THE INTERACTION OF SKIN AND HYPOTHALAMIC TEMPERATURES AS THERMOREGULATORY DRIVES IN THE UNANESTHETIZED CAT

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ABSTRACT

THE INTERACTION OF SKIN AND HYPOTHALAMIC TEMPERATURES AS THERMOREGULATORY DRIVES IN THE UNANESTHETIZED CAT

By

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Although average skin ($\bar{T}_s$) and preoptic hypothalamic (T_{hy}) temperatures have been identified as separate thermoregulatory inputs in warm blooded animals, the nature of their possible interaction in a homeothermic control system has not been thoroughly examined, or well defined. To this end, $\bar{T}_s$ and T_{hy} were independently varied in 116 experiments on 6 lightly restrained, unanesthetized, adult cats (2 to 5 kg. body weight) of both sexes. Measurements of metabolic heat production (M), respiratory evaporative water loss (E), respiratory frequency (f), and internal abdominal temperature (T_{re}) defined resultant steady state thermal balance as $\bar{T}_s$ and T_{hy} were set at various levels.

T_s was adjusted between 33.9°C and 38.3°C by allowing each animal to reach a thermal steady state at mild cold (23°C), thermoneutral (29°C) or mild heat-stressing (35°C)

ambient temperature (T_a). T_{hy} (monitored by an implanted thermistor) was adjusted in increments between 0.1 and 2.3°C above or below a resting level by using a water-perfused heat exchanger chronically implanted in the sphenoid sinus. Hypothalamic heating or cooling did not affect the vasomotor state (as indexed by skin temperature) of the extremities (ear, forefoot, lower hind leg, and tail) or central skin (chest, upper hind leg) when $\bar{T}_s$ was low (T_a = 23°C); f and E were also unchanged, but M varied directly with T_{hy}. T_{re} varied inversely as T_{hy}. When T_a (and consequently $\bar{T}_s$) was at thermoneutral level (29°C) hypothalamic heating and cooling produced peripheral vasodilation and constriction respectively, but f, E, M, and T_{re} were unchanged.

At high $\bar{T}_s$ levels (T_a = 35°C), hypothalamic heating produced little peripheral vasodilation in addition to the near maximal vasomotor state induced by high $\bar{T}_s$; hypothalamic cooling produced vasoconstriction in the extremities; f, E, and T_{re} varied directly as T_{hy}, while M was not affected by experimental alteration of T_{hy}.

The results of this study were interpreted as indicating that although both $\bar{T}_s$ and T_{hy} function as thermoregulatory control inputs, the influence of each is modulated by the other to a degree dependent upon the thermal environmental conditions.

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I. INTRODUCTION

In homeotherms, the maintenance of deep body temperature within narrow limits is attributed to a neural control system with controller components located in the hypothalamus. As with other homeostatic control systems, the neurophyiological temperature regulator has been shown to have characteristics of feedback, input, output, error detection, error signaling, and other properties of a closed-loop control system (Hardy, 1961; Hammel, 1965; Adams, 1970). The ultimate description of the nature of body temperature regulation in terms of these properties is as yet largely incomplete. Nonetheless, it is becoming clear that the control system for internal body temperature and total body heat content in warm blooded animals can be described as possessing analogs of generalized control systems (Hardy, 1961; Hammel, 1965; Stolwijk, et al. 1966).

It is currently accepted that information processed by the hypothalamic controller arises from both central and peripheral portions of the body (Hammel, 1968; Benzinger, 1969). Deep body temperature influences thermoregulatory controller action via thermosensitive neurons in the anterior hypothalamus (Nakayana et al., 1963; Eisenman, 1965; Hellon, 1967; Wit and Wang, 1968) as well as from thermoceptors

within the viscera (Bligh, 1957; Rawson and Quick, 1970), and possibly other deep body sites (Kosaka et al., 1969; Thompson and Barnes, 1970). Peripheral thermosensory input to the controller is from heat and cold receptors distributed principally in the skin.

The hypothalamic controller activates two interrelated sets of thermoregulatory reflexes, one for heat conservation, and the other for heat dissipation. In general, heat conservation involves increases in tissue thermal insulation through peripheral vasoconstriction (which decreases radiative, conductive and convective heat loss) plus increases in heat production. Heat dissipation is affected by decreasing tissue insulation as a function of peripheral vasodilation (which usually increases radiative, conductive, and convective thermal exchange). Heat is also dissipated by water evaporation attendant to panting and/or sweating.

Within the past three decades it has been demonstrated that homeothermy is achieved as a balance between central and peripheral drives transduced and integrated centrally, and implemented through an equilibrium of effector responses associated with heat conservation and dissipation. However, the interrelationships between central and peripheral thermoregulatory drives have not been adequately quantified.

It is the aim of this study to partition central and peripheral thermal drives by experimentally varying skin and hypothalamic temperature separately in the unanesthetized cat.

II. LITERATURE REVIEW

The primary function of the nervous system is integration. Inherent in investigations of any neurally involved biological control system is the necessity to elucidate the components of such integration. Control mechanisms for homeothermy have been reviewed earlier (Barbour, 1921; Bazett, 1927; Deighton, 1933; Burton, 1939; Strom, 1960; von Euler, 1961; Hardy, 1961; Carlson, 1962; Bligh, 1966; Hammel, 1968; Benzinger, 1969). The present review will focus on those research contributions which indicate the integrative role of the nervous system in temperature regulation.

Although Claude Bernard introduced the concept of autoregulation with his hypothesized, relatively constant "milieu interne," the idea that there was central neural control in physiological homeostasis, including that of body temperature regulation was not in early reports. Claude Bernard published research results related to thermoregulation (1876), but apparently considered only cutaneous thermal sensation as the drive to a constant and controlled body temperature.

In 1845, Bergman postulated mechanisms for controlling thermally-induced vasomotor activity, and offered two explanations. An increase in blood temperature may: 1) have

a direct effect on cutaneous blood vessels which would cause vasodilation, increased heat dissipation and the restoration of blood temperature, and 2) act on temperature sensitive brain structures governing vasomotion. At that time, however, there was no experimental evidence to support Bergman's concept of thermoregulatory responses being activated by heat sensitive areas in the brain.

In 1882, Fredericq produced evidence from experiments on himself and on rabbits that modification of central temperature (by respiring hot air at 100% relative humidity) could elicit physiological responses appropriate to a heat stress although the subject was in a cold environment. Similar trials with cold air and ingestion of ice water failed to produce analogous results. These data were among the first which implied that control inputs other than those in the skin, as proposed by Bernard, were important in body temperature regulation.

As described by Cabanac (1961), Charles Richet (1898) exposed dogs to warm sunlight, and observed that the onset of polypnea was followed by the lowering of internal temperature. Richet's conclusion was that the polypnea was initiated through cutaneous receptors activated by the solar (thermal) radiation. Using forced muscular work, electrical tetanization of somatic muscle, or the administration of convulsant drugs to increase internal body temperature in dogs, Richet observed polypnea in the absence of cutaneous thermal stimulation.

Once the concept of two major thermal inputs (i.e., cutaneous and deep body) to biothermal control was evident, investigators attempted to partition, control and experimentally vary those inputs to evaluate their separate influences in homeothermy. Early attempts to partition skin and internal temperature by immersion of the animal in hot or cold water were made by Bert (1885) and Lefevre (1898). Brodie, (1837) followed by Richet (1884) and Ott (1884 and 1887) localized a "heat loss center" in the tuberal region by mechanically creating lesions in the bulbar or thalamic regions of the brain. As discussed in Barbour's review (1921), Isenschmid and Krehl (1912), Barbour and Wing (1913), and Citron and Leshke (1913) also performed lesion ("puncture") experiments localizing the "heat centers" in basal regions of the forebrain.

The first attempt to vary brain temperature independently of body temperature was made by Arnheim (1894) who circulated hot water (70 to 100°C) around the carotid arteries of dogs; not surprisingly, his results were inconclusive. Kahn, (1904), and later Moorhouse (1911), using improved versions of Arnheim's carotid heating technique (and less extreme temperatures) observed peripheral vasodilation, sweating on the footpads, and increased respiratory rate. Heymans (1919), Jelsma (1930), Duschko et al. (1934), and Kure et al. (1930) repeated and confirmed the experiments of Kahn and Moorehouse, and expanded the scope of the experiments to include cooling of the carotid blood. The cooling

induced reduction in respiratory rate, peripheral vasoconstriction, augmentation of muscular activity with occasional shivering, and increased CO_2 production.

