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Cutaneous and Core Temperature Influences on Thermoregulatory Sweating

Robert Duncan Wurster
Loyola University Chicago

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CUTANEOUS AND CORE TEMPERATURE INFLUENCES ON THERMOREGULATORY SWEATING

Robert Duncan Wurster

A Dissertation Submitted to the Faculty of the Graduate School of Loyola University in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

1968
To my very lifeblood --- my Janes ---

Carol Jane and Jane Louise
LIFE

Robert Duncan Wurster was born on October 7, 1940, in Mishawaka, Indiana. He is the son of Dr. and Mrs. H. C. Wurster, physician and biologist, respectively.

He received his primary and secondary education in the Mishawaka public school system. During his high school and early college years, he was employed by Wurster Farms, Inc.

In September, 1957, he enrolled in Indiana University, South Bend Extension. In January, 1958, he transferred to Purdue University, majoring in biology and chemistry, and received a B.S. degree in 1961. During his last two years at Purdue, he was a technician for Dr. J. E. Wiebers, a physiologist.

In the Summer of 1961 the author initiated his graduate work at Notre Dame University, but in the Fall elected to transfer to the Department of Physiology of Loyola University. While at Loyola as a student of Dr. Walter C. Randall, he acquired a wide range of research interests in areas of cardiac, peripheral vascular, autonomic, and thermoregulatory physiology.

In 1963 he married Carol J. Nelson, also a graduate of Purdue University. In 1965 he became the father of a daughter, Jane Louise.
The author is a member of Alpha Epsilon Delta and an associate member of the Society of Sigma Xi and the American Physiological Society.
ACKNOWLEDGMENTS

The author wishes to express sincere gratitude to his adviser, Dr. Walter C. Randall, whose scientific and personal life will remain a lifetime inspiration.

The author likewise wishes to express appreciation to Dr. Robert D. McCook without whom little or none of this work would have been possible.

An expression of appreciation is also due for the high quality technical assistance of S. Maurer, C. Hassler, D. Randall, J. Brockhouse, and G. Tobelman and the superb secretarial aid of A. Jendrusiak.
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CHAPTER I

INTRODUCTION

External heat stress applied to the body surface has three basic influences (figure 1):

1) It may directly affect sweat glands without involving activity of the central nervous system.

2) It may heat blood returning to the body core; this, in turn, may stimulate thermal sensitive neural structures of the central nervous system. This may give rise to autonomic alterations in cardiac, vascular, and sudomotor (sweat gland) responses.

3) External heat also may alter thermal skin sensor activity. These sensors may provide thermal autonomic control at spinal and/or supraspinal levels.

Vast efforts have been expended investigating central nervous thermal sensitive responses in experimental animals. The applicability of these animal studies to man is questionable, and yet similar experimental procedures are impossible to perform on man.

Until recently, few have attempted to define the nature of cutaneous thermal sensory input to the thermoregulatory system of either laboratory animals or man.
FIGURE 1

General scheme --- effects of temperature upon human thermoregulatory control.
It is the designed purpose of this dissertation to investigate the qualitative nature of body core and cutaneous temperature factors in control of thermal regulatory sweating in man. It is hoped that such qualitative understanding will illuminate quantitative investigation of the various contributions to thermal control of sweat gland activity.
CHAPTER II

REVIEW OF THE LITERATURE

Cutaneous Thermal Sensors

The investigation of thermal sensors has been a multidisciplinary endeavor involving anatomist, physiologist, and psychologist. The early physiologist found himself employing both anatomical and psychological techniques. He relied upon morphological descriptions and subjective impressions of the human subject. Later, Zotterman's group applied newly acquired neurophysiological techniques to the recording of cutaneous thermal receptor fibers (290), thus introducing renewed interest in cutaneous thermal receptors.

In 1838 Johannes Müller (192) presented his "law of specific nerve energies" which states that no matter how a nerve is stimulated, it will elicit a response or sensation which is characteristic of the nerve and not the stimulus. Volkmann, 1844 (269), interpreted from Müller that different nerves were sensitive to specific modalities, e.g., temperature, pressure, touch, etc. Therefore, it is not surprising that when Wagner and Meissner (274) in 1852 described an end organ in the skin, many wondered if this were specific for one of the cutaneous
modalities. Meissner (187) and later Krause (169) concluded that these end organs were part of the nerve, for they degenerated when the nerve was transected.

In 1859, Krause (169) described end organs in the human conjunctiva and later in skin (170) which he called "Endknolben" or endbulbs. Other investigators observed end organ structures and called them such names as Browne, Hoggan, or Blackwell end-organs. Dogiel (57) listed as many as seven different forms of encapsulated nerve end-organs.

Ruffini, in 1905 (238), expressed difficulty in classifying encapsulated end-organs on a morphological basis because of the presence of so many intermediate forms. One of these intermediate types of endings, between the cylindrical end-bulb of Krause and the Pacinian corpuscle, still bears his name. The Ruffini end-organ has an elongated cylindrical capsule sometimes supplied with two myelinated nerves which richly branch to form a network of non-medullated fibers with flattened expansions at their terminations. Thus, because of the presence of so many intermediate forms, end-organs, in general, more closely resemble a continuum rather than specific endings (249,250).

In 1869 Engelman proposed that these end-organs were myelin, suggesting the possibility that the so-called end-organs might be due to faulty technique (65). Von Frey held that Müller's "specific energies" were due to anatomically different
types of end-organs or groups of end-organs (270-273). But Schiff pointed out that Meissner did not claim any specific function for the skin structures he observed (241). He noted, "they do not serve in tactile experience, for we feel touch with areas of skin where there are none present [hairy skin]."

While anatomists were examining the structures of skin receptors, physiologists and psychologists set out to learn the nature of cutaneous sensation. In 1884 Blix (33) placed warm and cold pointed metal probes on the skin, and mapped the location of both hot and cold sensitive areas. Blix found there was a far greater density of cold "spots" than warm "spots" with the greatest density on the head. To compare the density of cold "spots" on the upper and lower halves of the body, data from various investigators have been compiled [Beetz, 1936 (20), Goldscheider, 1926 (89), Hauer, 1926 (114), Hirsch and Schriever, 1930 (143), Rein, 1925 (230), Schriever and Strughold, 1930 (242), Speiser, 1931 (248), Strughold, 1926 (259), Strughold and Karbe, 1925 (253), and Strughold and Porz, 1931 (254)]. Mean upper and lower cold "spot" density was obtained by summatiing the number of cold "spots" per cm² for different parts of the skin multiplied by the relative percentage of total surface assigned to either upper or lower half of the body. According to these estimates, the upper half of the body has approximately 8.2 cold "spots" per cm² compared to 5.8 for the lower half of the body. The possible significance of this difference will be discussed later.
other investigators reported the thermal sensory "spots" varied in number and location on the surface of the body.

Von Frey (271) suggested the so-called Krause endcapsule was the sensory structure under each cold "spot." However, other investigators did not agree. Cold "spots" were located on the skin without identification of Krause endings in the underlying skin. Perez (211) noted the lack of encapsulated nerve endings in thermal sensitive hairy skin (which represents 90% of the body surface area).

Cauna studied the submicroscopic and histochemical make-up of the cutaneous nerves (43,44), finding no significant difference between them. He concluded the ability to discriminate different sensory modalities did not involve these structures, but suggested that differences may be due to tissue interposed between the surface and the receptor.

Sinclair and associates (246) also did not agree with von Frey. They showed that on the human auricle (skin where only free-endings existed), all four types of cutaneous sensations are experienced. Despite opposition, the notion of specific thermal receptors persisted with Krause endcapsules (cold receptors) and their counterpart, Ruffini end organs (warm receptors).
In the 1940's and 1950's, Weddell and co-workers (281, 178, 179) continued to investigate the encapsulated nerve endings. They believed such encapsulated endings were the result of irritated or damaged regenerating nerves. Weddell concluded that thermal sensitivity is mediated via free nerve endings and not by encapsulated nerve endings.

The question arises, what is the nature of the free nerve endings? Some believe that the free nerve endings form arborizations (141). Others hold that a protoplasmically continuous network is found in the skin (34). They note the presence of numerous syncytial contacts or bridges. Weddell's group found in the absence of hyaluronidase pretreatment, strong solutions of methylene blue, and fixatives such as formalin, degrade and distort the appearance of the filaments. Some of the filaments are completely destroyed. Others rupture at their terminations giving rise to structural artifacts which stain or impregnate, appearing similar to Merkel's disc (which are thought to be a specialized touch cell by some investigators). Weddell and Zander (281) found that even slight shrinkage of the preparations produced an appearance of fusion of afferent cutaneous nerves, thus accounting for reports of protoplasmically continuous nerve network in the skin.

Lele and Weddell (178) suggested the possibility of two phylogenetically different innervations in the skin. The older system consists of physiologically undifferentiated nerves feeding
into the spinothalamic tracts and spinal nucleus of the trigeminal nerve. This older system is similar to the innervation in amphioxus. The cornea has a similar innervation, being comparable to skin which has failed to evolve its neurohistological features and which is innervated by diffusely overlapping terminal filaments. A phylogenetically newer system is a "projection type" receptors in the skin, composed mainly of nerve endings related to skin appendages with terminals which are physiologically differentiated, capable of a high degree of localization, and which pass into the dorsal columns of the spinal cord. This is similar to the concept of Head (115-117) who described "protopatic" and "epicritic" sensory nerves.

The assessment of thermal input into the central nervous system (CNS) by means of subjective impressions from application of heated or cooled probes can be seriously criticized. The unknown element of perception complicates these data. It is conceivable that there is thermal input to the CNS which does not reach the perceptive levels of consciousness. It is also conceivable and quite likely that perceptive information is distorted from the actual peripheral nerve input. To assess the thermal input more properly, the preferred method consists of recording directly from the peripheral thermal fibers before the CNS can modify this information. As pointed out before, Zotterman, together with brilliant disciples such as Hensel, Iggo, Dodt, Witt, and Boman, developed such techniques.
Zotterman (290) and Hensel (123-134) recorded impulses from the lingual nerve of the cat containing thermal fibers from the surface of the tongue. They located the area innervated by a bundle of nerves by mechanically stimulating the tongue with a rod. After the receptor field was found, the individual fibers were teased loose and tested for thermal sensitivity. Accurate thermal stimuli were applied by means of a specially built thermode which maintained constant temperatures (±0.02°C) and constant pressure.

They roughly divided thermal fibers into two groups: "cold" and "warm" fibers. Before proceeding, it is important to define the meaning of these terms. "Cold" fibers are not necessarily responsible for the sensation of cold. It merely means that cooling the skin from the physiologically "neutral" range of 30-33°C (being somewhat higher in lingual preparations) to lower temperatures results in an increase of firing rate, and an increase of temperature a decrease in firing rate. Of course, the warm fibers would be those fibers which respond to a decrease in temperature with a decreased firing rate and to an increase in temperature with an increased firing rate. Hensel and Zotterman (130, 131) recorded from small A fibers finding cold fibers responsive in a wide range from 20-40°C with a rather rectilinear function to temperature. The maximum steady firing rate was 10/sec. The cold fibers seemed to be about ten times more numerous (291). The maximum frequency observed in warm fibers
occurred at temperatures between 38 and 40°C with maximum steady discharge of 1.5 to 3.7/sec which is about 30% of the maximum steady discharge of cold fibers. During steady discharge, the firing of "warm" fibers was irregular compared to cold fibers. The latency of the "off" discharge of warm fibers (due to decrease of temperature) was less than the latency of the "on" response of neighboring cold fibers. The latency of the "on" response of cold fibers was less than that for the warm fibers.

The following is a comparison of warm and cold fibers taken from Dodt and Zotterman (56):

<table>
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<tr>
<th>Range of Temperature</th>
<th>Type of Fiber</th>
<th>Steady Discharge at Constant Temperature</th>
<th>Steady Rate of Firing</th>
<th>Maximum Steady Frequency of Discharge</th>
<th>Nature of &quot;Paradoxical&quot; Discharge</th>
<th>Nature of &quot;On&quot; Response</th>
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<tr>
<td>Warm&quot;</td>
<td>20-47</td>
<td>38-43</td>
<td>3.6/sec</td>
<td>aperiodic</td>
<td>rapid fall of 8 to 15°C</td>
<td></td>
</tr>
<tr>
<td>Cold&quot;</td>
<td>8-41</td>
<td>15-35</td>
<td>9.8/sec</td>
<td>periodic</td>
<td>45 to 50°C</td>
<td></td>
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It is interesting to note that elevating the skin temperature from starting point of 10°C would result in an increase in firing rate of the cold receptor. This seems to agree with some perceptive observations that heating the skin from 20 to 35°C often results first in an increase in cold sensation (129, 130, 56, 279).
One should also observe that cold fibers are activated at high temperatures (45 to 50°C). Strangely, this coincides with the range of painfully hot sensation. Hacker (95) found in a skin area which was deprived of all cold "spots," temperatures above 45°C did not produce any sensation of hot. This suggests that the sensation of heat was a mixed sensation of warmth and "paradoxical" cold (5). Zotterman thought that the sensation of hot was dependent upon pain fibers and "paradoxical" cold fiber excitation.

The "paradoxical" warm fiber excitation is produced by a rapid lowering of skin temperature. This "paradoxical" firing is not known to have counterpart or parallel response to thermal perception.

Zotterman's group (131) also shed light on some thermal responses which had attracted Weber's attention in 1846. Weber (279) observed that after removing a cold stimulus, the cold sensation remained. He thought this was due to spreading of the cold to neighboring tissue giving rise to the sensation of cold. Hering, in 1877 (135), thought that Weber's explanation was inadequate because cooling in the neighboring region was far too slight. Holm (144) supported Weber, but Hahn and Boshemer (96) disagreed. The latter authors anesthetized the area around the cooled area and still the after sensation persisted. They concluded that the sensation arose from the cooled site itself. Others such as von Frey, Ott, and Schriever, 1930 (273), supported
Weber. Dodt and Zotterman (56) and Zotterman and Hensel (131) offered another explanation of Weber's observation. "When the cold sensation then slowly reappears, although the temperature of the skin is gradually rising, there will be very little interference from the rather scattered warm receptors. Thus the steady discharge of impulses from the cold receptors, which display their maximum sensitivity in just this temperature range, 25 to 50°C, will stand out still more conspicuously."

It should be pointed out that the most potent stimulus to a thermal receptor involves rate of change in temperature. The greater the rate of change, the greater the firing rate. Noting this, Zotterman (291) pointed to the similarity between thermal receptors whose rate response corresponded to that of the carotid sinus (176) and of the muscle spindle (160).

What is the adequate stimulus and mechanism of thermal stimulation? Bazett and McGlone (17,18), Ebbecke (63), Rein (229), Windisch (283), and Oppel and Hardy (204) all spoke of thermal gradients as being the adequate stimulus for thermal receptors. Oppel and Hardy heated the skin with penetrating and non-penetrating radiation with the hope of heating the deep layer and the surface of the skin separately. Because heating the outer surface caused a much stronger thermal sensation, Hardy postulated that a decrease in the normal temperature gradient in the skin may be responsible for the sensation of warmth. Lele (179), Tyrrell (263,264), and Williams (282) proposed the "thermocouple theory."
stimulation of thermal receptors was believed to require spatial thermal gradient between the superficial and the deeper layers of the epidermis. These authors felt that the proper stimulus was one creating a temperature difference between the nerve terminal and the stem of the axon (282). Under isothermal conditions, the nerve fibers will cease to discharge. According to this hypothesis, the responses are not dependent upon direction of thermal gradient. Thus, cooling or warming the skin surface with similar changes of the deeper layers will have no responses.

Hensel and Zotterman (133) occluded blood flow, and in other experiments cooled the blood in the lingual artery supplying the tongue while cooling the top surface of the tongue. The discharge was found to be related only to temperature, not the gradient of temperature. Hensel and Witt (128) cooled the inferior surface of the tongue while maintaining the superior surface at 32°C and recorded action potentials from thermal fibers innervating the upper surface of the tongue. Despite the gradient changes, the action potential traffic was again related to decline in temperature of the tongue, not gradient. These experiments have not been repeated in skin.

Murray (193,194) tested the spatial gradient theory on other types of thermal receptors, ampullae of Lorenzini of elasmobranches and the lateralis organs of Xenopus (a type of African frog). His conclusions agreed with Hensel and Zotterman. He also found that he could replace the thermal stimulus with a
constant current. Despite the fact that the current was main-
tained constant, the firing frequency dropped in a near
exponential fashion. This is identical to temperature rate re-
sponses. The high initial firing rate decreased because of
accommodation. Murray contended that this accommodation was not
due to changes in polarization of endings, for he maintained
polarization constant with his constant current stimulation, but
it appears that the latter contention is questionable.

Other theories of temperature sensitivity have been
offered. Bernhard and Granit (27) and von Euler (66) suggested
that the nerve fiber, not just the ending, may act as a thermal
receptor. Bazett and McGlone (17,18) suggested that blood acidity
might be related to thermal sensation. Jenkins (156) proposed a
concentration theory. He suggested that the bare nerve endings
would discriminate between catabolic and anabolic phases of some
chemical reaction brought about by a change in temperature. This
appears to be similar to suggestions made by Zotterman (292) who
proposed a two reaction theory to explain the rising and falling
frequency curve. In his hypothesis, the difference between "warm"
and "cold" receptors was dependent upon which of the two reactions
predominated at that temperature. He observed that the kinetics
of the two slopes were quite different, suggesting two different
mechanisms.

Another theory has been suggested by Nafe, Wagoner, and
Kenshala. In 1941 Nafe and Wagoner (197) and later Nafe and
Kenshalo (196) suggested that different cutaneous sensations have movement in common. They suggested that thermal sensation is aroused by movements of smooth muscles in the walls of cutaneous arterioles. They noted that Goldscheider (87, 88) saw blood vessels in the proximity of the cold spots. They suggested that heat relaxes the smooth muscle and cold causes it to contract. Nafe (195) noted an interesting relationship between temperature, sensation, and smooth muscle activity:

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<tr>
<th></th>
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<tbody>
<tr>
<td>Pain</td>
<td>Above 52</td>
<td>spastic contraction</td>
</tr>
<tr>
<td>Heat</td>
<td>45–52</td>
<td>constricting elements in dilating muscle</td>
</tr>
<tr>
<td>Warm</td>
<td>34–44</td>
<td>relaxation</td>
</tr>
<tr>
<td>Neutral</td>
<td>33</td>
<td>slight constriction</td>
</tr>
<tr>
<td>Cold</td>
<td>13–32</td>
<td>constriction</td>
</tr>
<tr>
<td>&quot;Cold heat&quot;</td>
<td>3–13</td>
<td>severe constriction</td>
</tr>
<tr>
<td>Pain</td>
<td>Below 3</td>
<td>spastic contractions</td>
</tr>
</tbody>
</table>

They believe that different receptors have a different orientation on the vessel or smooth muscle in a manner such as Fischer (70) has reported. Fischer noted two types of afferent terminals in smooth muscles --- one "spray-like" and another "spindle-like." The fiber size of these vessel afferents are in the range expected for temperature fibers and perhaps represent the two types of thermal receptor fibers.

