thermal receptors has only resulted in ambiguous structure-function relationships for afferent cutaneous nerves. As a result, any discussion which relates the effects of hormones on cutaneous thermal receptors is a moot point. Hardy and Du Bois (1940) found that women had a greater skinfold thickness than did men, and they calculated that the average difference represented a layer of fat about 4 mm thick. Further, they noted that the conductance of peripheral tissues was 20% lower than that of men. In this case, the additional adipose tissue might infiltrate the area around the thermal receptors resulting in partial insulation of the thermal receptors to external stimuli. Therefore, the presence of extra

subcutaneous fat in women may have diminished the effectiveness of the cold stimulus on the receptors.

Much evidence has accumulated which supports the presence of warm and cold receptors in the skin. Traditionally, cold receptors are thought to be superficial Krause cylinders, whereas warm receptors are believed to be the deeper Ruffini end-bulbs. However, free nerve endings have been implicated in thermal perception and should be included as a possibility at this time. Bazett (1941, 1951) is primarily responsible for building a strong case for the assignment of roles for the Ruffini and Krause receptors participating in warm and cold reception, respectively. Bazett, McGlone and Brocklehurst (1930) determined the interval for various depths of skin at which a cold stimulus when applied to the surface could be detected. On the basis of the anatomical locations of Krause and Ruffini receptors, stimulation of Krause receptors would occur 0-1.25 seconds following the cold application. Similarly, stimulation of deeper Ruffini receptors would require 2.7-6.5 seconds following the cold stimulus. The determination of these intervals support the probability of Krause receptors participating as the origin of the neural reflex to cutaneous cooling. The concept that cold receptors are found nearer the surface of the skin than warm receptors has been additionally substantiated in many respects (Rothman, 1954). Conduction of impulses produced by a cold stimulus are presently considered to occur in δ-group class A and/or class C fibers (Zotterman, 1936; Hensel, Iggo and Witt, 1960).

Many attempts have been made to map out the density of

these receptors on different areas of the body (Rein, 1925; Goldscheider, 1926; Strughold and Porz, 1931). However, Bing and Skouby (1949) discovered that the large variations between studies, and for that matter within the same subject, was most likely due to differences in skin temperature at the time of density measurement. They showed that the number of reacting cold spots within a given area of the forearm increased with the skin temperature from 17 at 25° C to 93 at 33° C. This fact alone diminishes the possibility of correlating the number of cold spots, previously mapped out on different skin areas, to the magnitude and duration of the reflex sweat rate responses due to cutaneous cooling of different skin areas.

On the other hand, if the density of cold receptors is assumed to be dissimilar in different skin areas, the results of cooling those skin areas might be expected to show a response related to that density. Using the results of cold spot mapping from different areas of the body by Strughold and Porz (1931), the back, which has a slightly greater density of cold spots than either the forearm or thigh, would predictably respond better to thermode cooling than would the other two areas tested. Furthermore, the hand, which exhibits a cold spot density nearly 5 times greater than any area cooled by the thermode, should produce a better reflex response to cutaneous cooling than any area tested with the thermode. The results of the present experiments in both men and women (Tables 2 and 3) are consistent with these hypotheses. Of all thermode cooling periods on all skin areas tested, the scapular area was the most sensitive. Whole hand

cooling was consistently successful in eliciting a reflex response. The reflex response is apparently present throughout the body, e.g., cooling the forearm skin resulted in a diminished scapular sweat rate and vice versa (Table 4). Frequency and duration of responses seem to be affected by receptor density and activation which are functions of the change in temperature and site of stimulation.

Recovery of sweat rate depression often occurred within 2 or 3 minutes following the initiation of thermode or whole hand cooling, although the stimulus was maintained for 5 minutes. At least two plausible explanations could account for this occurrence. (1) The reduction in evaporative heat loss momentarily drove the core temperature upward in addition to stimulating warm receptors in the skin. Subsequently, acting as a driving force to produce greater body heat loss, the increased core temperature and stimulation of peripheral warm receptors were reduced by the recovery in sweat rate depression (Bullard, Banerjee and Mac Intyre, 1967; Banerjee, Elizondo and Bullard, 1969). Therefore, the reflex response is probably in part inversely related to rate of heat loss as determined by the level of core temperature and input from the peripheral thermal receptors to the hypothalamus. This relationship was not quantitatively assessed in these experiments. (2) Acting alone or in concert with the need to reduce body heat, adaptation of thermal receptors to the cold stimulus could contribute to the reversal of sweat rate depression during the cooling period. In human volunteers, Hensel and Boman (1960) applied various cutaneous stimuli, including thermode cooling, to

the receptor field innervated by fibers which were isolated and monitored for rate of impulse discharge. Clearly, the impulse frequency dramatically increased concomitant with the onset of thermode cooling, but the rate of neural discharge slowly declined while the cutaneous stimulus was maintained.