The techniques of direct thermal stimulation of brain tissues was initiated by Barbour (1912) using a "U" shaped metal tube perfused with hot or cold water, or by heating the thermode with electrical current. He observed cutaneous vasodilation upon brain heating, accompanied by lowering of rectal temperature, and vasoconstriction. Elevation of rectal temperature was noted during cerebral cooling. Barbour and Prince (1914) observed changes in CO_2 output which varied in the same direction as heat or cold stimulation of the brain "heat center". Confirmation of the findings of Barbour and Prince was obtained in various species by Hashimoto (1915, rabbits), Prince and Hahn (rabbits and cats, 1918), and Moore (1918, rabbits).

O'Connor (1915) showed that shivering in cats and rabbits placed in baths at various temperatures depends more on the brain temperature than on that of the skin. Sherrington (1924) observed shivering in the anterior trunk region of dogs whose internal temperature was lowered by cold water immersion of the posterior part of animals which had been denervated by spinal transection. Uprus et al. (1935) observed similar results to those of Sherrington.

After Ott had reported localization of "heat centers" in the tuberal region, numerous investigators endeavored to

locate them more precisely by lesion, or "heat puncture", (Keller and Hare, 1931; Jacobi and Roemer, 1912; Barbour and Wing, 1913; Isenschmid and Krehl, 1912; Citron and Leschke, 1913; and Teague and Ranson, 1936) by electrical stimulation, Karplus and Kreidl, 1911), by decerebration and other types of ablation (Isenschmid and Schnitzler, 1914; Moore, 1918; Dusser de Barenne, 1919; Bazett and Penfield, 1922; Pinkston, 1934), and local thermal stimulation using smaller, more physiologically compatible thermodes than those initially used by Barbour (1912).

Keller (1933), using lesion techniques, reported support for the early hypothesis of Bergman, i.e., duel functional and anatomical "centers" in the hypothalamus which were related to body temperature regulation. Keller concluded that the anterior portion of the hypothalamus was concerned with heat dissipation, and that the posterior portion was responsible for heat conservation.

By the mid 1930's it had been possible to partially differentiate cold responses, and to demonstrate the existance of structures in various parts of the brain stem and spinal cord which could initiate thermoregulatory activity after ablation or lesion had eliminated the influences of other dominant, or active brain structures. Data pertinant to the analysis of neural connections and structures involved in thermoregulation, were gathered largely as a result of lesion, ablation, carotid warming, and the use of crude thermodes most of which were mentioned above.

In the late nineteen thirties there began a marked expansion in the number and the sophistication of analytical techniques for evaluating thermoregulatory reflexes. Various types of small, chronically implantable thermodes, improved techniques for electrical stimulation, and electrophysiological recording were developed. Along with these technological advancements, more precise quantitative experiments became possible.

A significant advancement in thermoregulatory experimentation was made by Magoun et al.(1938) who locally heated the brain of cats anesthetized with urethane using high frequency current. This method for local heating used two, 22 gauge, nichrome wire electrodes insulated except at the tips. These electrodes were positioned in the brain using Horsley-Clark stereotaxic techniques. The study demonstrated, a "reactive region which responded to heating by marked acceleration of respiratory rate, panting, and in some instances, by the appearance of sweat on the footpads". Further, it was concluded that the hypothalamic "reactive region" contained neural structures which were activated by rising temperature of the blood and led to heat loss activity in the normal animal.

Hemingway et al. (1940) implanted small, gold foil electrodes (for diathermic heating) in contact with the ventral surface of either the anterior or posterior hypothalamus of dogs. This study was significant because definite thermoregulatory responses were obtained in the unanesthetized

animal by local hypothalamic heating without damaging the brain tissues by the insertion of thermode or electrically stimulating probes. Unanesthetized animals were exposed to a cool environment to induce shivering and the brain was heated by passing a diathermic current between the brain electrode and an "indifferent" skin electrode. The hypothalamic temperature change (approximately 1 C) was sufficient to inhibit shivering in the cool environment, and to initiate vasodilation when the animal was exposed to a thermally neutral environment. However, panting could not be obtained in either environment by hypothalamic thermal stimulation.

After approximately a 10 year interval between 1938 and 1948 when very little information about control mechanisms in homeothermy was published (presumably due to the influence of World War II), local heating and cooling experiments were performed by Folkow (1949) and Strom (1950a, b,c,). Using anesthetized cats and dogs, Folkow observed pronounced vasodilatory responses following stimulation of the supraoptic region by diathermy. Those data were interpreted as indicating that vasodilation was the first response initiated by the hypothalamic heat loss mechanism. Strom (1950a,b,c), in a series of articles, published that using Folkow's method (1949), heating the anterior hypothalamus of anesthetized cats caused cutaneous vasodilation and increased respiratory rate. Cooling of the anterior or posterior hypothalamus did not produce any change in

cutaneous blood flow. The peripheral effect of hypothalamic heating was greatly influenced by local skin temperature, and the main action of local temperature effects on blood flow appeared to be produced mainly by direct action on the skin vessels, and not by reflex control. In a warm environment, local anterior hypothalamic heating in unanesthetized dogs (Strom 1950) produced marked vasoconstriction, but such changes could not be observed in a cool or neutral environment. Strom also indicated that no evidence was found for the existence of cold sensitive hypothalamic structures which influence skin blood flow.

Contrary to the findings of Folkow and Strom, Forster and Ferguson (1952) found no correlation between hypothalamic temperature of unanesthetized cats and vasomotor tone as indicated by ear temperature. However, above some critical ambient temperature, all cats observed under steady state conditions were peripherally vasodilated, and below that ambient temperature all cats observed were peripherally vasoconstricted.

Forster and Ferguson (1952) also reported that the hypothalamic temperature of unanesthetized cats showed small, irregular variations as much as 0.5 C, and that hypothalamic temperature was about 0.1 C below rectal temperature as averaged observations. Cats were classified as "central" panters, and "reflex" panters, indicating that in some animals central body temperature was correlated with polypnea and

panting, whereas in others peripheral temperature acted as a thermoregulatory respiratory drive. Panting increased the internal body (rectal) temperature-hypothalamic temperature gradient by decreasing brain temperature. Finally these authors stated that the thermosensitive, hypothalamic, temperature regulatory center of the cat is apparently a coarse thermostat, demanding changes of more than 0.6 C for activation.

Adams (1963a) reported data which not only confirmed Forster and Ferguson's observation of small, irregular variations in hypothalamic temperature of the cat, but also demonstrated that drinking cold liquid (5°C) resulted in an immediate depression of hypothalamic temperature accompanied by a period of peripheral vasodilation. This study further revealed that hypothalamic temperature is approximately 0.5 C lower during sleep, and varies within wider limits than in the awake animal. Other studies by Adams (1963b), dealing with both cold and non-cold acclimatized (unanesthetized) cats whose anterior hypothalamic temperatures were experimentally adjusted by a water perfused thermode (Adams, 1964) showed greater peripheral vasomotor and internal body temperature changes accompanying hypothalamic heating than cooling. Later, it was reported (Adams et al, 1970) that the cat appears to regulate internal temperature at higher levels when exposed to either heat (34, 38, 41 C) or mild cold stress (20, 23 C) than at normothermic exposure levels. Additional findings of Adams et al. (1970) indicate that evaporative

heat loss, respiratory frequency, and metabolic heat production were better predicted by average skin temperature than by rectal temperature. A "fine control" for thermal balance in the cat appeared as variable skin blood flow in the extremities at ambient temperatures less than 38 C, and as cyclic variations, in respiratory evaporative heat loss as the limits of vasomotor heat dissipation avenues were exceeded.

Using dogs anesthetized with morphine sulphate, sodium barbital or chloralose, Lim and Grodins (1955) recorded temperatures in the hypothalamus, subcutaneous tissue of the thigh, and the rectum while the animal was heated, or while the head and trunk were heated and cooled independently. Head temperature could be regulated independently by warming or cooling the carotid arterial blood while the vertebral arteries were ligated. Respiratory rates in excess of 100 per minute were designated as panting. In contrast to the results of Forster and Ferguson (1952), Lim and Grodins concluded that thermal panting could be obtained by central, but not peripheral heating alone. However, Lim and Grodins also noted that "central panting" can be produced in the anesthetized dog, but the hypothalamic panting threshold is higher with central heating alone than with whole body heating.