Lele and Weddell (178) worked on the thermal sensation from the cornea. They claim that thermal sensation is possible in
the absence of blood vessels. Kenshalo (164,165) has two criticisms of this cornea thermal sensation work. First, the sensitivity of the cornea is markedly less than that of skin. Second, Lele and Weddell used infrared heat as the thermal stimulus, which may have stimulated the iris rather than the cornea.

What is the geography of thermoreceptor fibers in the skin? Iggo (146) found that the receptive fields of C fibers, including temperature sensitive fibers, to be from 2 mm² to 5 mm². Using skin thermal conductivity and nerve conduction velocity, Hensel, Ström, and Zotterman (127) estimated the depth of thermal receptors to be 0.8 mm ± 0.04 mm under the surface of non-calloused skin. This is in good accord with histological indications of the depth of nerve endings in skin.

Most of the work described thus far emphasizes primarily A fiber recordings from the lingual nerve. A thermal receptive surface of greater importance is the skin. Hensel, Iggo, and Witt (126) studied the responses of C fibers in the saphenous nerve of cats. These C fibers conducted at a velocity of 1.1 m/sec. The "dynamic" sensitivity of a cold fiber was 30 imp/sec. (Sensitivity equals response per stimulus.) With the maximum frequency of 19.5/sec resulting from a temperature change from 16 to 27°C. A change of 0.1°C was sufficient to excite warm or cold fibers. The warm fibers found in the saphenous nerve were more sensitive than those found in the lingual preparations. These warm fibers in the saphenous also
showed no paradoxical response as recorded from the lingual preparation. Comparing the lingual to the saphenous preparations, Iriuchijima and Zotterman (147,148) found only a few thermal C fibers in the lingual nerve while the vast majority of the temperature fibers found in the tongue were small A fibers which conducted in the range of 3.2 to 11.4 meter/sec.

In 1960 Hensel and Boman (125) recorded from thermal afferent A fibers from conscious human subjects. Interestingly enough, the authors failed to find "warm" fibers.

Another important question concerning thermoreceptors is their specificity. Remembering the structural lack of specificity, it should be of no surprise that there is also a lack of response specificity. Weber (280), Kiesow (167), Goldschreider and Hahn (90), Hensel and Zotterman (132), Hunt and McIntyre (145), and others have all reported temperature sensitivity of mechanoreceptors. Zotterman reported an increased firing rate of 17 imp/sec in mechanoreceptors when the skin temperature was dropped from 32 to 8°C as compared to 100 imp/sec when the same fiber was mechanically stimulated.

Hensel (124) suggested that one should speak of relative specificity because of the difficulty of considering specificity on the basis of firing rate alone. Some temperature fibers have a maximum frequency which is lower than the maximum thermal response of mechanical receptor fibers. Whether these mechanoreceptors
furnish thermal drives for temperature regulation or perception is not known.

What type of fibers conduct thermal responses? Gasser and Erlanger (86) made several attempts to classify fibers according to modalities. Finally, Gasser (85) concluded, "fibres belonging to different modalities must be widely distributed throughout the various fibre sizes, and...there seems to be little possibility of associating any one sensation with an elevation in the electroneurogram."

Assuming that thermal afferents intimately are associated with thermal regulatory responses, Zotterman (292) suggested that the thermal afferent influence upon the thermal regulatory system would be directly related to the temperature and the area of the skin. Assuming an even distribution of receptors on the body, the "thermosensible tonus would thus be a direct function of the integral of skin temperature." He did not believe that there was an even distribution of receptors. He thought that the trigeminal and other areas would display a more dominant influence upon the regulator. Zotterman has noted the relatively small number of impulses and low firing rates of warm receptors compared to cold. It would seem likely that the cold receptors would have a more dominant influence upon the regulator, but there is, as yet, no evidence to support this supposition.
Effects of Pharmacological Agents upon Thermal Receptors

Pharmacological changes in sensitivity of thermal receptors may be due to changes in cutaneous blood flow, stimulation of autonomic fibers with the resultant release of their neurohumors, non-specific effect upon all nerves, specific action on afferents, or sole influence on thermal receptors.

When large doses (100 μg of acetyl-beta-methylcholine) of cholinomimetic agents were injected under the skin, generally, sensitivity first decreased as measured by either action potentials per sec per °C or the number of cold "spots" per square cm per °C (28,55). Secondary effects of large doses and the primary effect of smaller doses of cholinomimetic agents (e.g., 0.3 - 10 μg acetyl-beta-methylcholine) increased sensitivity up to 120%. Epinephrine decreased the number of cold "spots," but dibenamine had no effect. Neostigmine responses are similar to acetyl choline responses.

Hensel and Zotterman (134) found that topically applied menthol solutions increase sensitivity (firing rate/°C) of "cold" fibers, but not "warm" fibers. Menthol was not merely activating the nerve because it had no effect when temperatures were above "cold" fibers' normal response range. Helmendach and Meehan (119) confirmed these observations while studying the effects of topically applied menthol solutions upon thermoregulatory responses in animals.
The action of pharmacologic agents upon the cutaneous thermal receptors appears to be an interesting tool for studying the thermoregulatory contribution of the cutaneous thermal receptors. The marked influence of cholinergic agents and menthol on thermal receptors presents interesting possibilities. One might speculate that autonomic nerves release acetyl choline which could regulate thermal receptor sensitivity in a manner similar to that suggested for muscle spindles and carotid sinus baroreceptors, representing a possible feedback control.

Cutaneous Thermal Pathways in Central Nervous System

Conventional teaching indicates the thermal afferents enter the spinal cord by way of the dorsal roots and ascend or descend one to three segments in the dorsolateral fasciculus or the tract of Lissauer along with pain fibers. These fibers then synapse with other nerves from the substantia gelatinosa and the dorsal funicular gray. Some cell bodies of the substantia gelatinosa and the dorsal funicular gray make reciprocal connections with each other. Fibers from the substantia gelatinosa then may send fibers to upper or lower segments of the spinal cord. The distribution of these fibers from the substantia gelatinosa form a very complicated multilayer, multisegmental circuits. Certainly, this suggests that these circuits do not serve as mere
relay stations, but are no doubt performing highly integrated information processing (255).

Some of the cells from the substantia gelatinosa and dorsal funicular gray run ventrally and medially to cross to the contralateral side via the anterior gray commissure to form the lateral spinothalamic tract. The fibers in this tract are mostly 2 to 4 μ in diameter with most of the remainder being made up of fibers less than 2 μ and 4 to 6 μ in diameter. In the ascending tract the fibers from the upper extremity are ventromedial to those of the lower extremity. Some workers suggest that the thermal fibers lie more dorsally and medially, for lesions may remove pain without absence of thermal sensation (58,74). Others have reported absence of pain and cold sensation, but not warm sensations. Still others have doubts about the presence of temperature fibers in the lateral spinothalamic tract. White performed spinothalamic cordotomies and abolished deep pain in 10% pinpricks in 40%, and heat sensation in 25% of his cases. However, Schiff (241) and Brown-Séquard (39) made anterolateral spinothalamic lesions and abolished the sensation of pain, heat, and cold, but not position, vibratory, or tactile sensations.

As the fibers of the spinothalamic tract descussate and ascend, collaterals are given off to the ventral horn, substantia gelatinosa, and the dorsal funicular gray at different segmental levels. These synapses also occur in the brain stem reticular gray.
Other fibers from the dorsal funicular gray subdivide into a dorsomedial and ventrolateral portion (also called the intermediomedial and intermediolateral gray of the dorsal horn of Metter). The dorsomedial is associated with proprioceptive and tactile afferents while the ventrolateral portion is associated with pain and temperature (54).

Cells from the dorsal funicular gray may receive some temperature afferents. Secondary fibers decussate to a tract (spinotectal) which is on the medial border of the lateral spinothalamic tract. The spinotectal tract forms the most dorsal component of the ascending lemniscal system. Most of the spinotectal tract and some fibers from the lateral spinothalamic end in the superior colliculi. The other lateral spinothalamic fibers continue to the posterolateral ventral nucleus of the dorsal thalamus (54).

Temperature and pain fibers from the face are conducted via the trigeminal nerves. The afferent cell bodies are in the semilunar ganglia. These fibers enter at the level of the pons and descend in the spinal tract of the fifth nerve. They synapse with the nucleus of the spinal tract of the fifth nerve in the medulla and in the gray matter of the upper four cervical dorsal horns. From here they pass obliquely forward and decussate, forming the ascending ventral secondary tract of the fifth nerve. This tract ends in the posterolateral ventral nucleus of the dorsal thalamus. In the posterolateral ventral nucleus (postero-
ventral) of the dorsal thalamus, fibers from the head are posteromedial, from the tail are anterolateral, the back are superior, and the feet are inferior. Classically, the thalamic projections extend from this thalamic nucleus to the post central gyrus of the cortex.

It is interesting to note that when Penfield (210) stimulated the postcentral gyrus of conscious humans, the responses of these patients were described as tingling in corresponding peripheral areas, but never a clear sensation of touch, hot, or cold. This certainly weakens the idea of the representation of the four modalities, in this case temperature, in the cortex. Noting this, Schiller (240) suggested the idea of "locoception." Locoception is nearest the sensation of touch, but is not the same, for it evokes information of only location or "local sign." The main contributors to this sensation are thought to conduct via large myelinated fibers which conduct rapidly. This would involve time discrimination and location discrimination, behavior such as vibratory sensation, two-point discrimination, stereognosis and kinesthesia. To support this idea, he noted that increased frequency of vibration or electrical stimulation of the skin does not produce a sensation of greater intensity, but instead an increased repetition of the stimulus. It is possible that the sensation of temperature is similar to the sensation of pain which is not considered to occur at cortical levels, but instead at thalamic levels. Thus, the application of
hot or cold probes to a surface consists of a thermal sensation combined with a lococeptive sensation. It is interesting that the sensation of heat without accompanying touch is very poorly localized.

Other peripheral sources of thermal afferents are those which travel in the sympathetic nerves. These afferents are generally classified as "visceral afferents" despite their origin although the term "sympathetic afferents" is commonly used. These fibers travel to the cord in the dorsal root and terminate in the region known as the secondary visceral gray. Fibers rising from the secondary visceral gray region travel crossed and uncrossed up and down in the secondary visceral tract which is found ventral to the intermediolateral cell column. Multisynaptic connections are thought to be made with the entire spinal cord, the tectal region, and the diencephalon.

Are the thermal afferents responsible for thermo-regulatory reflexes found in the somatic afferents or the "sympathetic afferents"? Foerster (73) had noted thermoregulatory responses on intact areas of paraplegic patients upon cooling the isolated areas despite the absence of thermal sensation from this isolated area. Cooper and Kerslake (52) selected a patient who was to have a lumbar sympathectomy. Before surgery with blood flow stopped by means of an occlusion cuff around the leg, the legs were heated. Blood flow in the forearm increased during the heating of the leg. When the same patient was tested after
surgery, they found that the reflex vasodilatation was abolished despite the fact that the patient still could feel the heat on the leg. They concluded that the afferent fibers which are traveling with the sympathetic nerves are responsible for the thermal reflexes.

Rawson and Hardy (227) tested this hypothesis from another standpoint. They heat-stressed two groups of subjects: one group had lumbar sympathectomies and the other had cord lesions at the T12 level. While measuring evaporative sweat loss from the portion of the body above the lesion or sympathectomy, the legs were suddenly cooled while blood flow was occluded. Sweating on the upper area was inhibited by cooling the legs of the sympathectomized patient, but not in the paraplegic. The paraplegic had near normal sympathetic innervation and presumably normal visceral afferents, but no somatic afferent innervation between the isolated cord and the remaining CNS. They concluded that intact somatic sensory afferents are essential for the sweat inhibition.

However, Hardy (106) in another publication confirmed Cooper and Kerslake's observations on vasodilatation. Therefore, the matter is not entirely clarified.

There is little doubt that thermal receptor information reaches the CNS, for one perceives the difference between hot and cold. There is a great deal of information suggesting the involvement of cutaneous thermal receptors in temperature
regulation, but the site of this integration is unknown. Most have presumed this integration to occur in the hypothalamus. Unfortunately, very little information has been obtained to support this contention.

Feldman (68) has shown that afferents do travel to the hypothalamus although he has not specified their nature. He has stimulated the sciatic nerve or lemniscal tracts and evoked short latency potentials in the posterolateral hypothalamus. Longer latency responses were evoked in the posterior and anterior hypothalamus. It is possible that fibers may descend from the afferent projection areas in the thalamus to the hypothalamus, but such functional pathways have not been shown. Feldman's work suggests a different explanation. Because of the nearly simultaneous evocation of responses in the thalamus and hypothalamus, parallel rather than series pathways with the thalamus are suggested.

Recently, Wit and Wang (286) have presented the first indication of thermal afferent activity in the hypothalamus. Recording single unit activity in the preoptic and anterior hypothalamic region, they reported evoking responses related to peripheral thermal receptors.

The possible distribution of thermal afferent pathways in the CNS appears almost fathomless. Further complication of thermal afferent conduction is apparent, for some areas of the CNS can modulate afferent conduction in the CNS. Tolle, Feldman, and
Clemente (262) have shown that ascending visceral afferents (and perhaps thermal afferents) can be blocked at cord levels by stimulation of the ventromedial reticular formation. Other types of stimulation can block multisynaptic conduction of afferents to the hypothalamus. Presumably, the segmental and intersegmental reflexes are also regulated by suprasegmental nervous structures.

History of Supraspinal Thermoregulatory Areas

1874 - 1929 --- The Importance of Suprasegmental Control

The first clear indication of the possible role of the suprasegmental neural structures in temperature regulation was presented by Goltz in 1874 (91). Goltz observed that heating and cooling the carotid sinus blood could initiate thermal responses in animals. Ten to twenty-one years later, Ott (205-208) and Richet (231) observed that hyperpyrexia resulted from lesions in the basal region (areas adjacent to the corpus striatum). Kahn, 1904 (158), heated the heads of dogs and observed that rectal temperature fell; cooling produced elevation in rectal temperature. Karpus and Kreidl, 1911 (159), located heat regulation areas at or near the base of the optic thalami and upon heating these areas observed sweating on the cat's foot pad. The same year, Moorehouse repeated Goltz's experiment with similar results and conclusions (191).
In 1911, Garrelon and Langlois (83) and Nicolaides and Dontas (203) placed lesions in the anterior medulla. Polypnea, which was usually observed upon heating, was blocked while the animal remained self-respiring. The authors concluded that some structures above this region were responsible for the thermal polypnea, but not normal respiration.

Barbour, 1912, circulated hot and cold water through silver thermodes near the basal ganglia of anesthetized dogs (12). Heating the basal ganglia resulted in lowering of the body temperature, whereas cooling evoked a rise in body temperature. In 1913 Citron and Leschke (45) and also Barbour and Wing (14) supported the view of a subthalamic location of a thermoregulatory region. Further support of a corpus striatum location came from Hashimoto (112), 1915, Prince and Hahn (214,215), and Moore (190).

Isenschmidt and Schnitzler, 1914, directed their emphasis away from the role of the corpus striatum and toward the hypothalamus (149). The striatal importance was further challenged by work of Sachs and Green (239), who found inconsistent results from heating the striatum. Hasama, 1929, supported the hypothalamic localization, by heating the base of the hypothalamus and preoptic region of cats while observing sweating on the foot pad accompanied by falling rectal temperatures (111).

Clearly, most investigators recognized the importance of suprasegmental neural control of temperature regulation. The
thermoregulatory "spotlight" was turning from other CNS structures to the hypothalamus.

1930 - 1960 --- Age of Elucidation of Hypothalamic Role

Despite the work of Isenschmidt and Schnitzler (149) and others, the area of primary regulatory control was not convincingly localized in the hypothalamus (13). However, from the 1930's to the present, a voluminous quantity of work has been performed supporting the role of the hypothalamus in temperature regulation. This work generally stemmed from combined efforts of groups led by Keller, Hemingway, Brobeck, Anderson, and Ranson and Magoun.

In the early 1930's, Hammouda implicated the hypothalamic role in temperature regulation (100). He perfused the third ventricle, which represents the medial aspects of the hypothalamus, with warm saline and noted polypnea and panting.

Starting in 1913 and continuing into the 1960's, Keller and co-workers have stirred controversy about the hypothalamic role (161-163). They have removed the posterior hypothalamic gray bilaterally which resulted in deficits in heat gain mechanisms, but with only a raised threshold to heat loss mechanisms. Transverse sections just rostral to the chiasma, unilateral hypothalamic sections, and bilateral extirpation of the ventral
third of the hypothalamus produced no gross impairment of temperature regulating ability. Even with complete removal of the hypothalamus, thermal panting was observed although again the "threshold" was significantly altered. Panting started with a rise in rectal temperature and stopped when rectal temperature fell. This work is reminiscent of observations of Bazett and Penfield (19) who reported thermal polypnea in bilaterally decerebrate animals. Keller reported that the ability to regulate to cold with these lesions was remarkable in cats, but dogs encountered much more difficulty.

Thauer (258-261) noted that cats with high cord lesions or brain stem lesions maintained ability to regulate against mild cold. These observations stand opposed to those of Sherrington who noted the lack of body temperature maintenance after cord section (244,245). The difference may be related to the degree of cold stress used by Sherrington and Thauer.

Probably the most notable work on the hypothalamic role in temperature regulation was done by Ranson and his group of coworkers. In 1936 Teague and Ranson (257) and later Clark, Magoun, and Ranson (46,47) observed the inability of animals to regulate in warm environments with lesions in the thermal sensitive preoptic region. Simultaneously, Frazier, Alpers, and Lewy observed similar results (78). In both experiments, no loss of heat production ability was noticed. Magoun, Harrison, Brobeck, and Ranson (185) heated the preoptic area of cats with RF currents,
inducing an increased respiration rate and panting, together with foot pad sweating. These responsive thermosensitive areas were found as far posteriorly as the anterior border of the midbrain.

Results of lesions in the hypothalamus are suggestive of its importance as a thermoregulatory "center." But some investigators question whether the hypothalamus is merely a conduction pathway from other areas. Bard and Rioch (15) and Pinkston (212) performed chronic bilateral decortications, removal of neopallium and archipallium, including the hippocampus, with no impairment of regulating ability.

Hemingway and co-workers have restricted their investigations primarily to control of shivering (120-122). They observed that heating the anterior hypothalamus inhibited shivering, whereas stimulation of the medial part of the posterior hypothalamus induced shivering. This suggests that shivering control is primarily located in the dorsal posterior hypothalamus with warm inhibition from the anterior hypothalamus. Such a view is not in full accord with Keller's work (161) in which lesions in this location still permitted shivering upon cold stress. Hemingway has argued that in Keller's experiments the amount of shivering and its threshold were questionable.

Brobeck repeated the preoptic lesions done by Clark et al (47) and confirmed their observations and conclusions (101). Brobeck placed lesions in the ventromedial nucleus observing no impairment of heat loss mechanisms except possibly during exercise,
Other hypothalamic lesions also were made, but they seemingly induced no impairment of heat loss mechanisms.

Anderson and co-workers likewise validated Magoun and Ranson's conclusions by stimulating the anterior hypothalamic and preoptic region of goats to abolish shivering without panting (7-9).