The quantity of positive responses appeared to be influenced by the rate of change in temperature of the applied stimulus. Whereas the absolute thermode temperature was varied with each stimulus (Tables 2 and 3), the rate of temperature change was similar in all cases. Regardless of the absolute temperature applied as the stimulus, the observed responses occurred in similar frequency. Why more reflex responses to thermode cooling did not occur is not clear. The rate of heat loss may have been sufficiently high to overcome the thermal stimulus applied via the thermode. In addition, if the interval between thermode cooling periods was too short to allow full recovery of tissues to control temperatures, maximum effects produced by application of the second or third cold stimulus may have been attenuated. Although the temperature of each thermal stimulus on any one area was progressively lower, the number of positive responses was not larger for the first thermode cooling compared to the second or third cooling periods (Tables 2 and 3). This would indicate that residual tissue effects were small from one cooling period to the next, and that the interval between thermal stimuli was long enough to allow full recovery. These observations further substantiate the assertion that the receptors respond to rate of change rather than to the absolute temperature applied (Zotterman, 1959;

Banerjee, Elizondo and Bullard, 1969). Figure 4 shows that a cool stimulus of 32° C, which reduced the skin temperature of the hand from 37 to 34° C, elicited a reflex sweat rate reduction for the duration of the cooling period. This observation is contrary to those of Benzinger (1961, 1964) who insisted that skin temperature must be 33° C or less in order for peripheral cold reception to inhibit (influence) the hypothalamus which in turn would suppress sweating.

On day 1 of menstruation, the women appeared to be 7-9% more responsive to cutaneous thermode cooling compared to day 15 of their cycle (Table 5). The reason for this difference is not clearly apparent, since the experimental conditions were similar for each of 4 experiments in all subjects and since the number of observations was large and similar for days 1 and 15. Davis and Fugo (1948), Buxton and Atkinson (1948), and Israel and Schneller (1950) have demonstrated the pyrogenic effect produced by progesterone which is more likely responsible for the increased body temperature associated with the luteal phase of the menstrual cycle. Kenshalo (1966) determined that women were more sensitive to threshold cool stimuli between ovulation and onset of menses (luteal phase). The increased sensitivity, associated with increased cutaneous vasodilatation, was related to release of progesterone by the Graafian follicle. Progesterone derivatives, when given prior to ovulation, produced the same effect on the cool threshold as though ovulation had occurred. Effects of estrogens and progesterone on thermal receptors remains obscure. Conceivably, progesterone could be responsible for the increased

responsiveness to cutaneous thermode cooling on day 1 of menses as compared to day 15.

In a further attempt to show that the reflex response to cutaneous thermode cooling was affected by the sex and menstrual cycle of the subjects, latency periods to threshold of sweating during an increasing ambient temperature were determined concomitant with changes in skin and core temperature (Table 6). Any acclimitization effects produced were obviously minimal since there were no apparent trends in latency times, environmental, rectal and skin temperatures between the first and second experiments. Since the increase in ambient temperature was similar in all cases (Figures 6 and 7), the results were grouped according to sex and menstrual cycle. Like Kawahata (1960) and Fox, Lofstedt, Woodward, Eriksson and Werkstrom (1969), the latency period to onset of sweating was found to be much longer for women as compared to men, when both groups were exposed to a similar T_A. Furthermore, the T_A, at which sweating began, was 6-10^{o} C higher for women, depending on which time during the menstrual cycle the test was performed. There would appear to be at least two reasons for these observations. First, the smaller increase in metabolic rate exhibited by the women, when they were exposed to the same environmental stress as men, allowed them to approach thermal equilibrium by convective and radiant heat losses rather than by sweating (Hardy and Du Bois, 1940; Hardy, Milhorat and Du Bois, 1941). Second, the skinfold thickness, which is nearly twice as large in women, creates insulation from the heat in two directions. The cutaneous and subcutaneous fat act as a heat sink, insulating

the core from the environmental stress. In addition, as the core temperature increased, the onset of sweating would be delayed by the vasomotor mechanism of increasing flow of warm blood away from, and cooler blood towards, the core. The significantly higher $\Delta\overline{T}_S$ observed in the women as compared to the men illustrates the important capability of the skin in regulating heat loss and gain by the organism.