To test the "dual center" concept, which implies that receptors for cold should reside in the posterior hypothalamus, Freeman and Davis (1959) used temperature calibrated, water perfused thermodes to heat and cool the anterior and

posterior hypothalamus of cats both acutely and chronically implanted with thermodes. They observed peripheral vasodilation and constriction as well as behavioral responses appropriate to heating and cooling the anterior hypothalamus, but panting and shivering were not obtained in response to central thermal stimulation. Thermoregulatory responses were not obtained by thermal stimulation of the posterior hypothalamus. In view of these data, it may be suggested that receptors for both heating and cooling are located in the anterior hypothalamus. Later, recordings were obtained from both warm and cold sensitive neurons in the anterior hypothalamic preoptic region of dogs (Hardy et al. 1964, and Cunningham, 1967), but only for warm responsive neurons in the cat (Nakayama et al. 1963). Recently Edinger and Eisenman (1970) have reported recording from neural units located in the tuberal and posterior hypothalamus of cats. There were both warm sensitive and cool sensitive units (Q_{10}>2) in these regions; however, the authors classified the units as interneurons, since their activity seemed to be subordinate to the influence of warm sensitive preoptic units. On this basis, Edinger and Eisenman question the existence of terminal cold sensitive units, at least in the cat. Other studies (Cabanac, 1968; Hellon, 1967) have disclosed the presence of cold sensitive units in the preoptic-anterior hypothalamic region of the rabbit.

Mestyan et al. (1960) reported that elevated anterior hypothalamic temperature induced by a high frequency current

in the cat resulted in reduced body temperature, as well as increased respiratory frequency, which approached panting levels. Exposure to a cold ambient temperature did not diminish the peripheral vascular response to hypothalamic heating in the cat, but did reduce that response in the rat similarly exposed.

In a series of articles, Fusco (1959, 1963), and Hammel et al. (1960) using unrestrained, unanesthetized dogs implanted with diathermic, or water perfused thermodes reported data which indicated an interaction of central and peripheral thermoregulatory drives resultant to a summation of those two influences. Those investigators also found that central thermal stimulation could be facilitated by thermosensory input from the body periphery. They offered additional evidence that thermal receptors responsive to less than 1°C cooling reside somewhere within the core (i.e. deep body areas) of the dog.

Other evidence for the interaction of central and peripheral thermoregulatory drives was presented by Andersson (1957) and Andersson et al. (1956, 1957) who electrically stimulated the hypothalamus of unanesthetized goats exposed to hot, neutral and cold environments. Exposure to cold (-5°C) increased the threshold and latency for panting and vasomotor responses resultant to electrical stimulation. Shivering could be inhibited by stimulation of the anterior hypothalamus, and could be produced by stimulation of the

area medial and dorsal to the "panting center". Exposure to cold facilitated electrically stimulated shivering, and a rise in body temperature diminished or abolished the shivering response.

Results of experiments focused on the relationship between the thermoregulatory component of metabolic rate and preoptic temperature when ambient temperature is set at normal, high, and low levels, (Jacobson and Squires, 1970) indicated that at normal preoptic and skin temperature, oxygen consumption was not at its lowest level, but could be further reduced by warming the skin or the preoptic hypothalamus. On exposure to cold, the cat appeared to maintain an increased oxygen consumption even if preoptic temperature was raised, and the adjustment of oxygen consumption was considered to be the "important thermoregulatory process even at high ambient temperature". At lowered ambient temperature the preoptic temperature threshold for thermal polypnea was found to be increased.

As experimental evidence indicative of the thermoregulatory roles, physical properties, and anatomical relationships of various components of the thermal homeostatic mechanisms became known, different opinions arose as to how those components act in concert to affect homeothermy. These different opinions resulted from different interpretations of data relative to the concept of a physiological "set point" for body temperature regulation, and upon the degree of dominance exerted upon the central integrative mechanism by

peripheral, or central thermally sensitive units. Two recent reviews (Hammel, 1968, and Benzinger, 1969) present the several viewpoints.

Briefly, there is general agreement that it is hypothalamic temperature which is regulated during thermoregulation, (Benzinger, Hardy, Hammel, etc.), but the nature of the "set-point", or even its actual existence as such is in contention.

Hammel (1965) concludes that the anterior hypothalamus is equally responsive to both moderate heating and cooling; that the reference input signal ("set-point") is not an invariant temperature, but may be adjusted by various factors such as skin temperature, core temperature, exercise, sleep, pyrogens, and the effects of humoral agents acting on hypothalamic neurons; and that the action of any input or feedback function on the central controller for homeothermy adjusts the functional set temperature rather than changes the proportionality constant or gain of the controller.

Benzinger (1963, 1969) proposes that there are two central sites involved in the integration of thermoregulation. One site resides in the anterior hypothalamus, acts as a terminal sensory receptor for warmth, is responsible for vasodilation and sweating, and functions independently of heat stimulus from the skin. Control of metabolic heat production is mediated within the posterior hypothalamus, which receives and transduces afferent impulses from cold receptors

in the skin. According to Benzinger, the posterior hypothalamic function is not affected by its own temperature, but is under the influence of input from the anterior hypothalamus. Cooling the anterior hypothalamus releases the normally inhibitory function of its warm sensitive neurons on the posterior hypothalamus which in turn increases metabolic heat production. Cold sensitive hypothalamic neurons act only under severe cold stress to elicit the metabolic response to cold, and initiate shivering. The central cool sensitive neurons in Benzinger's scheme are much less thermally responsive than are those for warmth. Andersson (Andersson et al. 1963) holds a view similar to Benzinger's regarding the role of the central reception in control of shivering.

Hardy has suggested that the regulation of body temperature in cold and thermoneutral environments is largely affected by action of the peripheral receptors, whereas in hot conditions, and during work the regulation appears to be more strongly influenced by the control of central receptors. He also suggests that the set point is established by differences of static firing rates of warm sensitive, cold sensitive, and possibly thermally insensitive neurons in the preoptic-anterior hypothalamic regions, and that the action of the regulator mechanism possesses the characteristics of both proportional and rate control.

The conclusions of Keller and McClaskey, (1964) are that

the subthalamic and cephalic midbrain level of the brain stem is responsible for heat dissipation and that except for a possible permissive function, heat dissipation is independent of the hypothalamus. They have also concluded that neural integration resulting in defense against hypothermia is "wholly dependent upon the anatomical integrity of the hypothalamic grey, and is completely independent of tissues lying cephalad to the hypothalamus".

Chatonnet (1967) states that the thermoregulatory response is a central nervous interpretation of inputs coming from both central and peripheral sensors and is delivered as a complex function of the inputs from those two major sources.

Currently, evidence is accumulating that there are thermosensory inputs other than just those of the hypothalamus and skin. Guieu and Hardy (1970) demonstrated that rabbits anesthetized with urethane and implanted with a steel thermode in the spinal canal (between T6 and C7) showed increased respiratory rate subsequent to heating the spine to 43-44C. Cooling the spinal cord did not affect polypnea precipitated by preoptic heating, but cooling the preoptic region completely inhibited polypnea caused by heating the spinal cord. Simultaneously cooling both the spinal cord and preoptic hypothalamus did not change respiratory rate. The authors concluded that thermal polypnea is simultaneously controlled by effects of temperature in the spinal cord preoptic hypothalamus and elsewhere in the body core.

Similar findings in rabbits were reported by Koska et al. (1968, 1969). Shivering was initiated by spinal cooling in unanesthetized dogs by Simon, 1965. Chai et al. (1965) diathermically stimulated urethan-anesthetized cats as well as unanesthetized decerebrate cats and observed that the lateral reticular formation of the medulla was as sensitive to thermal stimulation as the anterior hypothalamus. No physiological signficance of these findings has as yet been proposed.

Following the suggestions of Bazett (1951) and Robinson (1962, 1965) concerning the existence of thermal receptors lying deeper in the soma than dermal receptors, Thompson and Barnes (1970) presented evidence suggesting that the femoral vein contains temperature sensitive neural elements. Further, Downey et al. (1969) interpreted the results of their study in spinal man to indicate the presence of "deep temperature sensitive structures", and "a possible interrelationahip between skin and central temperature regulatory structures".

Rawson and Quick (1970) employed four chronically implanted heat sources to vary the internal heat load of ewes. When the temperature of the heat sources was raised, in neutral or warm environments, an almost immediate rise in respiratory rate and evaporative heat loss followed. This response was accompanied by a marked decline of hypothalamic temperature, but no change or decline of vaginal temperature. In cold exposure, metabolic heat production was depressed presumably due to the imposed heat load. The study provides

strong evidence for the existence of deep body thermoceptors.

An interesting opinion concerning the influence of the thermosensitive units in various parts of the body was asserted by Barker and Carpenter (1970). After presenting evidence of thermal sensitivity by neurons in the sensorimotor cortex of the cat, the authors suggest that "the thermosensitivity of a neuron does not necessarily indicate a role for that neuron in transmission of thermal informaion or in thermoregulation as has been implied in previous studies". Of course, even if there are no thermally sensitive units in the cortex, the emotional and behavioral influences of the cortex on thermoregulation are well known, at least empirically in man, and have been discussed by Benzinger (1959, 1969), Adams (1962) and Hammel (1968).