Further support of Magoun and Ranson's observations was offered by Donhoffer (59,60), Ström and Folkow (75,251), and Kundt, Brück, and Hensel (172) who studied control of panting, vasodilatation, sweating, and shivering.

Lim and Grodins (180), Hardy, Hammel, and co-workers (82), and Anderson (7) observed that responses to heating or cooling the anterior hypothalamic and preoptic region depended upon the ambient temperatures. Cooling the skin inhibited panting, and warming the skin inhibited shivering. In some cases, it was possible to induce animals to pant and shiver at the same time.

A new mechanism of temperature regulation has been suggested by Feldberg (67) who noticed that infusion of norepinephrine into the third ventricle lowered a pyrogenic fever to normal temperature. It has been found that 5-hydroxytryptamine (5-HT) produces fever upon intraventricular infusion. This fever is alleviated by infusion of norepinephrine or epinephrine. High concentrations of 5-HT and norepinephrine have been found in the hypothalamus. Pyrogens increase the sensitivity of the
hypothalamus to 5-HT. This suggested to Feldberg that temperature
responses were influenced by the relative amounts of 5-HT in the
hypothalamus. If the pyrogen increases sensitivity to 5-HT, the
balance of 5-HT to norepinephrine is upset and fever results. The
role of 5-HT and norepinephrine in normal non-pyrogen temperature
regulation is not known.

It has been surmised from the literature that if lesions
are placed in the anterior hypothalamus and preoptic region,
impairment in heat loss mechanisms are induced, but heat gain or
conservation mechanisms remain intact. What is the origin of the
thermal drive for heat gain or conservation when the anterior
hypothalamus and preoptic region are damaged? Is this due en­
tirely to afferents from skin, viscera, muscle, etc.? It would be
interesting to see if a thermode placed in the posterior hypo­
thalamus of these animals might evoke heat gain and conservation
mechanisms upon cooling. Another challenging question may be
posed. What is the stimulus for the thermal polypnea observed in
Keller's midbrain animals?

Electrical Activity of Central Thermoreceptors

Experiments involving surgical and electrical lesions,
electrical stimulation, or stimulation by heating and cooling have
strongly suggested the presence of central thermal receptors in
the diencephalon's anterior hypothalamus and the telencephalon's preoptic region. Recording of electrical activity is necessary to verify the presence of thermal sensitive structures in the hypothalamus.

Von Euler recorded slow potentials from the anterior hypothalamus (270). The D.C. potentials, as well as the incidence of panting, correlated with a rise in anterior hypothalamic temperature.

Freeman, in 1957, failed to record any gross changes in AC potentials in the anterior hypothalamus when it was heated (79). However, this work may be inconclusive since a small population of discharging fibers may very well go undetected.

The first recording of single cell unit activity from the thermal sensitive neurons in the anterior hypothalamus was reported by Nakayama and Eisenman (198-200). The firing rate in a typical sensitive unit was 7.2/sec at 36.8°C, 15/sec at 38°C, and 21.2/sec at 38.7°C. These units showed very little adaptation at a given temperature. Rapid elevation in temperature sometimes resulted in an initial fall in firing rate, e.g., from 9.5 to 6, followed by an elevation to 28/sec. Other units showed initial decrease in firing rate, followed by an increase in firing rate as temperature was reduced. Hardy, Hammel, and Nakayama (108) and Nakayama, Hammel, Hardy, and Eisenman (200) reported the results of over 500 unit recordings in the preoptic region. One out of five active cells increased its firing rate with increased
temperature, having a Q10 of five to ten. A majority of units showed a Q10 of one to two. The highly sensitive units increased their firing rate 2 to 10 impulses/sec per 1°C change in temperature. No thermal sensitive units were found in the supraoptic nucleus, posterior thalamus, or thalamus. Respiration rate also increased during the heating, but not in proportion to the firing rate of thermal sensitive units. When the hypothalamus was cooled the unit activity decreased while respiration increased.

More recently, Cabanac and Hardy (41) reported the recording of two distributions of cells, suggesting sensors in both a "cold" and "warm" range. Intravenous injection of pyrogenic substances decreased the activity of the warm units from 50 to 100% after a latency of seven to thirty minutes.

Wit and Wang (286) also recorded from thermally sensitive units in the preoptic and anterior hypothalamic region. Some units responded with increased firing rate with an increased preoptic and anterior hypothalamic temperature. Others responded with an increased peripheral temperature, as well as with a rise in brain temperature. The authors suggested that these units represent a possible site for the convergence and integration of central and peripheral components in temperature regulation.

However, one cannot assume that these cells represent true receptors as is the case with peripheral temperature receptors. It is entirely possible that temperature may alter synaptic function in such a manner as to facilitate or inhibit
activity originating from other cells. It would be interesting to know how thermal sensitivity of these units may be altered if the preoptic and anterior hypothalamic areas were isolated from other CNS structures.

Central Sensor Temperatures

The discovery of the relative constancy of body temperature and interest in thermoregulation were parallel developments. Dr. Hardy (105) has well stated the viewpoint of many investigators, "It has been a natural feeling on the part of those studying temperature regulation that there should be in the body a location in which the temperature is relatively constant (and therefore regulated) even during the exposure of the animal to severe thermal loads." However, thermal constancy of a structure may be de facto, rather than the result of active control.

Because of convenient location and stability, rectal temperatures were commonly measured. Investigators such as Tanner (256) and Ivy (153) measured rectal temperatures in hundreds of subjects and arrived at similar average values of 37.1°C (SD ± 0.23°C). For similar reasons, oral temperatures were measured and found to average about 0.4°C lower than rectal. Also, many other deep body temperatures have been measured, e.g., esophagus, stomach, central blood vessels, chambers of the heart, mucosa of accessory nasal sinuses, tympanic membrane, etc.
The location of a sensor which serves as the regulator in the location which shows the longest time constant results in poor regulation of the entire system (see discussion on control theory). Several experiments can be cited comparing the temperature variability of various structures during procedures such as intravenous infusion of hot or cold plasma, rapid heating of entire body, and fever. These procedures produced rapid changes which induced temperature alterations in the great veins, followed by esophageal, oral, cranial, and finally, rectal temperatures (42,51,53,81,82,186). This relative constancy or lack of variability in rectal temperatures is best explained by the large thermal capacity and relatively low blood flow of the pelvic organs surrounding the rectum.

Numerous authors have observed thermoregulatory responses occurring before changes in rectal temperature, consequently, other locations for the control sensor were sought, e.g., the hypothalamus. Benzinger (23,24,26) attempted to find a convenient location in intact humans to measure temperatures which were similar to those of the hypothalamus. He suggested the tympanic membrane, for it lies roughly 5 mm from the ascending internal carotid artery; he thought the tympanic membrane's main heat source was the internal carotid artery. To support the validity of this location, Benzinger measured on one patient temperatures of structures which are near the hypothalamus (the anterior wall of the sphenoid sinus), which are supplied by the
internal carotid artery (Rosenmueller's fossa). He found that the tympanic membrane was from 0.15 to 0.27°C warmer than the nasopharynx or sphenoid sinus temperatures. It is interesting that Benzinger did not record oral or esophageal temperatures. Minard and Copman (189) have accumulated a table of average resting internal temperature gradients taken from several authors. In this table, oral, nasopharynx, and sphenoid temperatures are identical. One might conclude that oral temperatures are a better estimate of internal carotid artery temperatures than tympanic membrane temperatures.

Benzinger presumed that the heat source of the tympanic membrane is almost entirely from the internal carotid artery. "The eardrum is near the hypothalamus and shares a common blood supply with it from the internal carotid artery [24]." However, the tympanic membrane is supplied by two to three branches of the external and one branch of the internal carotid artery. The blood supply to the nasopharynx and nasosinuses is not simple, being supplied by both external and internal carotid arteries (247). Correlation of hypothalamic temperatures with Benzinger's measure of cranial temperature is further complicated by differences and variations in local metabolism and blood flow of these structures.

Benzinger cautioned against the use of tympanic membrane temperature in environments of less than 30°C, unless the earlobe and surrounding area is insulated. He attributes this artifact to the return of relatively cool blood from the lobe and
surrounding skin via descending veins passing adjacent to ascending arteries which supply the tympanic membrane. Other possible "counter-current" exchange areas have been suggested. Rubenstein, Meab, and Eldridge (237) observed a fall of 0.2 to 0.5°C in common carotid temperature when ice packs were applied to the "homolateral side of the anterior aspect of the face and forehead." This area of the face and forehead was previously shown to have a high blood supply and arteriovenous thermal exchange (64).

Randall, Rawson, McCook, and Peiss (226) have questioned the identity of tympanic and hypothalamic temperatures. They occluded the common carotid artery of cats producing an elevation in hypothalamic temperature, but a reduction in tympanic membrane temperature. This was interpreted to indicate the tympanic membrane was heated by the carotid blood, whereas the hypothalamus was cooled by carotid blood.

Minard (189) summarized the present status on the usefulness of the tympanic membrane temperature, "Benzinger concludes from his studies that temperatures measured in accessory nasal sinuses, in the nasopharynx, and at the tympanic membrane accurately reflect changes in temperature of the internal carotid artery. Hypothalamic temperature, he (Benzinger) believes, closely parallels that of blood supplied to it by the internal carotid. Both of these assumptions are still lacking in experimental proof."
Because of the unresolved significance of tympanic, oral, and rectal temperatures, the experiments to be described in this dissertation generally record all three measurements of central temperature.

Hypothetical Thermoregulatory Systems

Application of control theory to thermoregulation has shed light on numerous possibilities.

Hardy (105,109) has described four simple types of control systems for temperature regulation. The simplest type is the "on-off" in which the system is either completely off or maximally on. There is little or no evidence on which to base its sole existence in temperature regulation.

A second type is a continuous proportional control system in which there is a linear relationship between the error signal and the output. The error signal is equal to the difference between a set point temperature and the actual temperature of the controlled area, e.g., the hypothalamus. Such a system is most frequently suggested for temperature regulation.

Integral control is a third possibility. The output would be related to the magnitude of the error signal and the duration of the error. However, no evidence of integral control has been presented for temperature regulation.
A fourth type of basic controller is one which responds to the rate of change in temperature. Hardy has presented some evidence of central temperature rate responses (109).

Hardy placed most emphasis on the proportional control system. He first suggested that the thermoregulatory output was proportional to the error signal from the "tissue" plus the error signal from the brain temperature. In both cases these error signals represented the difference between the actual temperature of a structure and a set point temperature.

Burton (40) viewed the system slightly differently. He considered the output as being equal to a proportionality constant times the hypothalamic error signal plus a proportionality constant times a skin error signal.

Benzinger's modification (26) stated that the output was equal to a proportionality constant times the hypothalamic error signal plus the product of a proportionality constant times the difference between skin temperature minus 33°C. Skin temperature was limited at 33°C because Benzinger considered only "cold" receptors which he thought did not respond above 33°C skin temperature. Benzinger thought the hypothalamic set point was 36.9°C.

Hammel et al (98) have proposed a different relationship. The thermoregulatory output is equal to a proportionality constant times the hypothalamic error signal. The proportionality constant and the setpoint were a function of skin temperature, exercise, CNS excitability, feeding behavior, sleep, etc. No
values were given for the proportionality constant, nor the function of skin temperature of this constant or set point.

In another publication, Hammel, Jackson, Stolwijk, and Hardy (98) explored the possible applications of another control system. These authors proposed two types of thermosensors located in the thermosensitive region of the hypothalamus (See figure 2.). These two types of receptors have different Q10 relationships: one with a high Q10 and one with a low Q10. They proposed that the high Q10 receptors facilitated heat loss areas of the CNS which control respiration rate and sympathetic activity to the sweat glands. Such high Q10 receptors also inhibit heat gain and heat conservation areas of the CNS controlling shivering and cutaneous vasomotor activity. The low Q10 sensors inhibit heat loss areas and facilitate heat gain and heat conservation areas of the CNS. The net result from the high and low Q10 sensors in the hypothalamus is summative on the affected areas. Therefore, equivalent firing rates from both would cause no change in the output of the effectors and would represent the set point of the thermoregulating system. When relating hypothalamic temperature and firing rate for these two sensors, the set point or set zone temperature is the point where the curves for the high and low Q10 sensors cross over (See figure 3A.). Elevation of the low Q10 sensor curve would elevate the set point; lowering it would lower the set point. Raising and lowering of the high Q10 curve would have opposite effects. The gain of this hypothetical system
FIGURE 2

Hypothetical roles of the hypothalamus in temperature control (taken from Hammel et al [98]). This represents a sagittal section through the hypothalamus. High and low temperature coefficient thermoreceptors (high and low $Q_{10}$) are located in the preoptic region. Heat loss areas are located in the anterior hypothalamus, and heat gain and conservation areas are located in the posterior hypothalamus.
Variable set point hypothalamic control of temperature (taken from Hammel et al [98]). Firing rate of the high and low Q10 hypothalamic thermoreceptors was plotted as a function of hypothalamic temperature in various thermoregulatory states.
would be dependent upon the difference in the two slopes (of temperature change) for the sensors which would not change during alterations in the Q10 curves.

Other influences on thermoregulation were thought to facilitate or inhibit the high and low Q10 sensors, thus shifting the set point to a higher or lower hypothalamic temperature (See figure 3B.). "Warm" receptors as well as exercise facilitated the high Q10 sensors lowering the set point temperature. The reticular activating system (RAS) and "cold" receptors are pictured as facilitating the low Q10 sensors and elevating the set-point. Thus, during sleep, the decreased RAS facilitation results in lowering the set point. They proposed that pyrogens would decrease the activity of the high Q10 sensors resulting in an elevated set point.

When considering the possibility of slope changes of high and low Q10 sensors, the number of possible different set points becomes infinite. The set point and gain of the system becomes so variable that one cannot help but wonder about the set point concept. Until further evidence has been accumulated, this variable set point concept has no quantitative predictive value, i.e., knowing hypothalamic and skin temperature, one cannot predict the thermoregulator output.

The location of thermosensors can make significant alterations in performance of the control system. If the sensor is located in the region of the body in which temperature
variations have the longest time constant, the entire system will make large slow oscillations. If the location of the sensor is in a structure with a short time constant, smaller and more rapid oscillations will be observed.

Location of sensors at the region of ambient thermal disturbance (at the skin) provides corrections before the core temperatures show any disturbances and thus decrease variation in core temperature. The location of sensors in the skin which are rate sensitive is of special importance. Assuming non-varying time constant characteristics, the rate of change of skin temperature is proportional to a step change of environmental disturbance. Thus, thermoregulatory correction will tend to be proportional to the amplitude of the ambient disturbances before the full effect of the disturbance is sensed on any structure of the body.

Thermoregulation: Special Emphasis on Control of Sweating

The role of the hypothalamus in temperature regulation has been previously described; the present section will consider the role of other thermal sensitive structures in the skin.

Many workers have concluded that other receptors are involved in thermoregulation. Fusco, Hammel, and Hardy (82), Forster and Ferguson (76), Lim and Grodins (180), Bligh (30-32),
Strom and Folkow (252), Hardy (97,107,108), Downey, Mottran, and pickering (61) all noted that dogs, cats, goats, or calves shiver when hypothalamic temperature is above non-shivering control temperature when skin temperature is lowered. These animals also pant when hypothalamic temperature is below non-panting control temperature, provided skin temperature is elevated. Polypnea and panting occur in exercising animals when both skin and hypothalamic temperatures are constant or decreased (154). Pyrogens induce an elevated threshold for polypnea and panting in dogs.

Kundt (172) and Ebaugh and Thauer (62) found strong correlation between hypothalamic temperature and peripheral blood flow in dogs. Kruger, Kundt, Hensel, and Brück (171) observed that hypothalamic cooling elicited vasoconstriction in peripheral blood vessels, and this vasoconstriction was inhibited when the animal was exposed to warm ambient temperature ($T_a$) (33-37°C) during the hypothalamic cooling period. Cooper, Johnson, and Spalding (50) concluded that vasodilatation of hand or fingers in man was inhibited by trunk skin temperatures below 33°C or "central" temperatures below 36.5°C. This implicated the roles of both "central" and peripheral temperature in thermal control of blood flow in humans. Cooper (49) observed vasodilatation in the hand ten to fifteen seconds after initiation of radiant heating of trunk skin; this occurred before central temperatures could be elevated. Helmendach and Meehan (119) also implicated the peripheral thermoreceptors in temperature regulation. They
observed that "peripheral thermoreceptors of menthol-treated animals were apparently sensitized since these animals stopped panting and started shivering with less cooling than did controls.

Fox and Hilton (77) suggested that thermal vasodilatation in humans was a result of the release of bradykinin from activated sweat glands during thermal stress. Hertzman (138) contended that cutaneous blood flow in man was well correlated with skin temperatures, but not with sweating or elevations in central temperatures. McCook, Wurster, and Randall (186) also failed to support the bradykinin hypothesis. They reported that sweating and cutaneous vasodilatation could be temporarily separated by as much as thirty minutes either way.

The role of cutaneous thermoreceptors in the control of sweating in man is an unsettled question. Kuno (173) and later Randall (217) observed local sweating when local heating elevated skin temperatures to approximately 43°C. Gurney and Bunnel (92) noted the presence of this local sweating even after the severance of the sympathetic nervous connections. Van Beaumont and Bullard (264) and MacIntyre, Banerffe, and Bullard (184) induced local sweating upon local heating with more nearly physiological temperatures, but their sweating responses required the presence of intact nervous connections. They hypothesized that this local temperature affected the nerve-terminal-sweat-gland unit, but was not due to a thermal reflex.
Ladell (175) cited Carmichael who immersed an occluded limb in 45°C water. No sweating was observed until the occlusion was released resulting in a rise in internal temperature. Kuno (173), Randall (219), and Issekutz (151) occluded blood flow to a limb while heating or cooling the limb. They noted increase or decrease in body sweating related to the limb temperature. However, Brebner and Kerslake (37) could not confirm these observations.

Winslow (284) stated that upon whole body heating, average skin temperatures must be 34.5°C to initiate sweating. This was confirmed by Robinson (233). Brebner (38), Kuno (173), Nielsen (202), and Winslow and Gagge (284) noted that sweating during various levels of exercise correlated with internal temperatures, but not skin temperature. However, Robinson (234) showed that sweating at different ambient temperatures while working at constant rate correlated with skin, but not internal (rectal) temperatures. Bazett (16), McKerslake (166), and later Hatch (113) held that sweating under various types of heat stress correlated with calculated "deep skin temperatures" and not with superficial skin nor internal temperatures. It is interesting that estimated depths in the skin are not far from Hensel's calculated depth of cutaneous thermoreceptors (0.8 ± 0.04 mm).

Issekutz, Hetenyi, and Diosy (152) held that the thermal receptors involved in thermoregulatory reflexes were different from those involved in perception of temperature. They reported
that some substances (e.g., capsaicin) increased the sensation of warmth without affecting sweating. One may question whether the sweating they observed was being driven by cutaneous or by core temperatures.