The dermal recruitment pattern of sweat glands was similar to the observations of Randall (1963). However, subjects did not always begin sweating on the lower extremities, but began sweating simultaneously from the trunk, upper and lower extremities in 50% of the experiments. As a group, the women began sweating 20 minutes sooner on day 1 of the menstrual cycle and at a T_A of 4^{o} C lower than on day 15. $\overline{T}_{B_i}$ was higher in women on day 1, but $\overline{T}_{B_f}$ was essentially similar to that attained on day 15 at onset of sweating. The simplest hypothesis is that the higher initial body temperature on day 1 was due to the pyrogenic effect of progesterone.

Latency to threshold for whole body sweating was correlated with responsiveness to thermode cooling for each subject to determine if a knowledge of the former would allow a confident prediction of the latter (Figure 8). The correlation coefficient ($r = -.63$) indicates that latency to threshold may be inversely related to responsiveness of the sweat glands due to thermode cooling. However, this relationship, although approaching the 0.05 level of confidence, was not statistically significant. Accordingly, at the present time, knowing the latency to threshold for whole

body sweating does not allow a confident prediction of responsiveness of a subject to thermode cooling.

CHAPTER V

SUMMARY

Conclusions and Assertions

Relative to the five hypotheses stated in Chapter I, the following statements recapitulate the findings of this study:

1. The immediate reduction in output by eccrine sweat glands to contralateral cutaneous cooling appears to be neurally mediated, since the sweat gland response occurred within 3 seconds after initiation of the thermal stimulus.
2. Frequency and magnitude, the quantitative aspects of the reflex response, appeared to be affected by both the density and activation of receptors as well as the rate of heat loss of the subject during the test. Sweat rates responded to the change in temperature (gradient) rather than to the absolute temperature applied.
3. Men responded 8-10% more frequently than women to thermode cooling, the magnitude of responses being greater for the men. A lesser frequency of responses by the women might be attributed to the insulatory properties of subcutaneous fat about the thermoreceptors.
4. Women responded 7-9% more frequently to thermode cool-

ing on day 1 as compared to day 15. The increased frequency of responses (sensitivity) on day 1 could be attributed to effects produced by endogenous progesterone during the luteal phase of the menstrual cycle.

5. When confronted with an increasing T_A during rest, men exhibited a shorter latency to threshold for whole body sweating than did women. Further, the T_A at threshold for whole body sweating was much lower for men. On day 1 the women had a shorter latency and began sweating at a lower T_A as compared to day 15 of their menstrual cycle. In general, the longer latency and higher T_A at onset of sweating in women is attributed to the insulative and heat absorptive properties of the skin. Latency to threshold for whole body sweating cannot presently be used with confidence to predict responsiveness of a subject to thermode cooling.

Significance and Projections

Understanding the nature of the sweat gland response to cutaneous cooling enables greater understanding of peripheral (skin) influences on the central (hypothalamic) controller for sweating. Particularly, the afferent neural pathway demands attention since many investigations including this one have shown the peripheral input to the hypothalamus to be important in the regulation of sweat secretion. A more accurate mapping of cold spots throughout the body concomitantly with histological exami-

nations, using improved techniques, may prove more fruitful at a future time. More definitive studies are necessary to identify the skin receptors which actively participate in thermoregulation.

Occlusion experiments appear to be more of a detriment than asset since the responsiveness of the afferent nerves has been shown to be diminished by the anoxic condition. Although occlusion and subsequent cooling of a limb clearly showed the reflex response to be neurally mediated, the magnitude and duration of the response was apparently affected by the activity of the afferent nerves as determined by the duration of occlusion. Therefore, since the response has been shown to be neurally mediated, and since the anoxic conditions impedes a natural sweat gland response, occlusion experiments serve only to eliminate cardiovascular effects produced by prolonged cooling or heating of a large skin area.

Cutaneous cooling of more and different areas than those in this study should be performed, and the sweat rate responses assessed. Further, cutaneous cooling of 2 or more skin areas simultaneously and/or serially might provide additional information about the summative quality of peripheral input. Finally, cooling of large skin areas during prolonged exposure to various intensities of heat, to suppress sweating for as long as desired, would provide a modifying control of the thermoregulatory process.

Women provide problems of special interest since they appear both to be less sensitive to cutaneous cooling than men, and their menstrual cycle influences cold sensitivity. Definitive studies should be performed to elucidate the extent of modifying influences, both anatomical and menstrual, on cutaneous thermal

receptors. The ability of women to thermoregulate through more complex mechanisms than men raises additional questions, both anatomical and physiological, about woman's relationship to her environment.

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