Clearly a final description of biothermal control mechanisms is not close at hand. Major central and peripheral inputs have been established (i.e., hypothalamic and skin temperature), other inputs such as those from deep-body blood vessels, the viscera, the medulla oblongata, and spinal cord have been postulated, and strong evidence has been presented as to the thermal sensitivity of neural units residing in these areas but their specific role, if any, in thermoregulation has not been demonstrated for any of those inputs. It has been generally agreed that primary thermoregulatory integrational activity resides in the hypothalamus probably the posterior portion, but what inputs are integrated, and the degree of their influence on the final effector responses

are not agreed upon, and the feedback mechanisms, which are intrinsically associated with thermosensory inputs cannot be fully elucidated until more is known about the action of the integrational mechanism, primary inputs, and their interaction.

III. STATEMENT OF PROBLEM

From the earliest studies of body temperature regulation to the present, investigators have focused much of their attention on attempts to identify, isolate and/or control the various physiological control system elements involved in homeothermy. Some of those investigators have involved the experimental variation of peripheral and/or central temperatures (Lim and Grodins, 1955; Fusco, 1959; Adams, 1962; Forster and Ferguson, 1952; Whittow, 1968; Freeman and Davis, 1959) in various species of anesthetized and unanesthetized animals.

In many studies, experimental stimulation of the central thermally sensitive neural structures was greater than that which would be experienced under all but the most severe thermal stress. Others did not involve the neural tissue exclusively. It has been proposed (Freeman and Davis, 1959) that the temperature variations did not involve sufficient volume of the brain to stimulate enough thermosensitive neurons for a complete effector response. In no case has an unanesthetized animal been exposed to heat, cold, or thermoneutral ambient temperatures while a large number of thermoregulatory parameters were monitored under steady state conditions and a large volume of the diencephalon

experimentally heated or cooled without also involving the temperature of the head skin.

The present study was designed to test the hypothesis that thermal balance in the awake, normal animal is achieved by an interaction of both central and peripheral thermosensitive components, and that the greatest central response might be obtained experimentally by altering the temperature of a large volume of the diencephalon. Further, the intention was to make such an evaluation using measurement of an adequate number of parameters which would allow quantification of the thermoregulatory state of the animal.

IV. METHODS AND MATERIALS

4.1 Animal Selection.

Gentle, healthy, adult, short haired cats of either sex weighing between 2 and 5 kg were obtained from the Michigan State University Center for Laboratory Animal Resources (C.L.A.R.) and were "conditioned" (i.e. quarantine, vermifugation, and vaccination) under the supervision of Bruce W. Douglas, D.V.M., Ph.D. All animals were caged individually in stainless steel cages in the C.L.A.R. facility in rooms temperature controlled between 21 and 25C. and with a 12 hour light cycle. Animals were fed a diet of "Friskies" cat food except for approximately 1 week following surgery when they were fed softer, more easily chewed food (e.g. canned fish flavored meat).

4.2 Hypothalamic Temperature Control and Measurement.

The apparatus and procedures described below were constructed and designed for chronically implanting a thermode in the sphenoid sinus of cats (4.2.1), and monitoring brain temperature (4.2.4) changes precipitated by the thermode while the thermal environment was controlled by housing the animal in a specially constructed chamber.

4.2.1. Thermode and Adaptor.

The water perfused thermode was constructed by silver-soldering the open ends of two, size C 78, 79, or 80

(depending on the size of the cat to be implanted) stainless steel dental incisor crowns and a 5 mm length of 15g stainless steel tubing to form a hollow metal container with the tubing forming the only opening in the container (Figure 1 upper).

A 12 cm length of 1.2 mm O.D. x 0.8 mm I.D. silicone rubber tubing (Dow Corning Corp., Midland, Mich.) was inserted 1 cm into the thermode opening (Figure 1 lower), and an 11.5 cm length of 3 mm O.D. x 2 mm I.D. silicone rubber tubing (Dow Corning Corp., Midland, Mich.) slipped over the smaller tubing and onto the freshly primed (Dow Corning 1201 Primer), silicone rubber adhesive coated 15g tubing. The tubing was then secured to the stainless steel thermode outlet tube by several windings of securely tied, fine, nylon, monofilament thread. The thread and outer surface of the tubing were then thinly coated with silicone rubber adhesive (type A, Dow Corning Corp., Midland, Mich.). The free ends of the concentric silicone rubber tubes were attached to concentrically arranged stainless steel tubes protruding from the base of the head mount (Figure 1 upper).

4.2.2 Head Mount Construction.

The head mount unit (Figure 1 upper) served the threefold purpose of, 1) providing coupling between the thermode tubes and extracorporeal thermode perfusion apparatus (described in section 4.2.3) holding a 26 mm long x 0.45 mm O.D. glass or stainless steel thermistor probe (Figure 1 upper) for measuring anterior hypothalamic temperature, and 3) holding an electrical connector for coupling the thermistor

bead with its attendent electrical circuitry and recorder (see section 4.2.4 below).

The head mount unit was constructed by housing two stainless steel (21g and 15g) tubes (Figure 1 upper), the thermistor probe, and an electrical connector (MDBI-9SL2, ITT Cannon Electric Inc., L.A., Calif.) for the thermistor leads (Figure 1 upper) into a dental acrylic matrix. The proximal ends of two concentric silicone rubber tubes were attached to the metal tubes embedded in the head mount matrix by the same procedure (see above) used to attach the thermode at distal end of the outer tube. At the top of the head mount, the metal tubes were soldered to a male coupling, the base of which embedded in the acrylic of the head mount. Hydraulic perfusion of the thermode was facilitated by a female coupling connecting the accessory perfusion apparatus with the stainless steel tubes in the head mount (Figure 1 upper).

4.2.3 Thermode Perfusion Apparatus.

During thermode perfusion distilled water was forced by compressed air from a 2.5L capacity reservoir which had an air inlet, water filling tube, water outlet, and solenoid actuated air pressure release valve (Figure 2). Water passed from the reservoir through a water jacketed heat exchanger and through the thermode finally voiding to a catch vessel. Control of thermode perfusion (and consequently of brain temperature) was accomplished by modulating air pressure in the water reservoir, adjusting a valve controlling water flow through the tube leading to the heat exchanger, and setting

the temperature of the water jacket of the heat exchanger by a temperature control unit (Porta Temp, Precision Scientific Co., Chicago, Ill.).

4.2.4 Hypothalamic Temperature Measurement Probe.

Temperature of the anterior hypothalamus was measured by a small (0.4 mm diam., 32 A7, Victory Engineering Co., Springfield, N.J.) thermistor bead mounted in the end of a glass capillary or 26g stainless steel tube 30 mm long x 0.4mm O.D. x 0.25mm I.D. The 0.025 mm diameter, 3 mm long platinum leads from the thermistor bead were wrapped around and soldered to the bare end of 0.05 mm diameter teflon insulated copper wire (Thermo Electric Co., Inc., Saddle Brook, N.J.). The platinum thermistor leads and copper wire ends were electrically insulated with epoxy resin cement (Zynolyte Products Co., L.A. Calif.) used to hold the thermistor bead and its leads in the capillary tube. The wires were pulled through the tube until the base of the bead rested at the tip of the tube (Figure 3), and additional epoxy cement was used to hold the bead firmly in place. The connector in the head mount unit (Figure 1 upper) to which the thermistor leads were soldered, permitted incorporation of the thermistor into a Wheatstone bridge circuit (Figure 4), which was in turn coupled with one channel of a 2 channel strip chart recorder (Moseley 7100 BM, Hewlett Packard Corp., Pasadena, Calif.). Thermistor probes were calibrated against a National Bureau of Standards certified, mercury-in-glass thermometer in a well stirred, insulated water bath.

4.3 Surgical Procedure.

All surgical procedures were performed aseptically on anesthetized (pentobarbital sodium, 36 mg/kg ip) and atropinized (atropine sulfate 0.25 mg/kg iv) animals secured in a stereotaxic frame (Model 1430, David Kopf, Tujunga, Calif.). Body temperature was maintained by a heating pad.