Randall and Hertzman (223) and Hertzman (137) reported that sweating was initiated in a caudal to rostral order, i.e., sweating was first observed on lower areas of the body followed later by sweating on upper areas. Randall (219) and Randall, Peiss, and Rawson (225) have confirmed this observation. They noted that the order of recruitment of sweating was nearly opposite to the order of recruitment of warm sensation (i.e., heat sensation was first reported on the forehead, chest, abdomen, etc. with the sensation finally noted on the lower extremity). Like Issekutz et al they concluded that the receptors involved in thermoregulation were different from those concerned with perception of warmth. Randall and co-workers reported this caudal to rostral sweat recruitment even when only the rostral half was heated. They believed that this was probably due to a segmental gradation in excitability of spinal sudomotor cells, together with the total impulse traffic in cutaneous afferent temperature fibers. However, such segmental gradation in sudomotor activity may occur if one assumes that the receptor for sensation and thermal reflexes are the same. It is difficult to understand why Randall et al would expect to see the same recruitment order of sweating and sensation if only one type of receptor were involved. No doubt
perceptive interpretation of thermal afferent information may complicate the picture. To the present author's knowledge, no neurophysiologic studies have proved or disproved this hypothesis.

As will be discussed in a later section, the presence of thermal sweating in areas innervated by the "isolated" spinal cord in paraplegic patients has been denied by many authors (93, 181, 213). Seckendorf and Randall (243) reported definite sweating in response to thermal stimulus on areas innervated by the "isolated" cord. However, the possibility existed that other sympathetic pathways from "non-isolated" segments of the cord were involved. If such objections can be eliminated, the spinal cord in normal man may be shown to participate in thermoregulatory sweating.

Hertzman, Randall, Peiss, and Adams (139) Robinson (233), Bazett (16), and Hardy (103) have concluded that total sweat output is determined by the total impulse traffic in the cutaneous temperature fibers, together with levels of excitability of central pathways, in part determined by central (hypothalamic) temperatures.

In the past decade, this role of cutaneous thermal receptors in control of sweating has been challenged by Benzinger (22-25). Combining rest and exercise data from human subjects, he deems the relation between sweating rates and skin temperatures as "senseless;" but he shows a nearly linear relationship between sweating and "cranial" temperatures. However, in Benzinger's view, when skin temperatures are below 33°C, sweating
is dependent upon both cranial and skin temperatures. He explains that below 33°C "cold" receptors inhibit the thermoregulatory heat loss system. It seems strange that at 33°C the "cold" receptors of man would suddenly inhibit sweating for they continue to fire at skin temperatures of up to 40°C. Hensel and Boman (125) described a nearly linear relationship of skin temperature to impulse frequency which exists between 20-25 and 40°C.

The role of skin temperatures above 33°C is masked by combination of exercise and resting data. When analyzing either Benzinger's resting or exercise data separately, a linear relationship is seen between skin temperature above 33°C and sweating. It is the contention of the present author, as well as others such as Hertig and Belding (136), Robinson (234,235), Asmussen (11), Minard (188), Bradbury (36), Keller (162), and Nielsen (201), that resting and exercise states are not comparable. Benzinger himself observed such thermoregulatory changes during exercise when comparing cutaneous blood flows ("conductance") at different skin and cranial temperatures.

Van Beaumont and Bullard (265,266) applied an occlusion cuff to the upper arm of their subjects before they performed isometric exercises of flexor muscles of forearm. Sweating on the same arm as well as contralateral arm and feet increased 1 to 2 seconds after initiation of exercise. In another procedure the cuff was applied 5 seconds before cessation of exercise to hold warm venous blood in veins and muscle of the forearm. Upon
cessation of exercise, sweating decreased immediately despite the pooling of blood. This procedure along with the rapid onset of sweating, argues against the role of venous and/or muscle thermal receptors in sweating induced by exercise. They held such sweating was due to either muscle receptors or irradiation of motor neural activity from cortex to autonomic control areas of the CNS.

The "set point" of cranial temperature in Benzinger's experiment averaged 36.69°C. If the standard deviation is calculated (SD = ± 0.42) on the seven subjects which he listed, 95% of the population would have a variation of set points from 35.85 to 37.53°C (assuming normal distribution and typical sampling). Considerable differences also exist in the ratio of sweating rate per change in cranial temperature although this was not mentioned by Benzinger.

In another series of experiments, Benzinger attempted to drive skin temperature and internal temperature in opposite directions by heating the carotid artery by microwave diathermy or by ingestion of ice. In either case, skin temperature curves moved in opposite directions from "cranial" temperatures; sweat loss followed a course nearly parallel to cranial temperatures. Benzinger concluded that sweating is proportional to the elevation in cranial temperatures above their "set point" as long as skin temperatures are above 33°C.

Adolph (3) and Randall (218) noted initial light sweating occurs with elevation in skin temperatures; profuse sweating
appears after a positive heat storage or elevation in central temperatures. Wyndham (288,289) observed similar relationships, reporting that regulator commands from the core temperature are at least four times as effective as those from skin temperature.

CENTRAL AND PERIPHERAL NEURAL PATHWAYS TO SWEAT GLANDS

Classic descriptions of autonomic innervation to sweat glands has been provided by Langley (177) and by Gaskell (84). Each described a very orderly picture of the preganglionic fibers leaving the anterior root and ending in the sympathetic ganglia. Synapses are made with the postganglionic fibers which re-enter the spinal nerve and distribute to the skin. Coldwater et al (48) challenged this orderly picture, for they found that it was impossible to predict the precise level of preganglionic entry except by direct nerve stimulation with recording of sweat responses. Patton stimulated single anterior roots and found that as many as eight ganglia were affected. If one single fiber was stimulated, the distribution was limited to only one or two segments (220).

Ring and Randall (232) traced small myelinated and non-myelinated fibers from the distribution of the spinal nerve to the glandular body. These fibers ramified and passed along the tubule where they entered the basement membrane and terminated near the
myoepithelial and secretory cells. Randall, McDonald and Stalzer (224) argued against the syncytial or plexiform network concept of this terminal innervation of sweat glands which Boeke (34,35), Kuntz and Napolitano (174), and others have suggested. Randall supported Hillarp's basic contention that the postganglionic fibers divide into smaller branches which innervate several sweat glands (142). Randall called the sympathetic fiber and its sweat glands a "sudomotor" unit somewhat analogous to a skeletal motor unit. At the postganglionic termination acetylcholine is thought to be released. However, iontophoresis of catecholamines also have effect, but non-physiological concentrations are required.

Foerster (71,72) described inhibitory innervation to sweat glands. He noted decreased sweating when the peripheral end of a cut posterior root was stimulated. The possible transmitter mediating this response is unknown.

Supraspinal neural structures modulate activity of sudomotor preganglionic sympathetic fibers. Much work on suprasegmental neural structures has been performed on the control of foot pad sweating of cats. Certainly one may question the similarity of the cat pad sweating to human thermolytic sweating. However, one is tempted to associate cat foot pad sweating with human palmar and plantar sweating. This association is not consistent because foot pad sweating is activated during central nervous heating whereas human palmar and plantar sweating is generally thought to be unrelated to thermoregulation.
Adamkiewicz (1,2) observed foot pad sweating produced by medullary stimulation in a narrow zone on each side extending from the other side of fovea inferior toward the calamus scriptorius. Wang and co-workers (275-78) have devoted a great deal of attention to suprasegmental control of cat footpad sweating. They find that neural structures such as cerebellum, cortex, midbrain, pons, and medulla may modulate sweat activity.

Pathways from these suprasegmental structures to the preganglionic cell body are difficult to localize. Roth and Johnson (157,236) indicated that sudomotor pathways are widely distributed in the anterolateral columns of spinal cord of humans. Wang finds some sudomotor pathways in cats in the pyramidal or corticospinal tracts. Other pathways exist from hypothalamus to the cord. These pathways are most like multisynaptic and probably traveling through the reticulo- or tecto-spinal tracts in the intermediolateral cell column.
CHAPTER III

METHODS

Experiments on human subjects were performed in adjacent and inter-connecting twin climate chambers. One of the chambers was equipped to provide ambient temperatures in the 10°C to 45°C range, while the other provided ambient temperature of 30°C to 95°C. The climate chambers were heated and cooled by means of convection. The walls were painted a non-glossy black allowing nearly maximal radiative heat exchange between the wall and nearby black body skin surface. Generally, adequate time was allowed for the air and wall temperatures to equilibrate.

Both chambers were provided with external heaters which were controlled by either a thermostatic or proportional controller. The lower ambient temperature chamber had an air conditioner placed in series with the air stream before the heater. The air conditioner was left on while the heaters were controlled to maintain the desired temperature. Air velocities were maintained relatively high to minimize thermal gradients within the chambers.

Water content of the air was measured but was not controlled. It was dependent upon the ambient water content, the water loss from the subjects and technicians, and the temperature of the chamber.
The subjects were placed on a frame which suspended them on a layer of copper screen (figure 4). The copper screen minimized insulation effects, allowing free thermal and water exchange of the subject with his environment. The subject was, thermally speaking, nearly floating in air. The two head boards, as well as a special partition to be described later, were designed to seal a common passageway between the two adjacent climate chambers. The bed was equipped with wheels which ran in U-shaped aluminum tracks. These tracks guided the movements of the bed and allowed rapid, smooth transfers from one chamber to the other in two to three seconds.

Thermistor leads were brought from the surface of the subject to the side of the bed where connections were made with long cables. The latter ran to the back of the head board of the bed where they plugged into a small metal box. A multiple pair cable went from this box through the ceiling. The cable was suspended so that it remained in one climate chamber even when the bed was in the opposite chamber. The cable left the climate chamber and was carried over to another small metal box located near the relay rack. From this box, individual channel leads plugged into the bridge panel in the relay rack. The output from the bridges was connected to one channel of a Grass Model 5 or Model 7 Polygraph.

Twelve skin temperatures were measured each minute by means of YSI thermistor probes (Model 421) which were cemented on
FIGURE 4

Diagram of the twin adjacent climate chambers.
to "flying-saucer" probes (figure 5D). The author designed the "flying-saucers" to hold the thermistor firmly and flatly to the skin. This mount decreased the tendency of the thermistor to roll and permitted free heat and water exchange between adjacent skin and the environment, thus circumventing a major problem in use of skin thermistors, i.e., the floating off of the adhesive or tape holding the thermistor when the subject was sweating. These probes were held to the surface by loose-fitting rubber bands going around the trunk or extremity and attaching to small hooks on the side of the probe. To minimize the influence of ambient temperature on the skin probes, the probe leads usually passed near the skin for about 6-8 cm.

One problem with most cutaneous thermistors or thermocouples is that the environmental heat causes errors of a couple of tenths of a degree as compared to radiometer measurements of skin temperature. Radiometer readings are impractical for measuring the twelve different skin temperatures as rapidly as was desired in these experiments. Another problem with most radiometers is that transients in environmental temperature of the equipment make the readings unstable and unreliable.

Oral temperatures were measured by means of a YSI thermistor probe (Model 421) without a "flying saucer." When subjects kept their mouths closed and the thermistor well under the tongue, reliable oral temperatures were recorded.
Circuit diagram, thermistor holders, and sample tracing of temperature recordings. A: electronic circuit for direct recording of separate skin temperatures as well as continuous electronic computation of mean skin temperature. T represents the recording thermistor or equivalent resistor for calibration. Resistors R1 through R6 were selected to balance each bridge at the designated temperature (1-6 at 37°C, 7-23 at 30°C). SUM indicates the Grass 5P1 preamplifiers modified to give an isolated 2-kiloohm input impedance. Points A1-A24 and B1-B24 are connected to their respective positions on the selector switch. B: earmold custom made for each subject from dental acrylic. C: temperatures were sampled successively at 5-sec intervals from the tympanic membrane (Ttm), 37°C calibration, 39°C cal, oral cavity (T0), 36°C cal, 30°C cal, ambient temperature in each of the chambers, 30°C cal, 25°C cal, 40°C cal, palm, forearm, forehead, upper chest, lower chest, upper abdomen, lower abdomen, medial thigh, lateral thigh, calf, dorsum foot, plantar foot, and mean skin temperature. The base line for the first six (internal) temperatures is 37°C and for the last 18 (external) it is 30°C. D: thermistor holder applied to the skin by elastic bands.
Rectal temperatures were measured by means of a YSI thermistor rectal probe (Model 401). The subjects generously lubricated the probe with petroleum jelly and inserted the probe 8 to 10 cm into the rectum. Except for an initial discomfort, no problems were encountered.

Tympanic membrane temperatures were measured by means of a YSI probe (Model 520). Each subject was fitted with a custom ear mold designed by R. Tinsley of Zenith Hearing Aid Corporation and the author (figure 5B). These ear molds differed from the standard hearing aid mold in that they extended considerably deeper into the auditory meatus, 2 to 5 mm from the tympanic membrane. A small hole was drilled the length of the mold, and a polyethylene tube cemented into the aperture. This tube terminated flush with the internal tip of the mold, but extended about two centimeters from its base. The subject placed the ear mold in the meatus after lubrication with mineral oil. The thermistor probe was passed down the polyethylene tube until the subject reported a scratching sound or a sharp pain associated with contact with the tympanic membrane. To fix the position of the probe, a miniature flat-nosed alligator clip or bull-dog clamp was placed on the extended polyethylene sleeve. After a short period of time, no pain, discomfort, or sensation was associated with the probe and mold.
Ambient temperatures were assessed by a YSI thermistor probe (Model 405) which was placed in the middle of each chamber a few feet above the subject.

These thermistors (T) formed one limb of a wheatstone bridge shown in figure 5A. Balance resistors for the tympanic membrane, oral, and rectal thermistors as well as for two calibration resistors were set at a resistance equivalent to 37°C. This included bridges one through six. Bridges 7 through 24 were zeroed at an equivalent resistance of 30°C. The bridges 7 and 8 were for the ambient thermistors, bridges 9 through 11 were spare skin temperature bridges, and bridges 12–23 were standard skin temperature bridges. In order to calculate mean skin temperature, the outputs from the bridges 12–23 were weighted by variable resistors according to the per cent of total surface area (Hardy [102]) and summed.

The output sensitivities of the bridges were determined by series resistors which attenuated the voltage output per degree of temperature. E.g., central temperatures - 200 Kiloohm resistors, ambient temperatures - 2 megohm, and skin temperatures - 1 megohm. This allowed the recording of small changes in central temperatures and large changes in ambient temperatures at the same amplifier sensitivity.

A twenty-four position solenoid-operated step switch sampled the twenty-four channels recording every two minutes. Channel number 24 was the calculated mean skin temperature. The
switch output was connected to a Grass 5P1 Preamplifier modified to give an isolated 2 Kilohm input impedance. This was displayed on one channel of a Grass polygraph (figure 5C).

Using photographic film, a transparent calibrator was designed with the appropriate scales for each of the 24 channels. The film was attached to the bottom of a plate of plexiglass to increase its rigidity. In order to prevent parallax errors, the emulsion side of the film was placed on the bottom of the calibrator. The calibrator was lined up with calibration channels provided on each 2-minute scan of the 24 channels. This corrected for any recording paper or electrical drifts that might occur. By such means, central temperatures could be read to the nearest 0.01°C although accuracy of the calibration beyond 0.04-0.05°C is questionable. Upwards of 900 temperatures were read per experiment in this manner.

Sweat activity was assessed by the iodine-starch-paper technique (Randall [216]). This technique involves the application of iodine-alcohol solution to a small area of shaven skin. The alcohol evaporates, leaving a coating of iodine on the skin. A small bead of sweat emerges from the sweat duct opening and dissolves a small amount of iodine from the skin. Precut strips of paper sized with starch are applied to the iodine-coated skin for twenty seconds.

A small amount of iodine is transferred to the starch paper by the bead of sweat. The iodine and starch react, leaving
a purple-brown spot on the paper indicating the activity of a single sweat gland. The number of spots or active sweat glands per square centimeter were counted with aid of a dissecting microscope and a glass lantern slide calibrated in square centimeters.

One technician took four such sweat records per minute. Generally, seven to eight areas were sampled per minute requiring two technicians. During a typical experiment, some 600 to 1,000 such sweat records are obtained, carefully examined, and counted. Despite the crudity of the technique, this provides the only method of assessing the number of active sweat glands per area of skin. Unfortunately, this does not tell how much sweat is being produced. Such equipment to measure continuous local sweating is now being tested by the author.

Each experiment requires the co-ordinating of four to five personnel: one subject, two sweat samplers, one man to operate bridges and polygraph, and occasionally one to perform special functions.
CHAPTER IV

EXPERIMENTS

The role of cutaneous temperatures in control of sweating remains unresolved. Benzinger concluded that sweat responses were positively correlated with central but not with cutaneous temperatures. However, he failed to perform the converse experiment, that is, to raise and lower skin temperature while core temperature was maintained constant. Consequently, it was important to repeat Benzinger's observations, together with these additional procedures.

To date, most of the investigators assign the role of integrative control of thermal sweating entirely to the hypothalamus. Seckendorf and Randall did not agree, for they observed sweating in skin of the paraplegic patient (lesion between T3 and T8). It was necessary to repeat these observations in patients with cord lesions situated above the anatomical outflow of sympathetic preganglionic fibers.

If the recruitment order of sweating could be reversed by specific changes in manner of exposure to hot environments, the relationship of cutaneous afferents to the control of thermal sweating may be examined in greater detail. Alterations in regional cutaneous thermal drives were further investigated by
comparing the sweating responses to cooling upper and lower portions of the body. Responses to cooling still smaller fractions of total skin area were also studied. Further, contralateral and ipsilateral stimulation, with recording of responses from both lower extremities provides information on segmental mediation of thermal reflexes. These experiments may provide information on the distribution of thermal receptors in the central nervous system.

Knowledge of the distribution of cutaneous receptors, as well as the nature of their sensitivity to temperature, is critical to understanding of their role in temperature regulation. Neurophysiological recording of their activity (123) and observation of responses during rapid changes in ambient temperature suggest that thermal afferents were highly sensitive to rate of change in skin temperature. Accordingly, experiments were designed to test this relationship.

The almost universal use of tympanic and oral temperatures in assessing operation of thermoregulatory mechanisms suggest that skin temperatures of the face, or temperatures within respiratory passages may play a role in thermoregulatory reactions.
Separation of Cutaneous and Core Sudomotor Drives

The relative participation of peripheral and central thermoreceptors in the regulation of thermolytic mechanisms has been vigorously debated. Benzinger (25) used temperatures recorded at the tympanic membrane ($T_{tm}$) as a correlate of hypothalamic temperature and presented arguments for its primary control function. While studying the changes in each of the avenues of heat loss, he emphasized the importance of complete separation of peripheral and central drives by holding one constant while varying the other. However, his demonstrations were limited to lowering $T_{tm}$ while skin temperature was held constant and to altering internal temperature by exercise or diathermic heating of carotid arterial blood during exposures of the subject to warm or cool environments. The complications produced by exercise prevent a clear evaluation of mechanisms.

The author does not accept the implication that temperature recorded at the tympanic membrane truly represents hypothalamic temperature (226). However, it may indeed reflect important changes in the temperature of blood which supplies the brain. The following four experimental procedures represent a direct extension of Benzinger's concepts.