4.3.1 Head Mount Implant.

The skull was exposed by a 3 cm incision in a frontal plane approximately 14 mm anterior to the interaural line. Muscles, connective tissue and periosteum were scraped free of the skull surface and retracted. The thermistor probe of the head mount unit was lowered into the brain through a 2 cm diameter hole in the skull. With the probe tip stereotaxically aligned in the hypothalamus (A 14.5, L 0, V-4), the head mount unit was stabilized on the skull using dental acrylic which extended peripherally from the base of the head mount, and over the heads of 4 stainless steel screws previously mounted in the skull (Figure 6). Before closing the incision around the head mount by a size 00, black silk, purse string suture and several interrupted sutures, the thermode and silicone rubber tubes, presurgically connected to the head mount, were threaded subcutaneously, following the path of a curved trochar from the top of the head along the natural curvature of the skull and neck posterior to the ear, to a 1 cm long incision in the skin just posteroventral to the angle of the jaw.

4.3.2 Thermode Implant.

The animal, still in the stereotaxic frame, was rotated to a supine position. The mouth was blocked open, the tongue secured in a fully extended position, and a 2 cm midline incision made in the soft palate. This incision extended posteriorly from the posterior border of the hard palate. Working through the retracted incision a small diameter (2 cm) dental trephine was used to remove portions of the palatine presphenoid, and alisphenoid bones forming the floor and medial septum of the sphenoid sinus (Figure 5). A thin (less than 1 mm) layer of dental amalgum was contoured to the roof of the sinus and formed to match the surface of the thermode. The thermode and attendant tubing extending from the neck incision, were passed through a trochar which pierced the nasopharyngeal wall at the angle of the mandible, and just posteroventral to the parotid gland. A thin layer of thermoconductive silicone-based paste (DC-Z9 G.C. Electronics, Rockford, Ill.) was spread over the amalgum. This layer filled the space between the thermode and the amalgum and increased thermal conduction between the thermode and the overlying tissue. The palatine incision was sutured using size 000 gut, and the neck incision closed with size 00 black silk suture. Figure 6 displays radiographs of the thermode, thermistor probe, and head mount after implantation. Postoperatively, the animals were treated with antibiotics (Longicil, 0.8 cc/cat, Fort Dodge Laboratories Inc., Fort Dodge, Iowa).

4.3.3 Thermode Function Evaluation.

Temperature effects induced by the thermode system were evaluated in a block of agar and in the brains of anesthetized cats held a stereotaxic frame with the body of the animal immersed in a thermostatically regulated water bath, as described earlier (Hunter, 1965, 1970). Isotherms (reported in Results) measured in a series of tests on animals, and in similar tests in agar, were determined using an array of four needle-mounted (26 gauge) copper-constantan thermocouples (40 gauge) separated laterally by 4.0 mm. The thermocouple probe assembly was held in a stereotaxic electrode carrier aligned over the animal's head. Thermocouple measurements were referenced against an ice-water bath and emf's recorded on a temperature calibrated, multipoint, strip-chart recorder (Leeds and Northrup, Speedomax W, AZAR). During steady-state heating of the brain with the thermode, temperature measurements were made dorsoventrally at 2-mm intervals, at planes 4 mm posterior to, and at the level of the anterior hypothalamus (14.5 mm anterior to the level of the stereotaxic earbars). For the purposes of these tests, ventral brain temperature was changed a maximum of 2.1°C. Although representative of hypothalamic temperature adjustments appropriate to thermoregulatory responses of the unanesthetized animal exposed to thermal stress, this level of adjustment does not reach the limits of temperature change possible with this thermode system. The pressure-activated hydraulic system used in conjunction with this thermode allows fine adjustment of

brain temperature by the control of water perfusion rates through the unit.

4.4 Temperature Measurement by Thermocouples.

Temperature of the exposure chamber, hood, volume flow meter, humidity sensor, seven skin sites, (see section 4.4.2) and rectal temperature (see section 4.4.1) were monitored by 36g copper-constantan thermocouples in a circuit described in Figure 7. The emf output of each thermocouple was recorded every 12 seconds by a multipoint recorder (Speedomax W. Leeds Northrup Co., Philadelphia, Penn.).

4.4.1 Rectal Temperature.

Rectal temperature was recorded by means of a polyethylene plastic probe (PE 280), housing the thermocouple in its tip, inserted 10 cm into the sigmoid colon and taped firmly but not constrictively, at the base of the tail.

4.4.2 Skin Temperature.

Skin temperature of the forehead, ear pinna, dorsal front paw, chest, upper hind leg, and tail (see Figure 8) were recorded after clipping the fur from a small (approximately 1-2 cm^2) area, removing the remaining short hair with a dipilatory ("Neet", Whitehall Laboratories Inc., New York, N.Y.), washing the area with mild soap and water, spraying the dry skin with a resin compound (Ace Adherent, Becton, Dickinson and Co., Rutherford, N.J.) and securing the thermocouple in place with a 1-2 cm length of 1 cm wide plastic surgical tape (Blenderm surgical tape, Minnesota Mining and Manufacturing Co., St. Paul, Minn.). On skin

areas which had long fur such as chest, tail, and upper hind leg, the surrounding fur was arranged over the thermocouple attachment to provide near-normal insulation.

4.5 Exposure Apparatus.

4.5.1 Restraint Device.

Each animal was trained to rest in a sling made of plastic screen wire mesh (approximately 1 mm^2 mesh) supported by a metal frame (Figure 8) which permitted free air circulation around the animal. A wide mesh screen (mesh approximately 1.5 cm^2) supported the feet 8 cm above the floor of the exposure chamber.

4.5.2 Chamber and Hood.

The exposure chamber was a 70 x 33 x 60 cm acrylic plastic box with walls 0.5 cm thick. The animal's head was enclosed in a 13 cm I.D. acrylic plastic hood which fastened to the frame of the restraint device. The outside of the chamber was insulated with a covering of 1 cm thick polyurethane foam. Air flow in the chamber was separated from that in the hood by a sheet of rubber dam which fit snugly, but not constrictively around the animal's neck, and sealed between the hood and a flat plastic plate at the anterior end of the frame (Figure 8).

4.5.3 Temperature Control.

Air temperature in the chamber was adjusted by passing hot or cold water through exposed tubing (radiator) in the ducts attendant to the chamber (see Figure 8). Two fans, one located behind the tubing, and one behind a dehumidifier

coil (Figure 8) provided air circulation through the chamber. A baffle at the chamber air inlet distributed air flow such that thermal uniformity inside the chamber was maintained within 0.6C. Air temperature was regulated by a thermo-regulator unit (model 71, Yellow Springs Instrument Co., Yellow Springs, Ohio) which alternately actuated pumps to circulate hot or cold water from reservoirs through the radiator.

Air temperature in the hood was regulated by a second Yellow Springs instrument thermocontroller which actuated a pump from a cold water bath, and alternately actuated a resistance wire heater. Both the 1/4 in. copper tubing cooling coil and the resistance wire heating coils were located in the bottom of the hood, and were separated from the cat by 1/4 in. mesh screen wire. Two small (blade length 7 cm) fans provided mixing of the air and promoted thermal uniformity inside the hood. Hood and chamber air temperature were regulated separately to the same setpoint in all experiments.

4.5.4 Humidity Control.

Relative humidity of air in the chamber was maintained constant between 25 and 35% for different experiments by a dehumidifier unit interposed between the chamber and air circulation duct (Figure 8).

4.6 Respiratory Measurements.

An air flow system for the hood separate from that of the chamber, facilitated sampling of expired gases, and the

subsequent calculation of metabolic heat production (M) and respiratory evaporative heat loss (E). Air flow through the hood (20L/min) was continuously monitored using a calibrated volume flow meter ("Vol-O-Flo", National Instrument Laboratories Inc. Rockville Md.). Air was drawn into the hood from the chamber by a high volume vacuum pump and exhausted outside the chamber. Air samples for O_2 content and E determinations were drawn from the excurrent air stream at the point of exit from the hood by smaller (20, and 200 ml/min, respectively) vacuum pumps which directed the sample air into the associated sensor.

4.6.1 Metabolic Heat Production.

Oxygen content of air leaving the hood was monitored by a Beckman F-3 oxygen analyzer (Beckman Instruments Inc., Fullerton, Calif.) electrically coupled with one channel of a Moseley 2 channel strip chart recorder (Model 7100 BM, Hewlett Packard Corp., Pasadena, Calif.). This instrument was calibrated against known gas mixtures such that full scale deflection of the recorder pen represented a change of 1.375% in the oxygen content of the air sample drawn from the hood effluent. Metabolic heat procution (M) was calculated as:

$$M = \dot{V}_{O2} \cdot K_h \cdot C_m \qquad (1)$$

Where:

M = metabolic heat production ($^{watts}/_{m^2}$)

$\dot{V}_{O2}$ = oxygen consumption ($cc/m^2 \cdot min$; STPD)

K_h = caloric equivalent for O_2 (4.8 $^{Kcal}/_{cc}$)

C_m = 69.77; factor to convert Kcal/min • m^2 to watts/m^2

Oxygen consumption (V_{02}) was calculated as:

$$\dot{V}_{02} = \frac{(\dot{V}_0)(K_{STPD})(F_{in_{02}} - F_{out_{02}})}{S_a} \qquad (2)$$

Where:

$\dot{V}_{02}$ = oxygen consumption (cc/min . m^2)

$\dot{V}_0$ = observed air flow from hood (cc/min)

K_{STPD} = conversion factor to convert $\dot{V}_0$ to STPD units.

$F_{in_{02}}$ = fraction of oxygen in air entering hood.

$F_{out_{02}}$ = fraction of oxygen in air leaving hood.

S_a = body surface area of experimental animal (m^2)

4.6.2 Respiratory Evaporative Heat Loss.

Relative humidity of air entering and leaving the hood was measured by a resistance hygrometer (Model No 15-7012, Hydrodynamics Inc. Silver Spring, Md.) whose electrical output was recorded on the second channel of a two channel strip chart recorder used to record O_2 content (see section 4.6.1). Respiratory evaporative heat loss (E) was calculated as:

$$E = \dot{V}_{H2O} \cdot K_V \cdot C \qquad (3)$$

E = evaporative heat loss (watts/m^2)

$\dot{V}_{H2O}$ = volume rate of water evaporation (gms/min)

K_V = 0.575; heat of vaporization for water at body temp. of 39°C (Kcal/gm)

C = 69.77; factor to convert Kcal/min • m^2 to watts/m^2

The rate of water evaporation was calculated as:

$$\dot{V}_{H2O} = \frac{(\dot{V}_O)(rh_{in} - rh_{out})(Q_{H2O})}{Sa} \qquad (4)$$

$\dot{V}_{H2O}$ = rate of water evaporation (gms/min)

$\dot{V}_O$ = observed hood air flow (cc/min)

rh_{in} = relative humidity of air entering hood (%)

rh_{out} = relative humidity of air leaving hood (%)

Q_{H2O} = saturation density of water at sensor temperature (gm/cc)

Sa = body surface area of experimental animal (m^2)

4.6.3 Respiratory Frequency.

Respiratory frequency was measured using a mercury-in-rubber strain gauge attached by a velcro strap around the chest. Respiratory movement was recorded at 5 min intervals on one channel of a Grass oscillograph (Model 7, Grass Instrument Co., Quincy, Mass.) which received the output from a plethysmograph bridge (Model 270, Parks Electronics Laboratory, Beaverton, Ore.) coupled electrically with the strain gauge.

4.7 Experimental Procedure.

Animals were exposed in individual tests to ambient temperature of 23, 29, and 35°C. After reaching a thermal steady state at any exposure (minimum of 50 minutes), 6 readings of each parameter at 5 minute intervals were used to index thermoregulatory adjustment. Whole body thermal equilibrium was described as a result of levels of hypothalamic heating and cooling (0.5 and 1.0°C) for each test ambient temperature. One hundred and sixteen experiemtns were

performed in 6 cats.

4.8 Temperature Calculations.

4.8.1 Average Skin Temperature.

Average skin temperature ($\bar{T}s$) was calculated as:

$$\bar{T}_s = T_e K_e + T_f K_f + T_h K_h + T_{ch} K_{ch} + T_{uhl} K_{uhl} + T_{lhl} K_{lhl} + T_t K_t \quad (5)$$

Where:

$\bar{T}_s$ = average skin temperature (^oC)

T_e = ear temperature (^oC)

T_f = dorsal front foot temperature (^oC)

T_h = forehead temperature (^oC)

T_{ch} = chest temperature (^oC)

T_{uhl} = upper hind leg temperature (^oC)

T_{lhl} = lower hind leg temperature (^oC)

T_t = tail temperature (^oC)

K_e = skin surface proportioning factor for ear

K_f = skin surface proportioning factor for foot

K_h = skin surface proportioning factor for forehead

K_{ch} = skin surface proportioning factor for chest

K_{uhl} = skin surface proportioning factor for upper hind leg

K_{lhl} = skin surface proportioning factor for lower hind leg

K_t = skin surface proportioning factor for tail

$\bar{T}_s$ was calculated from the mean of 6 readings made during each rest and experimental period using skin surface area proportioning factors selected on the basis of animal weight

from data reported earlier (Vaughan and Adams, 1967) and listed in table A of the appendix.

Average temperature of the skin of the extremities (T_E) was calculated as:

$$\bar{T}_E = T_e K_e + T_f K_f = T_{lhl} K_{lhl} + T_t K_t \qquad (6)$$

Where:

T_E = average temperature of the extremities (^oC)

T_e = ear temperature (^oC)

T_f = foot temperature (^oC)

T_{lhl} = lower hind leg temperature (^oC)

T_t = tail temperature (^oC)

K_e = skin surface area proportioning factor for ear

K_f = skin surface area proportioning factor for foot

K_{lhl} = skin surface area proportioning factor for lower hind leg

K_t = skin surface area proportioning factor for tail

The proportioning factors represented the fraction of the total extremity surface area represented by each regional measurement site and were derived from data reported by Vaughan and Adams (1967).

In the same manner, constants were derived for central skin sites and average temperatures of central skin calculated as:

$$\bar{T}_c = T_h K_h + T_{ch} K_{ch} + T_{uhl} K_{uhl} \qquad (7)$$

Where:

$\bar{T}_c$ = average temperature of central skin (^oC)

T_h = forehead temperature (^oC)

T_{ch} = chest temperature (^{o}C)

T_{uhl} = upper leg temperature (^{o}C)

K_{h} = skin surface area proportioning factor for forehead

K_{ch} = skin surface area proportioning factor for chest

K_{uhl} = skin surface area proportioning factor for upper hind leg

4.9 Statistical Methods.

Mean ($\bar{x}$) and standard error of the mean (see Appendix C) was calculated for sets of 6 readings for each measured parameter during an experiment. In some instances the grand means ($\bar{\bar{x}}$, see Appendix C) were calculated for all sets of readings during hypothalamic cooling or heating in all animals tested.

Regression lines were drawn after determination of their equations by continuous simple linear regression (see Appendix C), and critical values for Students t-distribution were used to determine the probability that the slope of a given regression line was not different from 0 (Appendix C).

FIGURE 1

Head Mount

a. Upper: cutaway view of acrylic "head mount" into which are molded concentric stainless steel tubes (SS) leading to paired hydraulic connections on top of the unit (HC), electrical connections (EC, front of mount) for the thermistor (Tm), and glass or stainless steel tube (T) containing the thermistor at its tip. Flange (F) at the base of mount facilitates attachment to the animal's skull. Threaded upper part of mount (A) receives external hydraulic connector, and serves as an attachment site for a protective cover when the unit is not in use.

b. Lower: cutaway view of thermode showing location of concentric silicone rubber tubes (SR); smaller tube extends into thermode lumen, while larger silicone tube is attached to stainless steel water exit tube of the thermode.