1) $T_{tm}$ was forced up by rapid ingestion of hot fluids while mean skin temperature ($T_{ms}$) was maintained constant with the subject in an ambient temperature ($T_a$) of approximately 30°C.
2) $T_{ms}$ was rapidly elevated by moving the subject from a $T_a$ of 30°C to approximately 50°C while $T_{tm}$ was constant or falling.

3) $T_{tm}$ was forced down by rapid ingestion of cold fluids with $T_{ms}$ constant and a $T_a$ of 50-68°C.

4) $T_{ms}$ was rapidly lowered by moving the subject from a $T_a$ of 50°C to a cool environment while $T_{tm}$ was constant or rising.

A total of 48 experiments were performed to test the above procedures, using six nude, male human subjects, all of whom were members of the research team and thoroughly familiar with the technology and objectives. The subject reclined on a copper screen bed in one of the two interconnected climate chambers. The bed could be moved quickly from one chamber to another. Each chamber could be maintained at a different preset $T_a$. As described previously, $T_{ms}$ was computed; oral temperature ($T_o$), $T_{tm}$, and eight areas of sweating were recorded (186). The requirements of the four experiments necessitated that $T_{ms}$ and $T_{tm}$ be controlled independently. The subject was given hot or cold flavored drinks to raise or lower his $T_{tm}$ without greatly affecting the $T_{ms}$. The $T_{ms}$ was raised or lowered by moving the subject from a neutral or low $T_a$ to a high $T_a$, or conversely, within a period of 1-3 sec. Meanwhile, $T_{tm}$ either remained constant, declined, or rose for several minutes. This occurred despite changes in $T_{ms}$ because of the inertia in heat loss or heat gain, respectively.
Figure 6 illustrates the changes in sweating when a subject ingested hot fluids in our first procedure. Sweating and temperatures are represented by lines. Photoelectric plethysmograph pulses are indicated by shaded areas, but will not be discussed in this dissertation. The subject rested quietly for approximately 40 min in an ambient temperature of 30°C before the experiment began. During the control period, his $T_{ms}$ varied slightly between 32.6-33.0°C. $T_{tm}$ oscillated between 37.35 and 37.40°C. $T_o$ remained steady at 36.58°C. No sweating was present on any of the eight test areas.

After 17 min, the subject rapidly drank 400 ml of flavored water at 50°C. During the succeeding 12 min, $T_{tm}$ rose from 37.33 to 37.52°C with no apparent change in $T_{ms}$. Except for very slight sweating on the dorsum and calf at the beginning of the drinking period, no sweating occurred in any of the test areas. Then, as $T_{tm}$ declined, the subject was moved from an ambient temperature of 30°C into the hot chamber at 50°C. $T_{ms}$ began to rise immediately with practically a simultaneous recruitment of sweating on the lower extremities and only a slight delay in the upper extremities and trunk. $T_{tm}$ did not rise until after sweating began, although it promptly followed skin temperatures upward. Sweating was firmly established on all areas before $T_{tm}$ attained the maximum reached earlier during ingestion of hot fluid when no sweating was elicited. $T_o$ lagged behind both $T_{ms}$ and $T_{tm}$. After sweating was well established, the subject was rapidly moved from
Responses of a nude subject in a comfortable environment ($T_a$ 30°C) to ingestion of hot drink and to movement into and out of a hot environment (50°C). During the period indicated by the horizontal arrow at the top of the figure, 400 ml of hot (50°C) flavored water was ingested. The vertical dashed lines indicate when the subject was suddenly moved into and out of a hot environment. Mean skin temperature ($T_{MS}$), tympanic membrane temperature ($T_{TM}$), and oral temperature ($T_O$) are plotted in the upper portion of the figure. $T_O$ was not recorded immediately before, during, and immediately after the drinking period. Records of sweating on the indicated cutaneous areas are depicted by the black lines in the lower portion of the figure. Sweating is expressed in terms of active sweat glands per square centimeter, although sweating in excess of 40 active glands is not shown to prevent overlap. The shaded portions represent volume pulse amplitudes on five different skin areas as recorded by the photoelectric plethysmograph, but should be ignored in this dissertation.
the hot chamber back into the cool chamber at 30°C. Sweating stopped completely within 30 sec following entry into the cool chamber.

In figure 7, in $T_a$ of 30°C, the subject's $T_{tm}$ was steady at 37.6°C and $T_{ms}$ at 34°C. At these threshold temperatures, sweating was present on the dorsum and calf, but absent on all other areas. The subject was then shifted into the hot chamber at 47°C with the induction of fairly prompt elevations in both $T_{ms}$ and $T_{tm}$. Sweat recruitment was complete although it was considerably more intense on the lower extremities than upon the superior portions of the body. At the signal, the subject drank 400 ml of fluid at 4°C. $T_{tm}$ began to fall while $T_{ms}$ remained constant. The number of active sweat glands showed a distinct decline on those areas in which sweating had not yet become intense. A modest reduction which occurred in the lower extremity is not shown because of the method of plotting the figure. However, while the $T_{tm}$ continued to fall, decreased sweating was temporary and again increased in intensity. The subject was returned to the cool chamber at 27°C when $T_{tm}$ began to rise. Again, sweating was precipitately reduced.

In figure 8, the subject's responses are shown as he rested in the cool chamber at 25°C. His $T_{ms}$ and $T_{tm}$ were 33.9 and 37.5°C, respectively. Sweating was present on the dorsum and plantar surfaces, but absent on all other test areas. At the signal, the subject drank 400 ml of cold fluid at 4°C, which
Responses to sudden exposure to a high ambient temperature, the drinking of cold liquid, and the return to a comfortable environment. The left vertical dashed line indicates the sudden change from $T_a$ of 30 to 47°C. The right vertical dashed line indicates the return from $T_a$ of 47 to 27°C. The horizontal arrow marks the period of ingestion of 400 ml water at 4°C. All calibration scales and symbols are as described in the legend of figure 6.
Multiple cutaneous sweating responses to sudden exposure to a high ambient temperature after ingestion of cold drink and return to a low ambient temperature after ingestion of hot drink. The left and right horizontal arrows indicate the ingestion of 400 ml of cold drink at 4°C and 400 ml of hot drink at 50°C, respectively. The left and right vertical dashed lines indicate the sudden shift from $T_a$ of 25 to 68°C and back to $T_a$ of 25°C, respectively. Calibration scales and symbols are as described in the legend of figure 6.
promptly elicited a marked decline in $T_{tm}$ from 37.5 to 37.2°C during the following 7 minutes. While $T_{tm}$ remained 0.3°C below its initial level, the bed was moved into the hot chamber at an ambient temperature of 68°C. $T_{ms}$ promptly increased while $T_{tm}$ remained consistently below its initial control level. Sweating was recruited on all test areas starting well before $T_{tm}$ increased to control levels. The subject drank 400 ml of fluid at 50°C while still in the hot chamber. This drove $T_{tm}$ to 37.9°C, while $T_{ms}$ remained constant at approximately 38°C. The subject was then moved back into the cool chamber at 25°C. Despite the fact that $T_{tm}$ remained unchanged at a significantly elevated level, sweating stopped completely on all areas. However, it reappeared in slight intensity on three areas as $T_{ms}$ rapidly fell.

Table I describes results of 24 additional experiments representative of the 48 experiments performed. Six are presented to illustrate each of the four experimental procedures. Certain intervals of time have been selected in order to most accurately present the data in as brief a form as possible. Also for brevity, the number of active sweat glands per square centimeter for each of the eight test areas was summated. Averages have been calculated for time, temperatures, and sweating, and these average responses are discussed in the following paragraphs.

In procedure I, average $T_{ms}$ remained relatively constant throughout the entire procedure at 34.1, 34.0, and 34.1°C. The subjects drank fluid at 50°C in order to elevate $T_{tm}$, which rose
## TABLE I

<table>
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<tr>
<th>Subject</th>
<th>Immed before Ingest Fluid at 50°C</th>
<th>During Last Minute of Ingest Hot Fluid</th>
<th>At Max T&lt;sub&gt;tm&lt;/sub&gt; as Result of Hot Fluid</th>
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<td>T&lt;sub&gt;ms&lt;/sub&gt;</td>
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### Procedure I

<table>
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<th>Subject</th>
<th>In Low T&lt;sub&gt;a&lt;/sub&gt;</th>
<th>In High T&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Sweat Recruitment on All Areas</th>
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### TABLE I (continued)

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<td>37.71</td>
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All temperatures are expressed in °C. Sweat values represent summated counts of active sweat glands simultaneously recorded per square centimeter from eight separate skin areas as follows: dorsum foot, calf, thigh, abdomen, chest, forearm, forehead, and palm. The four horizontal columns describe six individual and the average responses to Procedures I, II, III, and IV as set forth in the introduction. The four vertical columns state the specific experimental conditions which characterized each of the four procedures.
from 37.50 to a maximum of 37.66°C. Moderate sweating was elicited during ingestion of hot fluid, but distinctly declined immediately following its cessation. The significant increase in sweating during the drinking procedure is attributable to possible psychic factors and/or direct stimulation of receptors in the buccal cavity, rather than to a rise in T_{tm}. This is suggested by the rapid decrease in sweating promptly after the actual process of drinking was completed. It is apparent, also, that some increase in sweating was related to the rise in core temperature, but this was small compared to sweating induced at high T_{a} after similar T_{tm} elevations.

In procedure II, average T_{tm} remained constant for several minutes at 37.4°C, as the subjects were moved from a chamber at low T_{a} (30°C) to a chamber at high T_{a} (50-68°C). T_{ms} rose rapidly from 33.9 to 35.4°C in the first minute following entry into the hot room, when the first definite increase in sweating was observed. After an average of 3 min in high T_{a}, sweat recruitment had occurred on all test areas, accompanied by a continued rise in T_{ms} to 36.1°C, while T_{tm} remained unchanged.

In procedure III, the subjects reclined at rest in a low T_{a} when sweating was absent and average T_{tm} and T_{ms} were 37.53 and 34.2°C, respectively. The subjects were then shifted into a high T_{a} of 50-68°C, where recruitment of sweating was attained on all areas with T_{tm} 37.69 and T_{ms} 36.9°C. The accurately measured sweat count was assigned a value of 100%. The subjects then
ingested cold fluid at 4°C and, during the last minute of the ingestion, $T_{tm}$ had fallen to 37.56°C while $T_{ms}$ continued to rise to 37.1°C. The average sweat count increased from 190 to 207, or 109% (although sweating did not increase in all subjects), despite the fall of $T_{tm}$. Six minutes after completion of the cold fluid ingestion, but while the subject remained in the high $T_a$, average $T_{tm}$ had fallen to a minimal value of 37.47°C, while $T_{ms}$ rose to 37.3°C. Sweating declined to 155, or 86% of control value. It is interesting to note that $T_{tm}$ was 0.06°C below the initial non-sweating $T_{tm}$, yet sweating continued while $T_{ms}$ was 3.1°C higher than in the nonsweating control.

In procedure IV, the subjects were first placed in low $T_a$ with $T_{tm}$ at 37.51 and $T_{ms}$ at 33.9°C with absence of sweating. After quietly resting for 30-45 min at the low $T_a$, the subjects were shifted into a high $T_a$ of 50-68°C. The subjects were usually maintained in the high $T_a$ for 15-20 min and attained an average $T_{tm}$ of 37.71°C, $T_{ms}$ of 38.3°C, and a sweat count of 472, which was assigned a value of 100%. The subject was then shifted back into the low $T_a$. After 1 min in the low $T_a$, $T_{tm}$ had continued to rise to 37.74°C, while $T_{ms}$ had rapidly dropped to 37.3°C. Sweating decreased from a count of 472 to 111 (occurring in all subjects), which was 26% of control. Within 1-4 min (average: 3) later, minimal sweating was observed; meanwhile, $T_{tm}$ remained elevated at 37.73°C, while $T_{ms}$ rapidly declined.
Most investigators have based concepts of thermolytic temperature regulation in man on experiments which have not separated or defined the major central and peripheral factors. These factors commonly vary at the same time and in the same direction, thus making it difficult to assess the relative importance of each.

Benzinger et al (25) in an elegant piece of research attempted to evaluate the independent thermolytic effects of $T_{ms}$ and $T_{tm}$ by driving them in opposite directions while measuring caloric exchange. Under steady-state conditions, they showed a nearly linear relationship between rates of sweating and $T_{tm}$ during rest and exercise. The relationship between sweating rate and $T_{ms}$ was deemed "senseless." However, if the exercise $T_{ms}$ and resting $T_{ms}$ of Benzinger's data are examined separately, a nearly linear relationship between sweating and $T_{ms}$ will be found. The present author suggests the possibility of alterations in excitability of thermoregulatory areas during exercise. This suggestion should be of no surprise, for somewhat comparable relationships between exercise and resting conditions have been described for both respiratory and circulatory systems. Thus, clear separation of variables important to thermal regulation may have been obscured by combining exercise and resting data.

Belding and Hertig (21) exposed exercising subjects to different $T_a$, and found that alterations in sweating were roughly proportional to the increase or decrease in $T_{ms}$ during transient
changes in $T_a$. $T_{tm}$ sometimes increased, but often remained unchanged. During stable conditions, they found a high correlation between sweating and $T_{tm}$. They also confirmed Hatch's (113) observation that skin temperature correlated with the difference between metabolic heat production and the evaporative heat equivalent of sweating. They reported that this latter correlation was as good as the correlation between $T_{tm}$ and sweating.

The first procedure of the present series of experiments (figure 6) failed to elicit sweating, even though there occurred a rise in $T_{tm}$ of almost $0.2^\circ C$. After the subject had entered a higher $T_a$, sweating appeared well before any rise in $T_{tm}$ occurred. In this procedure, it is important to note that $T_{ms}$ was higher than $33^\circ C$, which was higher than values specified by Benzinger. Table I, procedure I, well documents the observations in figure 6. When the hot water ingestion experiment was repeated at a higher $T_{ms}$ (about $35^\circ C$), an increase in sweating with the rise of $T_{tm}$ was observed. This experiment was similar to the microwave heating experiment of Benzinger (25), in which the $T_{ms}$ was over $35^\circ C$. The relationship between sweating and $T_{tm}$ at higher $T_{ms}$ may be explained by increased facilitation by cutaneous receptors of central mediation areas in the hypothalamus and/or spinal cord.

All three figures (6, 7, and 8) and the data from Table I procedure IV, illustrate a precipitous decrease of sweating associated with the rapid shift from hot to cool environments. The
course of $T_{tm}$ was not consistent, but there were definite changes in $T_{ms}$ in all subjects at the cessation of sweating. The changes in $T_{ms}$, although small, were rapid. The present author suggests the hypothesis that this inhibition of sweating may be related to the rate of decrease of $T_{ms}$. This hypothesis is supported by Hensel's work (123) which demonstrated that thermal receptors respond more to a rate of change than to absolute temperatures.

As shown in figure 7 and in the data from Table I, procedure III, the sweating subject's $T_{tm}$ was decreased below initial nonsweating levels by drinking cold water. Sweating was temporarily reduced, but it quickly recovered without further change in $T_{tm}$. Meanwhile, $T_{ms}$ remained elevated. Benzinger's group (25) also performed this experiment and reported decreased, but not totally suppressed, sweating (heat loss decreased from 54 to 24 cal/sec).

In figure 8, $T_{ms}$ and $T_{tm}$ were forced in opposite directions, both on entry into, and exit from, the hot chamber (procedures II and IV, Table I). The recruitment and inhibition of sweating correlated more closely with $T_{ms}$ than with $T_{tm}$.

It must be pointed out that deep cutaneous, arterial, and venous temperatures were not measured. These temperatures deserve special attention, for certainly they are influenced by ambient conditions and by ingestion of hot or cold fluids. They may represent more accurate estimates of local temperature alterations of the sweat glands and blood vessels.
The involvement of temperatures of skin and other areas has been pointed out by other authors. In analyzing the triggering mechanisms of sudomotor activity, Veghte and Webb (267) suggested that no one factor accurately reflects onset of sweating in all circumstances. In precooled subjects, $T_{ms}$ as high as 40-45°C were observed without sweating. They also observed sweating at times when internal temperatures were considerably below normal. It is common experience that working man may sweat profusely with a low skin temperature. Hammel et al (98) believe that the central temperature regulatory mechanism is a proportional controller located in the anterior hypothalamus. Its set point may be modified by skin temperature, core temperature, state of consciousness, and perhaps other presently unknown influences. According to this hypothesis, when $T_{ms}$ is elevated in a hot environment, the steady-state firing of cold receptors declines to zero: and the firing rate of warm receptors may increase. Therefore, the set-point temperature is lowered below hypothalamic temperature resulting in increased heat loss. There is accumulating evidence that other areas in the central nervous system have thermal receptor functions (260). Seckendorf and Randall have suggested that the isolated spinal cords of patients with complete spinal transections may be capable of mediating sweating reflexes (243). Robinson's (235) group suggests that reflexes originating in thermoreceptors in active muscles or in veins draining warm blood from them may also excite sweating during exercise.
Recently, van Beaumont and Bullard (264) demonstrated what they think to be direct thermal effects on sweat gland activity. It is possible that this direct effect may explain responses which were thought to originate from thermoreceptors.

The author of the current paper reemphasizes the importance of skin temperature, as well as measures of core temperature, in thermolytic regulation, at least during transitory states of $T_a$. The role of cutaneous receptors during steady-state conditions is hard to analyze in man because of the difficulty in separating peripheral from central factors.

**THERMOREGULATORY SWEATING MEDIATED BY "ISOLATED" SPINAL CORD**

Sweating mediated by the isolated spinal cord of humans is not a unique observation. Head and Riddoch, (118) 1917, reported sweating accompanying spinal mass reflexes, and others have reported sweating reflexes, especially when the abdominal visceral organs were distended (Guttmann and Whitteridge [94] and List and Pimenta [181]). Thermoregulatory sweating was examined by Pollock (213), Guttmann and Wyndham (93). All of the above authors have denied the presence of thermoregulatory or thermal sweating. Seckendorf and Randall (243) and Randall, Guttmann, and Silver (222) reported the presence of spinal sweating in responses to
body heating. Patients of the former studies (Seckendorf and Randall) had spinal lesions between the third and eighth segments of the thoracic cord. It is conceivable that sympathetic preganglionic fibers left the cord above the lesion, entered the sympathetic chain, descended in the chain, and innervated somatic dermatomes below the level of the lesion. Thus, sweating during thermal stress could have occurred in response to possible hypothalamic or suprasegmental facilitation.

Prevalent concepts of the central nervous control of thermal sweating responses suggest that the hypothalamus solely mediates, integrates, or controls thermal sweating with or without some influence by peripheral thermal receptors (Benzinger [25] and Hammel and Hardy [98]). Firm scientific demonstration of the presence or absence of spinal thermal sweating will aid in the clarification of the roles of central nervous structures in temperature regulation.

It is imperative that thermal sweating be examined in spinal patients with lesions above the levels of the classical sympathetic preganglionic outflow, i.e., patients with cervical spinal cord lesions.

Seven patients were selected for this study. Medication was suspended for twenty-four hours before the day of experimentation. The subjects rested on a padded gerney bed for approximately one hour at an ambient temperature of 25°C. During this time
the experimental procedures were thoroughly explained and transducers were applied.