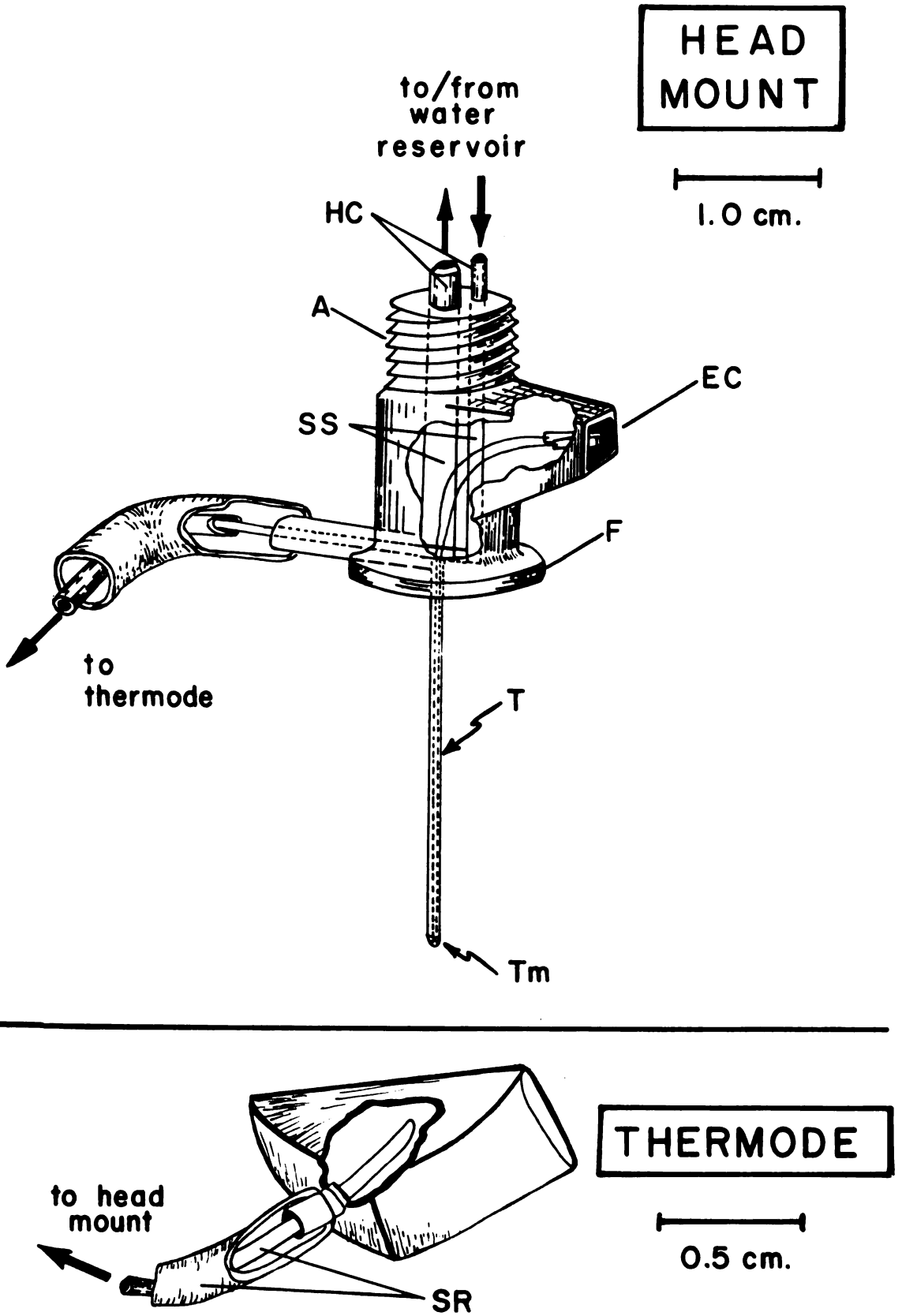

HEAD MOUNT
to/from water reservoir
1.0 cm.
HC
A
EC
SS
F
to thermode
T
Tm
THERMODE
to head mount
0.5 cm.
SR

FIGURE 2

Thermode Perfusion Apparatus

This diagram (not drawn to scale) indicates the relationship of components of the thermode perfusion system and path of water flow (arrows).

AT = Compressed air tank

PR = Pressure relief valve, solenoid actuated

S = Switch to activate pressure relief valve

WR = Water reservoir

1 = Water outlet tube

2 = Air inlet tube

3 = Filling tube

CV = Thermode water flow control valve

HX = Heat exchanger

TB = Temperature controlled bath

FC = Female coupling connecting external perfusion apparatus with head mount

HM = Head mount

C = Container to catch thermode effluent

TC = Tubing connecting head mount to thermode

T_h = Thermode

Tm = Thermistor

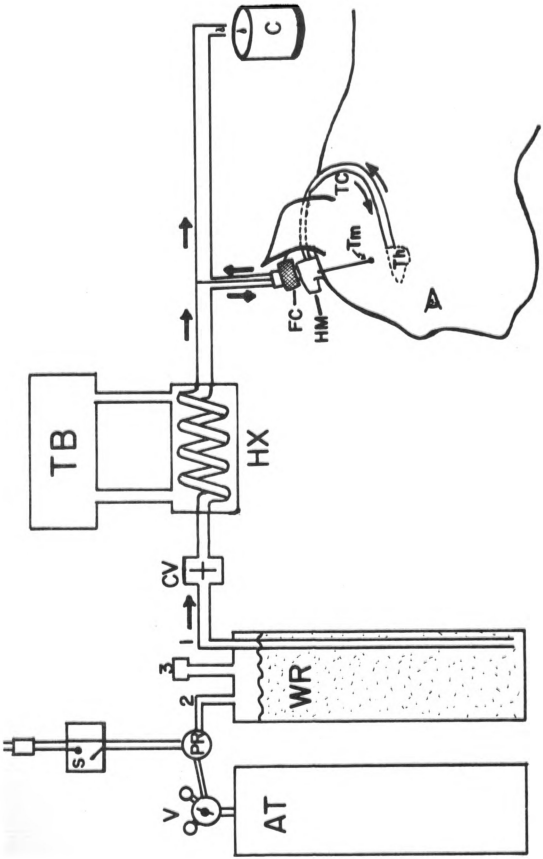

C
TC
Tm
Tn
A
FC
HM
TB
HX
CV
WR
AT
V
PR
S
1
2
3

FIGURE 3

Thermistor Probe

Schematic drawing of proximal and distal ends of thermistor probe (both glass and stainless steel probes were constructed in the same manner).

PW = Wall of stainless steel or glass tube

TW = Teflon insulated copper wire

EC = Epoxy cement

Tm = Thermistor bead and platinum leads

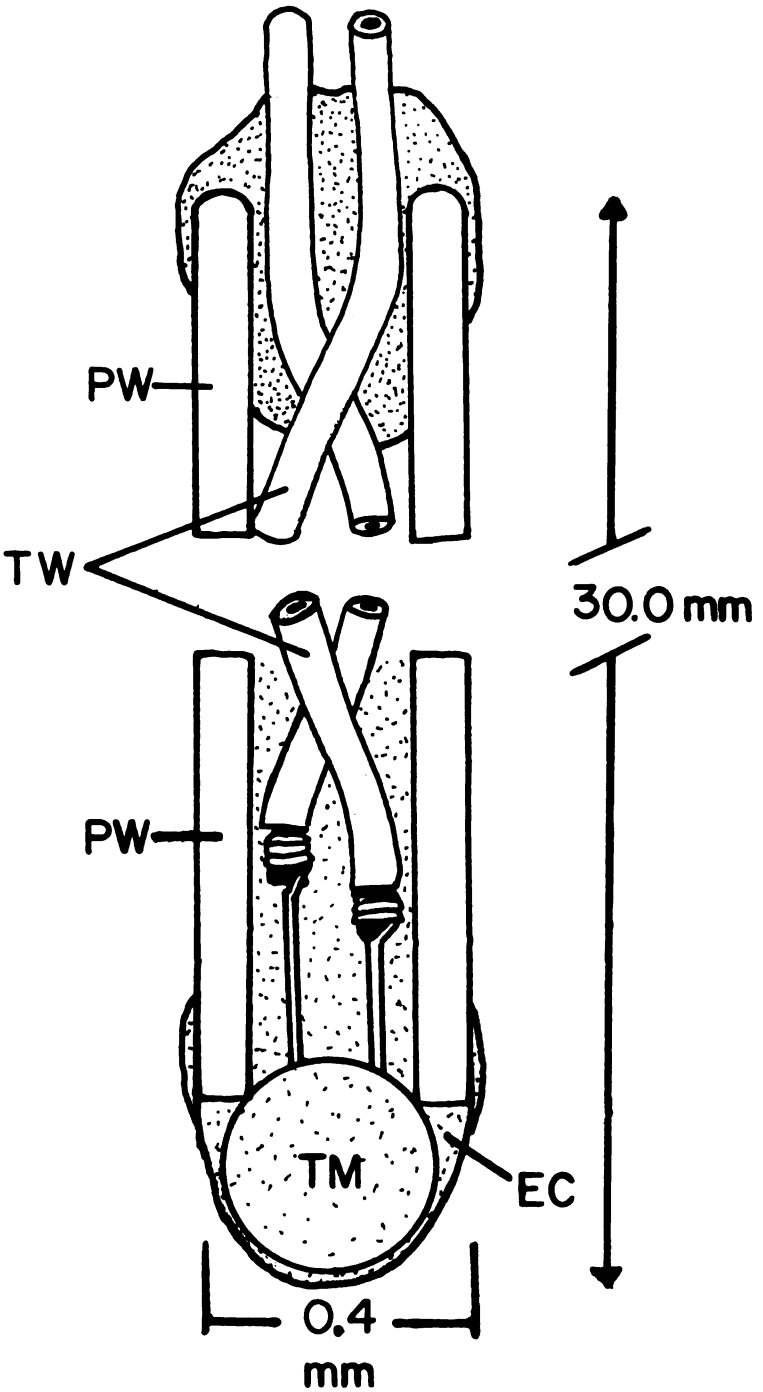

PW
TW
30.0 mm
PW
TM
EC
0.4
mm

FIGURE 4

Circuit diagram for hypothalamic thermistor and recording apparatus

S1 = Switch to activate bridge circuit

R1 = ¼ watt, 1.2 K ohm resistor

R2 = 1 K ohm potentiometer (coarse adjust for calibration)