Sweating was recorded by means of the iodine-starch-paper technique (Randall [216]) on eight different cutaneous areas: dorsum of the foot, calf, thigh, abdomen, chest, shoulder, forearm, and forehead. Nine cutaneous temperatures as well as rectal temperature were recorded at two-minute intervals by means of a YSI Telethermometer (Model 47) on one channel of an Offner Model R Dynograph. Mean skin temperature was calculated by weighting the response on each area by its per cent of total body area and summing. To monitor possible mass reflexes, electromyograms from the soleus muscle were recorded on the Dynograph during the entire experiment. To avoid responses resulting from stimulation of visceral reflexes, the urinary bladder was catherized and blood pressure was periodically monitored.

Control records were obtained at ambient temperature of 25-30°C. The ambient temperature was then gradually elevated to approximately 50°C and maintained. The duration of the heating was approximately 50 minutes, after which the room temperature was cooled to normal room temperature.

In figure 9 subject RPM (lesion C₄₋₅) was heated after an initial control period. Mean skin temperature was gradually elevated from 32 to 37°C while ambient temperature climbed to maximum of 52°C. Rectal temperature was elevated from 36.1 to 36.3°C by the end of the heating period. Consistent sweating was
Sweating responses as recorded by the iodine-starch-paper technique. Typical sweat responses were selected every five minutes for eight different skin areas on patient (RPM) with a lesion at C4-5, during gradual elevation in ambient temperature from 26 to 52°C. The patient sustained fractures of C4 and 5 in 1954 when his admitting diagnosis showed a clinically incomplete lesion with 60-70% loss of function at the shoulder joints, 70-85% loss at the elbow joints, complete loss in the remainder of the left upper extremity, and complete loss of function in the right upper and both right and left lower extremities. Note that sweating was completely absent from all areas during the control period, was sparsely recruited during heating, and was again completely absent following cessation of heating during the recovery period. Mean skin temperature increased rapidly with the rise in ambient temperature, and was followed by rise in oral and rectal temperatures. Note that sweating stopped on several areas while rectal temperature was still rising. Original sweat spots have been retouched with ink for purposes of photographic reproduction.
FIGURE 10

Sweating responses in a patient (RP) with an anatomically verified complete lesion at T₁, sustained when struck by a rifle bullet in Korea, 1950. Surgical exploration revealed complete severance of the spinal cord, and there is absence of sensation and motor power below T₁₋₂. Note that sweating was present in slight amounts on some areas during the control period, and that it was recruited on all areas during the elevation in ambient temperature. It ceased entirely on some areas and decreased in intensity on the remaining areas as the climate chamber cooled. Original sweat spots have been retouched with ink for photographic reproduction.
first observed on the dorsum, calf, shoulder, and arm. Some fifteen to twenty minutes later, sweating was observed on the abdomen and chest. The thigh and the forehead showed only sparse occasional sweating.

When the ambient temperature was lowered, the sweating decreased, while rectal temperature continued to rise to 37.6°C. The occurrence of sweating appeared to be more closely related to the rise and fall of mean skin temperature than to changes in rectal temperature. Sweating was observed to increase when rectal temperature was lowered and to decrease when rectal temperature was still rising. Complete cessation of sweating had occurred while rectal temperature was still 0.6°C above control.

In the middle of the heating period the subject's urine collection bag strapped to his lower extremity was emptied. Blood pressure was slightly reduced from 155/78 to 145/65, but no alteration in sweating was related to this maneuver. Electromyograph gave no evidence of spasms and no skeletal muscle contractions were observed.

In figure 10 subject RP was subjected to a similar heat stress. This subject had an anatomically verified lesion at the level of T₁ with complete loss of sensation and motor control below T₁-2 level. During the control period this subject showed light scattered sweating with rectal temperature at 37.1 and mean skin temperature of 34°C. As ambient and mean skin temperatures rose, sweating was recruited on all surface areas and increased in
intensity. Upon cooling a prompt decrease in intensity of sweating was observed on most test areas. Again the rectal temperature continued to rise. No elevation in bladder pressure nor blood pressure was recorded. No muscle spasms were recorded or observed.

Figure 11 illustrates sweat responses of patient NS with a clinically complete lesion at C4-5 who was exposed to the heat stress. Sweating is indicated by a continuous plot of minute-to-minute activity represented by the irregular line. Local cutaneous temperatures are represented by a smooth line.

During the control period sweating was observed on the forehead, forearm, and calf. As ambient and skin temperatures rose, sweating was recruited on additional areas. Following the period of heating, these temperatures fell and sweating decreased rapidly. Cycling of sweating was observed. Some of the cycles on different areas were in phase while others were out of phase with each other. Almost complete cessation of sweating was recorded within ten to fifteen minutes after the start of the cooling, despite the fact that rectal temperature continued to rise.

To summarize the results from the seven spinal patients, Table II was constructed. Listed is the maximal sweating on the eight tested areas as a result of heating the patient. The maximal change in mean skin, rectal, and ambient temperatures is also listed. Averages were calculated and given at the bottom of the Table. Sweat data from chest areas and above of patient HLT with
Sweating responses during exposure to rising ambient temperature of a patient (NS) with a clinically complete lesion at C₄-5. The lesion resulted from an automobile accident in 1952 and on admission to the hospital there was complete loss of motor function below C₆ and sensory function below C₄. Sweating is plotted at 1-min intervals as the number of active sweat glands, the brackets at the right indicating 50 active sweat glands per cm². Rectal (T_r) and skin temperatures are plotted throughout the period of observations. The period of heating is designated by changing ambient temperature (T_a).
### TABLE II

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lesion were not included in the averages. These patients showed about 20 to 30% of the normal responses with the exception of HLT. Patient HLT's sweating responses on innervated areas approached normal whereas those innervated primarily by the isolated spinal cord showed responses similar to the other patients.

Mean sweating was somewhat greater on the lower areas than on the upper half. Despite the sweating, rectal temperature was not maintained constant, for there was an average elevation of 1.1°C as a result of a 6.0°C rise in skin temperature when the subject was warmed from about 25 to 31°C ambient temperature.

Seckendorf and Randall (243) concluded that thermal reflex sweating occurred in spinal patients, but the possibility existed that sympathetic fibers leaving the cord from higher levels could descend to innervate sweat glands on lower areas of the body. However, observing dermatomal distribution of sweating as a result of direct stimulation of the sympathetic trunk, Randall and co-workers (220, 221) noted that such possibilities should be extremely rare, for overlap in pathways of more than two segments were not found.

In the present study six of the patients had clinically complete lesions. A patient with a clinically complete lesion has neither motor control nor sensory perception below the dermatome representing the level of his lesion. This is held by neurologists as evidence of a complete lesion, but it is not necessarily an anatomically complete lesion, for some small undetected
pathways crossing the lesion may still exist. One of the patients, RP, had an anatomically verified lesion (a surgeon saw both cut ends of the cord), and this subject showed sweat responses which were as convincing as those in the other patients. Therefore, it may be stated with certainty that thermal sweating does occur in spinal patients without suprasegmental control.

It is possible that temperature may influence the sweat glands directly. Such evidence has been presented by Randall (217), but such temperatures are much in excess of those observed in the present studies. It is possible that sweat glands of spinal patients may be supersensitive to direct heat effects. This is doubted for the sweat glands remained innervated, eliminating the possibility of denervation hypersensitivity. No experiments have been attempted to repeat Randall's direct heating experiment in the spinal patient.

Bullard and co-workers (264) have observed what they believe to be direct temperature effects at lower skin temperatures. More recently, they have narrowed this effect to the neural-sweat gland link (184). This effect would vary the output resulting from an ongoing response, but would not initiate the sweating response. In the present experiment, this does not appear to be true for the response was initiated with heating and ceased upon cooling. Seckendorf and Randall (243) and Randall, Guttmann, and Silver (222) have observed very rapid cessation of sweating upon rapid cooling, while skin temperatures were still elevated but
falling rapidly. Sweating in spinal patients is thought to be analogous to reflex sweating in the intact subject resulting from stimulation of cutaneous thermal afferents.

Macht (182) and Macht and Kuhn (183) observed thermal reflex responses occurring in the presence of an isolated spinal cord. This stands in opposition to Sherrington's (244,245) and Freund and Strasmann's (80) failure to observe such reflexes. Thus, it appears that thermal afferents can influence activity in the spinal cord. It is known that other types of afferent excitation, such as of visceral organs, may stimulate sweating in patients with an isolated spinal cord. It is clearly apparent that both efferent and afferent limbs of the necessary reflex arc remain anatomically patent and the present studies indicate they retain at least partial functional capability. However, other possible explanations should be mentioned. Thauer has shown that shivering can be initiated in spinal dogs by cooling the spinal cord (259,260). Thus, there exists the possibility of a receptor in the spinal cord which mediates spinal thermal sweating.

Koizumi, Ushiyama, and MacBrooks (168) have observed an increased excitability of spinal neurones as a result of hypothermia. They believe this increased excitability is due to an increased duration of afferent action potentials, thus prolonging the duration of facilitation. It is possible that such phenomena might explain responses such as those of Thauer's and perhaps is involved in spinal thermal sweating. This possibility of direct thermal
effects on the spinal cord seems doubtful in the present experiments because rectal temperatures were not related to the sweat changes, but there is no evidence that rectal temperature truly represents spinal temperature.

Some critics may challenge the suggestion of the thermoregulatory nature of the sweating responses, for rectal temperature is certainly not maintained constant. There is no doubt that these responses are only 20-30% of normal, and the spinal patient would have only 20-30% of normal ability to maintain temperature by vaporization. Absolute thermal constancy of the body is a misconception; even normal subjects experience increased rectal temperature under these conditions. In control theory terms this is expressed as the load error signal. It is possible that the spinal patient, because of the absence of suprasegmental facilitation, requires a greater error signal to activate the sudomotor system. An even stronger argument may be placed against this challenge. When a normal subject is placed in 100°C ambient temperature, are his sweat responses "thermoregulatory"? Most would consider these responses "thermoregulatory" despite inability to maintain constant central temperatures. In the same light the spinal patient's responses may be viewed as "thermoregulatory" although they have a markedly decreased thermal tolerable range. Their responses appear to be due to a thermal stimulus resulting in reflexes which "attempt" to regulate. Thus, the author feels it safe to deem these responses as thermoregulatory.
Reversal of Sweat Recruitment

The concept of a hypothalamic setpoint proportional temperature control in man has been challenged by many laboratories including our own (219). Hammel and Hardy (98) have suggested modifications in the concept such as variable setpoint regulators located in the hypothalamus. However, the basic requirements remain the same, i.e., the thermal afferent input, be it from the hypothalamus or the skin, must exceed a certain hypothetical set point in the hypothalamus to initiate thermal sweating.

Hertzman, Randall, Peiss, and Seckendorf (140) reported that sweating did not appear on the entire body surface at the same time. Instead they reported a progression of recruitment of sweating from the lower to the upper segments of the body, i.e., first on lower extremity, next on lower trunk, and followed by upper trunk and extremity and head. These basic observations were repeated in papers by Randall and Hertzman (223), Peiss and Randall (139), and Rawson and Randall (228).

The concept of differential sweat recruitment has obvious importance to the concept of a setpoint determining sweating on the entire body, for sweating is initiated on different areas at different central and skin temperatures.

It is the purpose of the present experiment to test the influence of heating and cooling the upper and lower halves of the body upon sweat recruitment patterns. The influence of skin
temperature upon recruitment patterns is vital to the understanding of temperature regulation.

In a 20°C climate chamber human subjects clothed in athletic shorts rested quietly on a copper screen bed for at least one hour before instruments were placed on the subject. The copper screen bed was designed so that the head boards of the bed sealed a passage-way in a common wall between twin climate chambers (figure 12). A third partition was designed to fit around the subject's body and was attached to the bed so that a portion of the subject's body could be placed in each of the two chambers simultaneously. The partition sealed the opening between the two chambers.

To minimize effects of heating the head upon oral and tympanic temperatures, a foam plastic box was fitted over the subject's head when the upper half of the body was placed in the high ambient temperature chamber. Ambient temperature around the head was maintained at or near that of the cool chamber's temperature by rapidly ventilation from large, well insulated pipes.

The instruments were applied to the subject while he rested in the cool chamber (20°C). Tympanic membrane, rectal, oral, and twelve skin temperatures were recorded, and mean skin temperatures for upper, lower, and total body were continuously calculated by an analog computer (186). Each minute seven areas of sweat gland activity were ascertained by means of starch iodine technique (216).
FIGURE 12

Bed design for upper half heating without heating head. The upper half of the body was placed in the hot chamber (right side of wall). A thick plastic head box was placed around the subject's head and neck. The box was maintained near the cool chamber temperature (left side of wall) by means of a fan which forced air at high flow rates through insulated pipes from the cool chamber to the head box and back to the cool chamber. The fan was located in the inlet pipe.
After a ten-minute control period the screen bed and the subject's upper half (or lower half) was moved into the high ambient temperature ($T_a$) chamber (60°C). The bed moved on rollers in a track and could be shifted in two to three seconds. The subject rested half in the 60°C $T_a$ and half in the 20°C $T_a$ until sweat recruitment patterns were established. Finally, the subject was returned entirely into the low $T_a$ chamber at 20°C for a period of recording until the normal state was recovered.

Figures 13 and 14 represent typical results of heating the lower and upper half of the body, respectively. Both records were taken from the same subject, RW, whose responses are also shown in the composite figure 15.

In figure 13 during a ten-minute control period with entire body at $T_a$ 20°C, body core temperature, rectal ($T_r$), tympanic membrane ($T_{tm}$), and oral ($T_o$) temperatures were falling, but upper ($T_{um}$), lower ($T_{lm}$), and whole body ($T_{ms}$) mean skin temperatures were steady. No sweating was observed on the seven test areas.

At the vertical dashed line, the lower portion of the subject's body was transferred into the hot chamber at $T_a$ 60°C. $T_{lm}$ and $T_{ms}$ rose rapidly while $T_{um}$ showed a slow decline. $T_{tm}$, $T_o$, and $T_r$ continued to fall until minute 30, whereupon they began to rise. At minute 41 sweating was first recorded on the dorsum of the foot. At this time $T_{tm}$ was 36.8°C, $T_o$ was 36.4°C, $T_r$ was less than 37.0°C and $T_{lm}$, $T_{ms}$, and $T_{um}$ were 38.8, 34.8, and 30.8°C respectively. Six minutes later sweating was recorded on the calf.
Sweat recruitment during heating of the lower half of the body. At the vertical dashed line on the left, the lower half of subject RW's body was moved from an ambient temperature of 20°C to 60°C. At the vertical dashed line on the right, the subject's lower half was returned to the 20°C ambient temperature. Mean skin temperatures were plotted for the total body (Tms), for the upper half of the body (Tum), and for the lower half of the body (Tlm). Rectal (Tr), oral (To), and tympanic membrane (Ttm) temperatures were also plotted. Sweating for seven cutaneous areas was represented as the number of active sweat glands per cm². Sweating greater than 40 units/cm² was not plotted. The time is given in minutes.
Sweat recruitment with heating of the upper half of the body except the head. At the left vertical dashed line, the subject RW's upper half of body was moved from an ambient temperature of 20°C to 60°C. At the right vertical dashed line, the upper half of the body was returned to the 20°C environment. Oral temperature ($T_o$) decreased to 34.5°C at minute 35, but was not plotted below 35°C. See figure 13 for explanation of symbols.
Accumulated sweat recruitment patterns of six subjects with heating upper and lower halves of the body. Time is given from the time of first recruitment. The presence of sweating on cutaneous area is indicated by a horizontal bar. The cutaneous areas are represented in a caudal to rostral order proceeding upwards from dorsum (Do), to calf (Ca), thigh (Th), abdomen (Ab), chest (Ch), forearm (Fa), and upper arm (UA). Paired diagonal lines seen on data from subject RW indicate a longer duration of sweat recruitment. See figures 13 and 14.
followed eight minutes later by thigh sweating. Eventually, complete sweat recruitment on all sampled areas was observed. A 91-minute delay existed between the first report of sweating on the dorsum until sweating first appeared on the upper arm. Core temperature began to level-off considerably before this sweating on the arm. Heavy sweating on the lower half of the body resulted in a small fall in skin temperature while the upper skin temperatures slowly rose. At minute 140 the subject's lower half was returned to $T_a \, 20^\circ C$. $T_{lm}$ and $T_{ms}$ fell with $T_{um}$ unchanged. Core temperatures showed little or no immediate change, but sweating was rapidly depressed on nearly all areas.

In figure 14 the opposite experiment was performed, the subject's upper half was heated with the exception of the head which was enclosed in the cooled head chamber. During the first part of the $60^\circ C$ exposure, $T_{tm}$ and $T_r$ showed a fall while $T_o$ fell more rapidly to a low of $34.5^\circ C$. Core temperatures were definitely rising during the 40th to 50th minutes. Sweat recruitment started on the upper arm and followed in a rostral to caudal direction, but with an extremely short delay between the first and last area to sweat. At the time of initiation of sweating $T_r$ was $37.1^\circ C$, $T_o$ was $36.6^\circ C$, and $T_{tm}$ was $36.7^\circ C$. Skin temperature again fell during the period of sweating. After returning the upper half to the $T_a \, 20^\circ C$, cessation of sweating was rapid with a concurrent fall in $T_{um}$ and $T_{ms}$. $T_{tm}$ and $T_o$ began to fall while $T_r$ continued to rise.
To summarize the recruitment patterns of the six different subjects for both experimental procedures, a composite figure 15 was constructed. The purpose of figure 15 is to establish the time and order of the sweat recruitment pattern. A horizontal bar represents the initiation and presence of sweat on a particular sampled area. The test areas are represented in a caudal to rostral order starting on the bottom with the dorsum of the foot (Do), calf (Ca), thigh (Th), abdomen (ab), chest (Ch), forearm (Fa), and upper arm (UA). In some cases no sweating was recorded on a particular areas, thus its horizontal bar remained open. On the plot showing heating of the lower half of the subject RW, paired short diagonal lines indicate a considerably longer duration was involved in sweat recruitment (figure 13).

Upon heating only the lower half of the body, sweating occurred in a caudal to rostral order and often failed to appear on some upper areas during the experimental period. While heating the upper half, sweating generally first occurred on the upper areas and was very quickly followed by sweating on the lower areas.

Table III lists temperature data from six subjects illustrated in figure 15. The time of first and last areas of sweat recruitment were selected to represent the data. $T_s$ represents temperature of the local skin on which sweating was recruited. In some instances more than one area began at a given time; the local temperatures of these areas were averaged together. On one
TABLE III

<table>
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### TABLE III (continued)

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<td></td>
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</table>
subject, RM, T_{tm} was not reported; but instead oral temperatures are underlined but were not averaged with the T_{tm}. At the bottom of the Table, averages have been calculated. Tympanic temperature was lower in nearly all subjects during heating of the upper as compared with the lower half. Cooling of the caudal half resulted in lower temperatures (about 1°C) as compared with cooling the rostral half. Sweating was generally initiated on areas that were being heated, consequently these areas generally have higher local skin temperatures.

In many papers, Randall and associates (223, 225, 228) have reported the general tendency of a subject to recruit sweating in a caudal to rostral order. This occurred despite the fact that areas such as the dorsum, which generally sweat first, had a lower skin temperature than areas which were often last to sweat (such as the forehead). This suggested that sweat recruitment was independent of local temperatures but was probably due to some variation of levels of excitability within the spinal cord. To further test this observation, Rawson and Randall (228) placed the upper (or lower) half of the body in T_{a} 60°C while the opposite half remained in a cool T_{a} ranging from 19-25°C. In either case the sweating was initiated on the lower or caudal areas first. However, they noticed a significant difference in the time between the onset of sweating on the first area to the onset on the last area; this delay always shortened when the upper half was heated.
The results of the present paper initially appear different, i.e., sweating invariably began on the upper half when it was heated and began on the lower half when it was heated. However, when these experiments were repeated at higher control ambient temperatures, e.g., 24-25°C, results similar to those of Rawson and Randall were observed. Cooler control ambient temperatures were required to suppress sweating on the caudal portions of the body, but suppression did occur. Some inhibition of sweating on the lower half of the body was shown by Rawson et al for the delay between initiation of sweating on caudal and rostral areas shortened. Thus, as the $T_a$ and skin temperature of the caudal half are lowered, the delay becomes shorter until actual reversal of recruitment occurs.

There are no doubt numerous possible explanations for these recruitment patterns and their reversal. One suggestion is that a gradation exists in levels of excitability of sudomotor cell bodies within the intermediolateral cell columns, or alternatively, a gradation exists in the influence of the superior portions of the CNS upon spinal segments. Neither suggestion appears to be entirely applicable for in almost all subjects sweating was initiated at the same or lower central temperatures when heating the upper areas and cooling the lower areas. The above hypothesis would require recruitment at significantly higher central temperatures.
The possible participation of peripheral receptors becomes more attractive, for strict explanation based upon exclusively central mechanisms is apparently inadequate. Two hypotheses are suggested here.

Thermal afferent primary or secondary fibers may influence preganglionic cell bodies as they ascend from lower segments. Such pathways have been described by Crosby et al (54). This hypothesis necessitates that these fibers have primarily inhibitory effects and are derived from "cold" receptors. This is in accordance with the observed predominance of "cold" fibers in peripheral nerves (125, 291).

A second hypothesis is that these "cold" thermal fibers from rostral areas have a greater influence upon rostral sudomotor outflow than do caudal fibers upon caudal sudomotor outflow. Thus, despite somewhat warmer temperatures on the upper than lower areas of the body, the total inhibition is normally greater on upper than lower portions. Assuming equal hypothalamic facilitation upon the preganglionic cell bodies of the cord, sweating would be initiated on lower areas first when the whole body was heated. Cooling the upper half while heating the lower half decreases inhibition on the lower half but increases inhibition on the upper half. The net result is further separation of the recruitment from lower to upper areas. In some cases total inhibition of sweating of the upper areas occurred with the presence of sweating on the lower half. Heating the upper half while
moderately cooling of the lower half resulted in sweating on the upper half. Marked cooling of lower half while heating upper half results in nearly simultaneous recruitment of sweating on the entire body or reversal of the recruitment pattern. More marked cooling of lower half caused definite reversal of pattern of sweat recruitment, starting first on upper areas and later on lower areas.

Either of the latter two hypotheses appears to fit the observed responses in this experiment, for they do not require higher central receptor temperatures. These hypotheses assume the control of sweat recruitment to occur in the cord; it is possible that such regulation may occur at suprasegmental levels although no such afferent or efferent segmental representation in thermoregulatory areas has been reported.

The basic hypothalamic set point concept states that thermoregulatory sweating is proportional to the difference between set point and hypothalamic temperature. It is difficult to speak of one set point, for central temperatures in one experiment for central temperatures may vary upwards of 1°C between recruitment on different areas of the body. This might suggest that different segmental levels have different set points. Because the recruitment patterns are dependent upon skin temperature, the segmental control must include skin temperatures from that segment and perhaps neighboring segments as well as contributions from central thermosensitive structures. No control circuit
yet described for thermoregulatory sweating has considered any segmental control.

It is concluded that reversal of the normal recruitment pattern is possible but requires marked cooling of the lower half while the upper half is heated. Sweating occurs on the upper half at the same or lower central temperatures as when the lower half is heated. This reversal or even the normal recruitment pattern presents problems to any set point hypothesis of temperature regulation for the set point temperature would depend upon the sweating area and the nature of the heat stress. Recruitment patterns also deem it necessary to consider the influence of skin temperature in any comprehensive explanation of thermal regulation.

Sudomotor Reflex Responses to Separate Cooling of Upper and Lower Halves of the Body

Experiments on the order of recruitment of sweating on different cutaneous surfaces suggested the possibility of different influences of cutaneous thermoreceptors located in superior and inferior portions of the body. Experiments were proposed to study the differences and, if possible, to illuminate the inherent mechanisms of control. Subjects were initially heated in 63°C environment resulting in complete recruitment of sweating on all test areas with elevated skin temperatures as well as core or
central temperatures. Either the upper or lower portion of the body was then moved into a chamber maintained at a cooler environmental temperature (See figure 16.). The change in sweating as a result of cooling a portion of the body (while the other portion remained in the hot chamber) was determined on the cooled and non-cooled surfaces of the body. Responses to cooling of both upper and lower portions were compared.

In these studies, the movable partition on the screen bed was located so that its diaphragm insert surrounded the subject's trunk at the level of the umbilicus. Following suitable control measurements, the bed was moved so that the portion of the body above (or below) the umbilicus was exposed to a cooler environment while the portion below (or above) remained in the hot chamber. Cutaneous and deep temperatures as well as sweating were recorded continuously throughout the experiment. Five different \( T_a \) ranges were selected for the "cool" environment: these were 37, 33, 29-30, 25-26, and 21-22°C. The upper half of the body was moved from 63°C to five different \( T_a \)'s, but the lower half was moved into only three of the \( T_a \)'s because little or no change occurred in \( T_a \)'s above 29-30°C. The subject remained in this half-and-half position for ten minutes after which the entire body was returned to the "cool" chamber.

Five subjects were used in each procedure. Mean skin temperatures were calculated for both upper and lower halves of the body. Mean sweating (number of active sweat glands per cm\(^2\))
Experimental procedures for rapid cooling of half of the body. Subject's entire body was first placed in low ambient temperature chamber (A). Entire body was then heated in high ambient temperature, 63°C (C). Then half of the body was returned to the low temperature chamber (B). The opposite half was later returned to the low ambient temperature chamber (A).
was calculated for the upper and lower halves of the body by weighting the responses from each area according to the per cent of total body area known to be characterized by the measured sweat rate and summating the products. To group the data from different subjects at the same environmental temperature, sweating was represented as per cent of control. The control period was arbitrarily established as the three to five minute period of maximal sweating immediately before returning half of the body to the lower $T_a$ chamber. Means from the five subjects were calculated for tympanic membrane ($T_{tm}$) and skin temperatures ($T_{ms}$).

Four figures were selected to illustrate typical responses on one of the five subjects (figures 17-20). The format for each of the figures is basically similar. After ten minutes of recording in the cool chamber, the subject was placed in the 63°C $T_a$ for twenty minutes. Next, half of the body was moved into the "cool" chamber at the predetermined $T_a$. Finally, the remainder of the bed was moved so that the entire body now rested in the "cool" chamber. Two to seven minutes after entering the 63°C $T_a$, sweating was initiated on the lower portions of the body, followed by additional recruitment on upper portions. Mean skin temperatures rose quickly while elevations in $T_o$ and $T_{tm}$ were considerably delayed. Often, $T_o$ fell before rising.

Light to moderate sweating was generally associated with the early rise in skin temperature with massive increases associated with elevation in core or central temperatures.
Effects of rapid cooling of the upper and lower halves of the body of the same subject in different ambient temperatures. At the left vertical line, the subject was transferred into 63°C ambient temperature. At the middle vertical line, half of the body was returned to the lower ambient temperature. At minute 41, the opposite half was also returned to the low ambient temperature (right vertical line). Tympanic membrane ($T_{tm}$) and oral ($T_o$) temperatures represent measures of central temperature. Mean skin and sweating were determined for both upper (solid line) and lower (dashed line) halves of the body. Sweating was given as average number of active sweat glands per cm$^2$. 
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Upon moving one half of the body to the lower $T_a$, mean skin temperature of that portion fell quickly while that of the opposite portion remained relatively constant at its high level. $T_{tm}$ and $T_o$ declined after about five minutes when the upper half was cooled (figure 20); but they usually continued to rise when the lower half was cooled (figures 17, 18, and 19). In all instances, sweating on all cutaneous surfaces decreased promptly. Sweating was invariably of lower intensity on the cooled surfaces as compared with that on the warm areas. Exposure of half of the body to the lower environmental temperatures (21°C, 25°C) depressed sweating to a greater extent on both upper and lower portions of the body. However, cooling the upper half at 30°C $T_a$ was more effective in suppressing sweating on both halves than was cooling the lower half at 30°C $T_a$. The marked suppression of sweating when cooling the upper half occurred well before $T_{tm}$ or $T_o$ had fallen. Such sweat inhibition can only be attributed to the alteration in skin temperatures (i.e., thermal stimulation of cutaneous receptors).

When moving the remainder of the body into the lower $T_a$, sweating was promptly and totally inhibited on the entire body, again with surprising rapidity, as $T_{ms}$ fell. $T_{tm}$ and $T_o$ declined only after approximately four to five minutes following the move, therefore permitting little doubt that sweat suppression was associated with declining $T_s$ rather than in central temperatures.
Figure 21 represents the average sweat responses of five subjects when only half of the body was cooled. Zero time marked the return of half of the body into the lower $T_a$. Cooling half of the body produces rapid decrease in sweating on both halves although the responses were more pronounced on the cooled area.

After the tenth minute, the opposite half was returned to the lower $T_a$. In most cases this led to a rapid cessation of sweating on both halves. Returning the entire body into 37°C did not totally inhibit sweating, but did significantly decrease sweating.

Cooling the upper half in $T_a$'s 25 and 21°C resulted in a decreased sweat rate followed by a rebound on the lower areas. This rise may have been due to the rise in the $T_{ms}$ of the lower portion of the body and/or decreased rate of fall on the $T_{ms}$ or the upper portion (See figure 22.).

Figure 22 depicts the changes in $T_{ms}$ of upper and lower halves of the body. Again, zero time (the first vertical line) represents the time when half of the body was returned into the lower $T_a$. After the tenth minute (the second vertical line), the opposite half of the body was cooled. Before the change in $T_a$, $T_{ms}$ was constant at 37 to 38°C. Upon cooling, an exponential-like decay curve was observed with an approximate time constant of five minutes. Returning the body into the lower $T_a$ resulted in lower $T_{ms}$ on the cooled areas. The maximum rate of decrease of $T_{ms}$ increased at the cooler ambient temperatures. Cooling the caudal
Average sweating responses to rapid cooling of half of the body for the upper (solid line) and lower (dashed line) halves. Sweating is expressed as per cent of control. One hundred per cent was equal to the average sweating five minutes before cooling half of the body. At time zero, half of the body was cooled. At the vertical line on the right of each diagram, the opposite half of the body was also cooled. On the right, the upper half was cooled from ambient temperature of 63°C to 37, 33, 29, 25, and 21°C. On the left, the lower half was cooled from 63°C to 29, 25, and 21°C.
Average mean skin temperature changes during rapid cooling of half of the body in different ambient temperatures. The upper (solid line) and lower (dashed line) mean skin temperatures of half the body were plotted before cooling half of the body. At time zero, half of the body was cooled. At ten minutes, the opposite half of the body was cooled. The diagrams at left represent changes during the cooling of the lower half first, whereas those at the left represent cooling of the upper half first.
half of the body produced lower caudal skin temperatures than cooling the rostral half upon rostral skin temperatures.

Figure 23 presents the mean tympanic membrane temperatures and reveals no consistent differences in \( T_{tm} \) as a result of exposing either the upper or lower portions of the body to the different environments. However, differences did appear when comparing cooling of the lower as contrasted with cooling the upper portion of the body. When cooling the lower half, tympanic membrane temperatures continued to rise throughout the ten-minute cooling period with decline only several minutes following return of the entire body to the "cool" chamber. When the upper half of the body was cooled, however, \( T_{tm} \) began to fall within 5-6 minutes and showed little response to cooling the lower half.

Cooling half of the body suppressed sweating on both halves of the body. Suppression of sweating on the opposite half of the body can only be explained in terms of reflexes which presumably originate from the cooled skin surface. Mechanisms of mediation within the spinal cord are largely conjectural, but theorizing is the sauce of science. If one assumes this to be a spinal reflex, afferents from the lower portions of the body must ascend and those from the upper portions must descend in the spinal cord. It is conceivable that such regulation could occur at suprasegmental levels in the brain-stem or cerebellum although no evidence for such intricate sudomotor control has been documented.
FIGURE 23

Tympanic membrane temperature changes during rapid cooling of half of the body in different ambient temperatures. At time zero, half of the body was cooled. At ten minutes (right vertical line), the opposite half of the body was cooled. On the left, tympanic membrane temperatures are plotted when the lower half of the body was cooled first; on the right, the upper half was cooled first. The curves represent the average of five subjects.
Sweat inhibition on the cooled surface of the body was always greater than on the opposite half. At least three possibilities for such differentiation exist. (1) Direct effects of temperature upon the sudomotor nerve endings and sweat gland unit. Such possibilities have been suggested by Bullard and associates (184,264). (2) Another possibility is one of more intense influence by thermal receptors upon the segmental level at which their different fibers enter the cord. (3) Finally, there may exist some form of suprasegmental representation of the segmental sudomotor distribution. Ascending thermal afferents could have distribution to nearly all representative segments, but exert a more intense influence upon those segmental levels which were cooled.

Figure 24 diagramatically represents these three possible explanations. Cooling may affect sudomotor-nerve-sweat gland units (See letter A.) or may affect thermal receptors. Thermal receptors may have a strong influence upon sudomotor pre-ganglionic cell bodies at the level of entry with a weaker influence at higher levels. (See letters B found on both upper and lower spinal segments.) The third possibility of differential control above the spinal cord with resulting descending motor fibers is represented by letter C.

If these experiments would be repeated on patients with cervical spinal cord lesions, the possibility of suprasegmental control (C) could be tested. If differential control was then obtained, it would suggest the possibility of A or B.
Diagram of three possible explanations to upper and lower differential sweat responses to cooling half of the body. See text for description.
Another interesting observation from these experiments is the difference in response from cooling the upper and lower halves of the body. Sweating was suppressed at higher $T_a$ and $T_{ms}$ upon cooling the upper half than the lower half of the body. These differences are not due to changes in central temperatures, assumed to be represented here by $T_o$ and $T_{tm}$, for they started to fall four to five minutes after sweating had been strikingly inhibited.

This difference in influence of cooling one half of the body suggests that Randall's normal order of sweat recruitment may be related to this observed difference. Heating the whole body may result in less facilitation of sweating on upper than lower portions of the body. Consequently, sweating would be expected to be initiated on the lower areas first.

Influences of Rate of Change in Skin Temperature on Sweating

There is little doubt that skin temperature influences thermoregulatory sweat responses in man (See previous sections.). Often it has been observed that rapid transfer of subjects from hot to cool environments inhibited sweating. This inhibition occurred while central temperatures were rising and skin ($T_s$) temperatures had fallen rapidly but were still elevated over
series, the environmental temperature (T_a) controls were regulated by means of precise proportional temperature controllers.

Figure 25 illustrates the responses of one subject to step changes in T_a. No sweating was recorded during a ten-minute test period while the subject was at T_a 25°C, with T_tm of 37.1 and T_ms of 34°C.

After ten minutes the subject was quickly moved into T_a 60°C, resulting in a great increase in dT_ms/dt. Rate of their change progressively declined in an exponential-like manner, while T_tm showed no significant change until approximately the eighteenth minute of exposure to the high temperature, after which it rapidly climbed to a value of 37.6°C. Active sweating was initiated at the twelfth minute and continued to increase for the duration of heat exposure.

After minute thirty, the subject was transferred into T_a 37°C. T_ms fell rapidly with a maximal calculated rate of change of -0.5°C/min. The rate of decline in T_ms progressively decreased as skin temperature of 36.1°C was approached. Eight to nine minutes after the T_a change, T_tm leveled off and started to fall.

Sweating was inhibited very rapidly, falling to zero by the third minute after the change. However, four minutes later sweating again appeared to increase gradually in intensity.

After the sixtieth minute, the subject was returned to the 60°C T_a with accompanying rise in rate of change in T_s and
Sweating responses to step changes in ambient temperature. Sweating is represented as the average number of active sweat glands per cm\(^2\) of skin calculated from seven representative areas of the subject. Mean skin temperatures (SKIN TEMP.) and tympanic membrane temperature (TYMP. TEMP.) are also given. The rate of change of mean skin temperature (\(dT_s/dt\)) is plotted at the top of the figure.

At the 10th minute, the subject was moved from \(T_a\) of 25 to 60°C. At minute 30, the subject was moved from \(T_a\) 60 to 37°C. At minute 60, the subject was returned to \(T_a\) 60°C and at minute 70 back to \(T_a\) 25°C.
T<sub>ms</sub>. T<sub>tm</sub> rose 8 minutes later. Sweating increased rapidly, leveled off, and then decreased.

Finally, the subject was returned to T<sub>a</sub> 25°C, resulting in a rapid fall in T<sub>ms</sub> and complete inhibition of sweating. This inhibition occurred at a time when T<sub>tm</sub> was rising.

Figure 26 represents summated data on four subjects of the first series. Immediately after the change from 60 to 37°C T<sub>a</sub>, T<sub>ms</sub> fell rapidly, resulting in an initially high rate of change. T<sub>ms</sub> leveled off at 35.7°C and then slowly rose to 35.9°C. On the other hand, T<sub>0</sub> and T<sub>tm</sub> continued to rise from 37.70 to 37.75 and 37.82 to 37.88°C, respectively. Three to four minutes after the sudden change in ambient temperature, T<sub>0</sub> and T<sub>tm</sub> also declined while T<sub>r</sub> continued to rise throughout the experiment.

Sweat gland activity fell quickly to the 10% range, subsequently rising again to the 20 to 30% range. It is important to note that sweating was inhibited while central temperatures were rising and skin (T<sub>s</sub> or T<sub>ms</sub>) temperature was falling to only 37°C. As the rate of change approached zero, sweating increased from 0 to 10% to 20 to 30% despite a fall in T<sub>tm</sub> and T<sub>0</sub>. The number of active sweat glands increased to a level which was higher than when mean skin temperature was more than 1°C higher and when T<sub>0</sub> and T<sub>tm</sub> were 0.1 to 0.2°C higher.
Average responses of four subjects to step changes in ambient temperature. The subjects were transferred from ambient temperature ($T_a$) of 60 to 37°C at minute five. Mean skin temperature ($T_{ms}$), as well as rectal ($T_r$), oral ($T_o$), and tympanic membrane ($T_{tm}$) temperatures, is represented. The rate of change of mean skin temperature ($dT_{ms}/dt$) was calculated and plotted. Sweating is expressed as per cent of control. One hundred per cent was equal to the average of the mean sweating for the five-minute period before lowering the $T_a$. 
In figure 27, the summated results of six subjects of the second series are represented. Fundamentally similar responses were observed.

Similar responses were observed in the preceding three figures. Sweating was inhibited during periods of rapidly declining skin temperature which later increased in sweating when the rate of fall declined and approached zero despite the fact of lowered skin temperature and declining central temperatures.

Hensel recorded directly from single cutaneous temperature fibers in man and animals. He found that the rate of change in temperature was a most important component of the thermal stimulus (figure 28, taken from Hensel's work [126]). "Cold" fibers respond with an increase in frequency as temperature is decreased, while increased temperature elicited sudden cessation of receptor firing. The "warm" fibers responded conversely with an increased frequency of impulse traffic while temperatures were increased. Thus, during the rapid changes in $T_a$ encountered in our experiments, it is probable that rate of change provided a significant increase in firing rate of "cold" fibers and/or decrease in firing rate of "warm" fibers. Static responses of "cold" fibers to different static skin temperatures are much greater than those of "warm" fibers.

To explain the observed responses, a hypothetical scheme is represented in figure 29. The assumption has been made that rate of change, together with absolute levels of skin
FIGURE 27

Average responses for six subjects in the second series to step changes in ambient temperature. Symbols and procedures are as described in the Legend of figure 26.
FIGURE 28

Typical responses of "cold" and "warm" thermoreceptors during changes in skin temperature. Thermoreceptor responses are given in impulses per second (IMPS. PER SEC.). (Taken from Hammel, Iggo, and Witt. J. Physiol. 153: 113-126, 1960.)
Hypothetical sweating responses to step change in ambient temperature. A step change in environmental temperature produced a near exponential cooling curve of skin temperature. The rate of change of skin temperature \((dT_s/dt)\) was calculated and plotted. The bottom curve represents the summation of the skin temperature and rate of change of skin temperature \((T_s + dT_s/dt)\). The dashed horizontal line represents the hypothetical threshold of the sudomotor preganglionic cell bodies. The segment of the \(T_s + dT_s/dt\) curve which is above the threshold line is proportional to sweat rate during the step change in ambient temperature.
temperatures have summative effects upon the frequency of firing of the cutaneous thermal receptors. Hensel's data generally confirm this assumption. A second assumption is that the cutaneous and central receptors have summative influences upon the sudomotor sympathetic preganglionic cell bodies. The author cautions one from assuming that spinal cord temperatures and associated central receptor sensitivity and effectiveness are known. Further, neither anatomical nor functional relationships between thermal receptor and sudomotor preganglionic cell bodies are known.

The upper curve of figure 29 shows a step change in ambient temperature resulting in an almost exponential decrease in skin temperature (the second curve). The third curve represents the differential of the skin temperature, i.e., rate of change of skin temperature ($dT_s/dt$). The fourth curve represents a hypothetical summation of the cutaneous temperature and rate responses. However, a proportionality constant must be introduced before such summations are meaningful. This summation is directly related to the net cutaneous thermal different inputs into the central nervous system, assuming "cold" fiber inhibition and "warm" fiber facilitation. Knowing that cutaneous afferents regulate at least in part, sudomotor responses, the influence of cutaneous thermal receptors would be a parameter of this summation. Assuming a direct function, the bottom curve can represent sweat rate (sudomotor preganglionic firing rate) or the summation of skin temperature and its differential.
The dotted line represents the threshold of the sudomotor sympathetic preganglionic cell bodies in the spinal cord. This threshold is most likely an inverse function of the temperature of the central receptor. The area of the curve above the dotted line represented the number and/or intensity of sweat gland activity.

Based on this hypothetical picture, one would expect, upon rapid cooling, total suppression of sweating in some subjects and temporary suppression in others, depending upon the temperature of the central "receptors" and their relative levels of sensitivity.

Despite the tenuous nature of some of the assumptions, responses observed in the present research were quite similar to those predicted by this hypothetical scheme. All predicted variations in hypothetical results were observed, with the latter being the most prevalent because of the elevated central temperatures.

The suggestion of rate of change effects in temperature regulation is not unique. Hardy theoretically considered rate of change of both cutaneous and central receptors, although only evidence for central rate responses was reported (109). Jacobson demonstrated phasic and static responses of "cold" receptors (155). To the present author's knowledge, the current paper presents the first clear implication of the importance of the rate of declining skin temperatures upon sudomotor control in humans. The
converse relationship, dependent upon rate of increase in skin temperature, is yet to be illuminated.

Another important observation can be made in these experiments. The drop of mean skin temperature from 38 to 36°C has a powerful, undeniable influence upon sweat gland activity taken in either the dynamic or static thermal state. Benzinger (25) observed that "the influence of skin temperature on sweating was zero throughout the warm range, 33 to 39°C." There is little doubt that his observations and concepts on the role of skin temperature and thermal receptors must be reevaluated.

In conclusion, the rate of decrease of skin temperature, as well as the static skin temperatures, are important determinants of sweat gland activity.

Sweat Responses to Unilateral Leg Cooling

Previous experiments demonstrated that cooling either the upper or lower half of the body inhibited sweating on the cooled and uncooled halves of a total sweat recruited subject. The sweat suppression was greater on the cooled half than the half which was still being heated. It was questioned whether cooling smaller surface areas of the body would induce similar responses. In addition, is the marked suppression of sweating on the cooled segment of the body a bilateral thermal afferent reflex?
To answer these questions, experiments were designed to record the changes in sweating when one leg was cooled while the other body surface areas were being heated.

Five male subjects clothed in athletic shorts rested on a copper screen bed which could be moved through a common passageway between twin climate chambers whose temperatures could be independently controlled. This bed was equipped with a partition designed to seal the common passageway (See figure 30.). The right leg was placed in the hole in the partition, and a thick foam rubber gasket was made to fit snugly around the leg and to seal off the gap between the partition and the leg. The left leg was placed off the side of the bed on a footrest which was attached to the bed.

The subject was placed entirely in the high ambient temperature (T_a of 60°C). After complete sweat recruitment was attained, the right leg was cooled by moving it into the lower T_a chamber. Following a fifteen-minute period in the lower T_a, the right leg was returned to the high T_a.

Temperatures of fifteen skin areas, tympanic membrane and oral cavity were recorded by means of thermistors (186). The number of active sweat glands was assessed by iodine-starch-paper technique (216) on ten areas every minute: right and left thighs, calf, and dorsum of the foot as well as the abdomen, chest, forehead, and forearm. Sweating for the right leg, left leg, and upper body was averaged separately, weighting the sampled areas
Bed design for cooling one leg while heating body. The subject's right leg was placed through a special partition fitted with a foam rubber gasket. The left leg rested on a footrest which extended off the bed. The subject's entire body was exposed first to the high ambient temperature \((\text{HIGH } T_a)\) and then the right leg was moved into the cool ambient temperature \((\text{LOW } T_a)\). Later, the right leg was returned to the high \(T_a\).
according to per cent of body surface area, thus condensing ten variables into three.

Sweating was expressed as a per cent. The sweating for the five minutes before the cooling of the leg was averaged and set as 100%. Mean values from the five subjects were calculated for the tympanic membrane, oral cavity, the right leg, and mean skin temperature, as well as sweating.

Figure 31 illustrates the averaged results of five subjects. At time zero, the right leg was cooled. This produced a rapid fall in the right leg temperature as well as a fall in sweating on all three body areas to 30-50%. Tympanic membrane temperature ($T_{tm}$) and oral temperature ($T_{o}$) continued to rise throughout the entire experiment. As the rate of fall of leg temperature decreased, sweating on the contralateral leg (left) and upper body returned to control levels (100%). Simultaneously, sweating on the cooled right leg increased from 30-35% to roughly 55%.

After fifteen minutes of cooling, the right leg was returned to the high $T_a$ chamber. Upon reheating, sweating on the upper body, left leg, and right leg showed a tendency to overshoot. A longer recovery duration would have been certainly helpful to clarify the recovery responses.

It is clear that cooling even the leg has a significant effect upon sweating on the entire body. The recovery to control levels (100%) of sweating on the upper body and the contralateral
Figure 31

Average sweating responses of five subjects to unilateral leg cooling. Tympanic membrane ($T_{tm}$), oral ($T_o$), mean skin ($T_{ms}$), and right leg ($T_{rt. leg}$) temperatures are represented at the top half of the figure. Sweating for the upper body (solid line), left leg (dotted line), and right leg (dashed line) are plotted as per cent of control. One hundred per cent is equal to the average of sweat responses during the five minutes before leg cooling. At time zero, the right leg was moved from ambient temperature ($T_a$) 60 to 20°C. At minute 15, the right leg was returned to the $T_a$ of 60°C.
leg and to a lesser degree (55%) on the right leg may be related in part to the rate of change responses of thermal afferents. These responses on the right leg are quite similar to responses seen from whole body thermal changes previously described. The influence of cooling the right leg upon sweating on the non-cooled areas of the body is best explained as reflex control via cutaneous afferents from the right leg, for no changes in central temperatures coincided with these changes.

The stabilizing of sweat responses of the right leg far below control sweating (100%) during the later half of the cooling period suggested two possibilities. Local temperatures may have a direct effect on the sudomotor-nerve-sweat gland unit as suggested by Bullard (184,264). This would produce a suppression of sweating directly on the cooled leg without the necessity of afferent neural reflexes. A second possibility is that thermal afferents have a dominant influence on sudomotor cells from the same limb upon which they originated. This dominance would appear to be unilateral, for comparable contralateral suppression was not recorded. The contralateral leg sweat responses were quite similar to those on other areas of the body.

When rate of change experiments were performed during cooling of the entire body, responses appeared quite similar to the responses of the right leg. It is likely that the entire body responds to afferent influences of rate of cooling as well as the
unilateral local temperature effects which may or may not be of thermal afferent origin.

These data suggest that sweat responses to cooling are composed of two elements. One element is a thermal receptor reflex with marked sensitivity to rate of change of temperature. This is in accordance with the nature of thermal receptors as revealed unilaterally on the areas cooled. The latter response may be a non-reflex response.

Role of Head Temperature upon "Central" Temperatures

Significant differences in tympanic membrane and oral temperatures were observed when the upper half of the body was cooled as compared to when the lower half was cooled. This suggested that ambient temperature ($T_a$) to which the upper half of the body was exposed played an important role in determining central temperatures as assessed by the tympanic membrane ($T_{tm}$) and oral ($T_o$) temperatures. To elucidate this possibility, a partition was placed at the level of the neck, and a diaphragm fitted to seal around the neck. The bed could be moved rapidly through a passageway between the two climate chambers in which temperatures were independently controlled. This permitted heating of
the body separately without directly heating the head and subse-
quently exposing the head to the warm ambient temperature \( T_a \).

Sweat records were taken on seven areas of the body. These results were weighted according to per cent of total body surface area and summated. Sweat data from five different sub-
jects were averaged together, or in some instances maximal sweat levels on each individual subject served as controls. Maximum sweat gland counts were designated as the 100% level, with changes expressed in per cent of this arbitrary sweat rate. The two methods gave qualitatively comparable results.

Tympanic membrane, oral cavity, and twelve skin tem-
peratures were recorded. Mean weighted skin temperatures were calculated and averaged, head temperatures being averaged separately.

In figure 32, during the first forty minutes of the ex-
periment, the entire body; except for the head, was exposed in the warm chamber to an ambient temperature which progressively rose from 22 to 50°C. Mean skin temperatures steadily rose from about 33 to about 37°C. Tympanic membrane and oral temperatures slowly declined about 0.2°C during the first 32 to 34 minutes, but by the fortieth minute began to rise. In some experiments \( T_{tm} \) continued to fall after sweating was first observed, and sweating continued to increase slowly until oral temperature started to rise, where-
upon sweat rate increased markedly.
Average responses of five subjects to heating the body with and without heating the head. Tympanic membrane ($T_{tm}$), oral ($T_o$), mean skin ($T_{ms}$), and head (dashed line) temperatures are represented in the upper half of the figure. Sweating responses are represented in two ways: average number of active sweat glands per cm$^2$ or average per cent of maximal sweating. During the first 40 minutes, the body was heated without heating the head (HEAT ALL XHEAD*). At minute 40, the head was then heated. At minute 52, the head was cooled. At minute 62, the body was also cooled.
At the end of forty minutes, the head was shifted into the hot chamber. The rate of rise in tympanic membrane temperature promptly and significantly increased, while $T_0$ showed only slight to moderate increase in slope (rate of change). Thus, the rate of increase in sweating showed an increase in slope as central temperatures climbed.

After twelve minutes in the hot chamber, the head was shifted back to $T_a$ 22°C. $T_{tm}$ and $T_0$ leveled off and $T_{tm}$ actually turned down. Sweating showed a transient decrease associated with the rapid change in head skin temperature.

After sixty-two minutes, the entire body was moved to the lower $T_a$ (22°C). The rate of fall (slope) of tympanic membrane temperature showed no significant change until ten minutes later, whereas the oral temperature remained stable for about four minutes before turning downward. Sweating was inhibited almost immediately and coincidentally with the rapid lowering of skin temperature of the body.

This experiment furnishes evidence of the influence of local environment upon commonly measured central temperatures, tympanic membrane, and oral temperature. This cannot be adequately accounted for by artifacts of recording techniques. The tympanic membrane probe was well-insulated by several centimeters of acrylic plastic composing the ear mold which penetrated to only 2-3 millimeters from the membrane. Subjects were trained to keep
their mouths closed and to hold the thermistor probe securely under the tongue.

Changes in rate of rise of $T_{tm}$ and $T_o$ occurred when the head was instantaneously shifted into or out of the hot environment. Unfortunately, it is difficult to ascertain whether the changes in rising slope occurred because of head temperature or whether they were about to happen despite the head temperature. For example, oral temperature had started to rise before and showed very little inflection during the heating of the head. The return of the head to the lower $T_a$ produced more convincing results because, not only did the rate of rise in $T_{tm}$ decrease, but it became negative ($T_{tm}$ fell).

Observation of such phenomena is not altogether new, for Benzinger (26) cautioned that tympanic membrane temperature is influenced by ambient temperatures:

In environments below 30°C, eardrum temperature changes perceptibly (0.1 to 0.2°C) when insulating material is placed upon or removed from the ear lobe and its surroundings. The lower readings prior to insulation are probably caused by cooler blood returning from the lobe and surrounding skin in descending veins adjacent to some of the ascending arteries which supply the tympanic membrane. It follows that in cool environments the lobe should be covered with approximately one-inch thick insulating material, or even better, with the palm of the patient's hand.

It seems quite strange that $T_a$ below 30°C should produce recording errors while no mention of such errors was made at $T_a$ of 45°C or above, which Benzinger often employed. The gradient
between average core temperature, approximately 37°C, and $T_a$ is the same but opposite in direction. Higher $T_a$ would induce increased cutaneous blood flow and elevated blood temperature. The thermal exchange between descending vein and ascending artery would be related to blood flow and the thermal gradient between venous and arterial blood. The nearly parallel courses of tympanic membrane and oral temperatures indicate that a much more extensive thermal exchange may be involved. It is likely that exchange of heat from veins to arteries occurs in the common supply to the tympanic membrane and the oral cavity. Blood returning from the upper respiratory tract and/or the face may pass near the ascending carotid artery with an exchange of heat.

Equally strange is Benzinger's insistence that the internal carotid artery is a heat source for the tympanic membrane despite the emphasis he placed on the influence of the external carotid artery when discussing $T_a$ influences. Anatomically, the tympanic membrane is supplied by two to three branches of the external carotid and one branch of the internal carotid artery. One may wonder concerning the temperature of blood within the internal carotid artery which supplies the hypothalamus.

In all of the present experiments, sweating was initiated while $T_{tm}$ was falling or remained constant after falling about 0.2°C. Sweating intensity increased when central temperatures started to rise, despite being less than non-sweating control levels. If these temperatures are representative of
directional changes in hypothalamic temperatures, it is suggestive that the central "receptor" is directionally sensitive. Receptors which are known to be directionally sensitive are generally rate sensitive. Hardy (109) reported what he thought was thermo-regulatory rate sensitivity of central receptors, but similar experiments done by his group did not support this observation.

The reverse technique should be tried, i.e., heating the head of the human subject while maintaining the rest of the body skin temperature constant. If elevation of central temperature is observed, it will support the present hypothesis.
CHAPTER V

CONCLUSIONS AND SUMMARY

Skin temperature has been shown to be an important drive to thermoregulatory sweating. This is especially noticeable during rapid changes in cutaneous temperatures. The influence of rate of change of skin temperature is best explained as due to the marked rate of change in response of cutaneous thermal receptor fibers. In addition, static skin temperatures modify the response to changes in core temperatures, e.g., lowering of core temperature below previous non-sweating core temperature results in continued sweating if skin temperatures are elevated.

Most investigators have assumed that the hypothalamic and preoptic areas of the CNS were the sole integrators or controllers of thermoregulatory sweating. However, this assumption must be reevaluated since thermoregulatory sweating has been observed on the areas innervated by the "isolated" spinal cord of patients with lesions above the conventional level of sympathetic outflow from the spinal cord. Sweat responses of spinal man parallel changes in skin temperature suggesting reflex connections in the spinal cord with sudomotor sympathetic outflow.

Reversal of the usual caudal to rostral sweat recruitment order was observed during marked cooling of the caudal half
of the body. Thus, skin temperatures play a role in controlling not only the initiation, cessation, and intensity, but also the location of sweating. Differential influences of skin temperatures are believed to contribute significantly to an explanation for the caudal to rostral sweat recruitment pattern when the body is exposed to high ambient temperatures. These skin temperature influences on sweating appear to consist of two elements: (1) thermal receptor influence upon the segment from which they originate, as well as from other segmental levels. This reflex is highly dependent on the rate of change (decrease) of temperature. (2) Unilateral reflex or direct (non-reflex) response on the cooled segment.

Cooling the head appears to affect the common measures of central temperature, i.e., oral and tympanic membrane temperatures. This may be due to the thermal exchange in the upper respiratory tract and/or skin of the head. This complicates the interpretation and separation of central and cutaneous temperature responses during body heating.

Thus, thermoregulatory sweating is held by the author to be a function of: (1) central thermal sensor temperatures; (2) skin temperatures; and (3) rate of change in skin temperatures. The relative roles on sweat responses of these, as well as other, functions remain to be evaluated.

Benzinger held that sweating was directly related to the elevation of the hypothalamic temperature above an unvarying
hypothalamic set point temperature. He believed that skin temperatures above 33°C have no influence on sweating. In the present treatise, skin temperatures above 33°C in transient and steady states are observed to have profound influences on sweating. Alterations in central temperature, and presumably hypothalamic temperature, were often accompanied by changes in sweating. However, no such unvarying set-point temperature could be found in any of the subjects. Therefore, it is concluded that both central and cutaneous temperatures play important roles in control of sweating, but their relative contributions cannot be quantitatively assessed at this time.
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APPROVAL SHEET

The dissertation submitted by Robert Duncan Wurster has been read and approved by five members of the faculty of the Graduate School.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the dissertation is now given final approval with reference to content, form, and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[Signature]

Date

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