R3 = 200 ohm potentiometer (fine adjust for calibration)

R4 = ¼ watt, 1.2 K ohm resistor

Tm = Thermistor

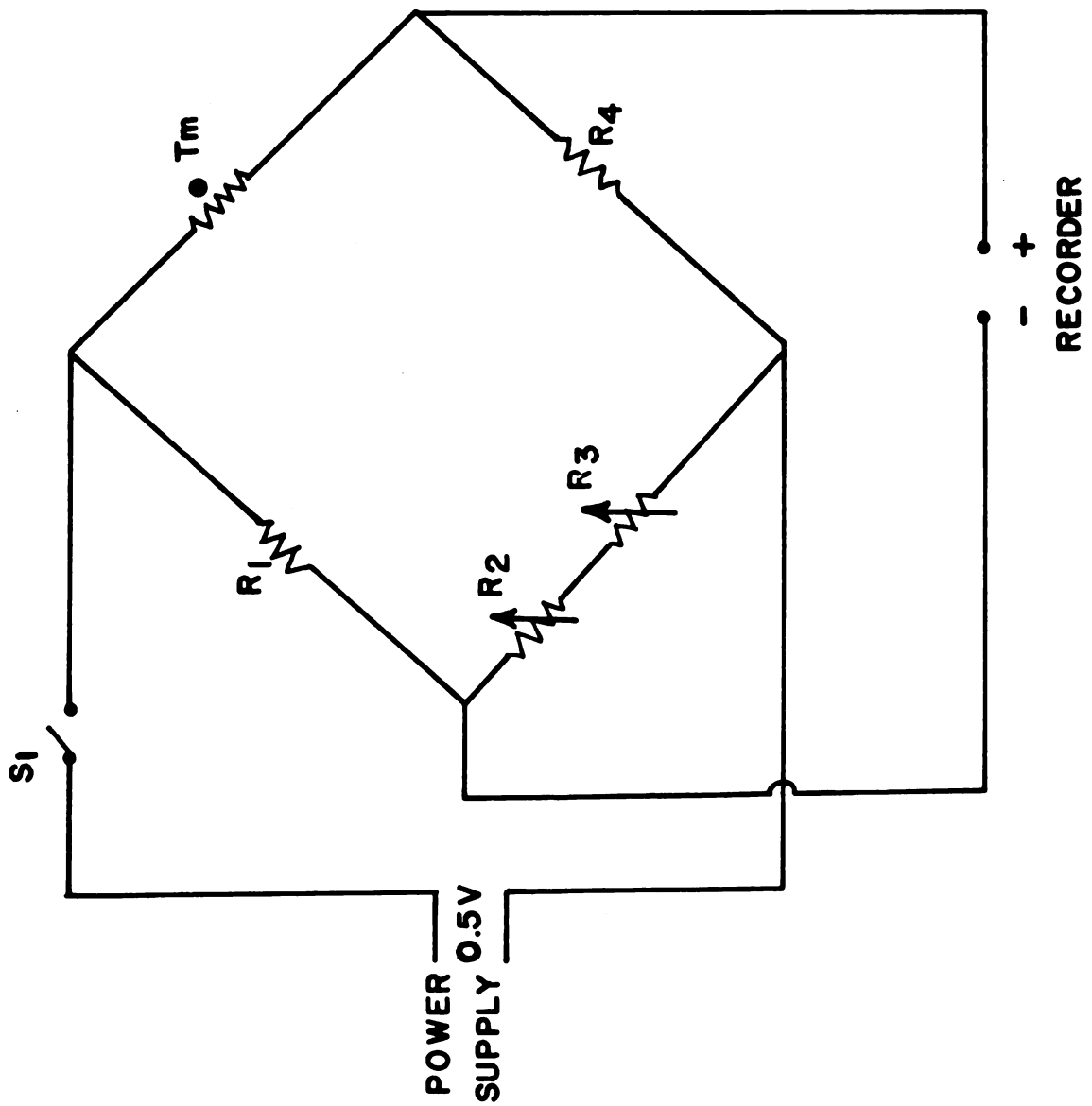

Tm
R4
R1
R2
R3
S1
POWER SUPPLY 0.5V
- +
RECORDER

FIGURE 5

Saggital midline sketch of cat's head

This sketch shows the sphenoid sinus (s) in relation to the cerebral cavity (C), hypophyseal fossa (h), cerebellar cavity (cb), nasal choanae (nc), frontal sinus (f), pterygoid bone (p), and stereotaxic reference (r; external auditory meatus). Floor of the sphenoid sinus is removed between dotted lines.

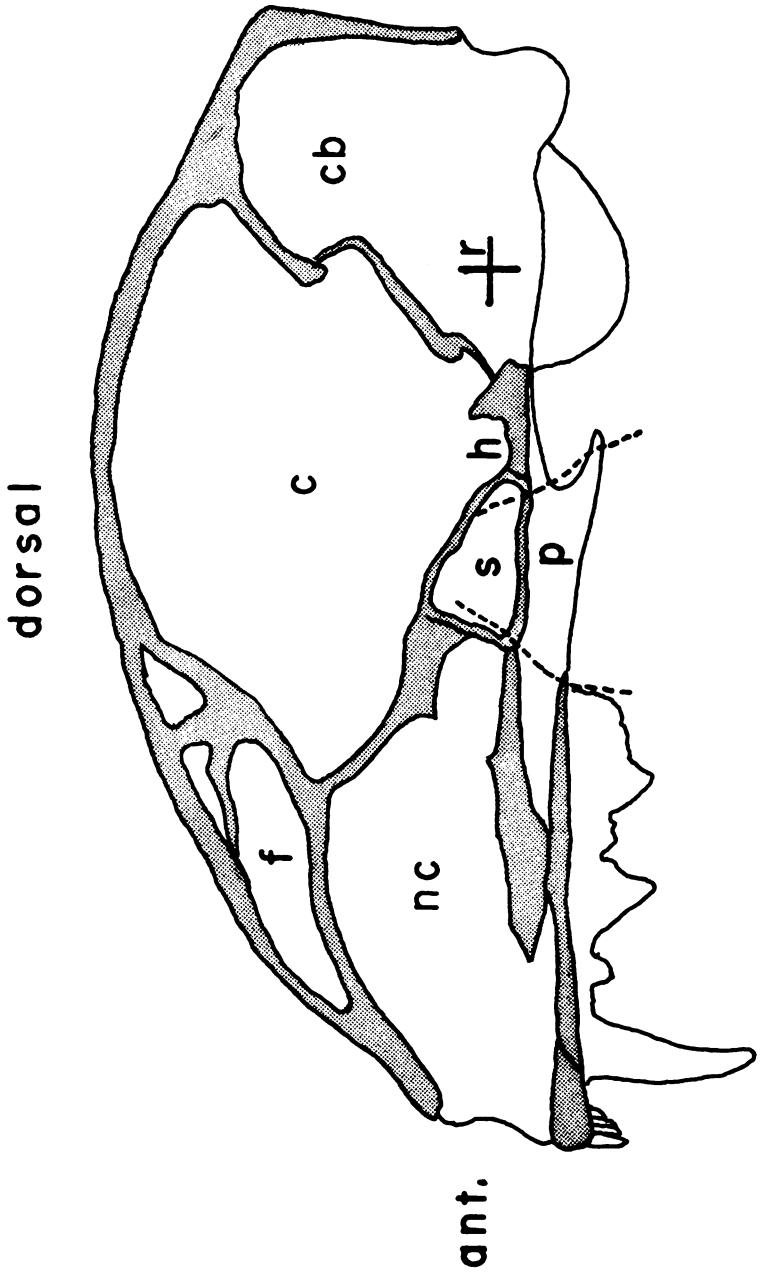

dorsal
ant.
cb
c
h
s
p
f
nc

FIGURE 6

Radiograph of head mount after implantation

Lateral view of the cat's head showing the implanted thermode at the base of the brain, connecting silicone rubber tubes to the acrylic "head mount" unit (not visible) secured on the dorsal surface of the skull with stainless steel screws, and shafts containing thermistors located in the anterior hypothalamus at the upper rear of the thermode. Electrical connections for thermistors extend forward and hydraulic connections upward from the acrylic heat mount.

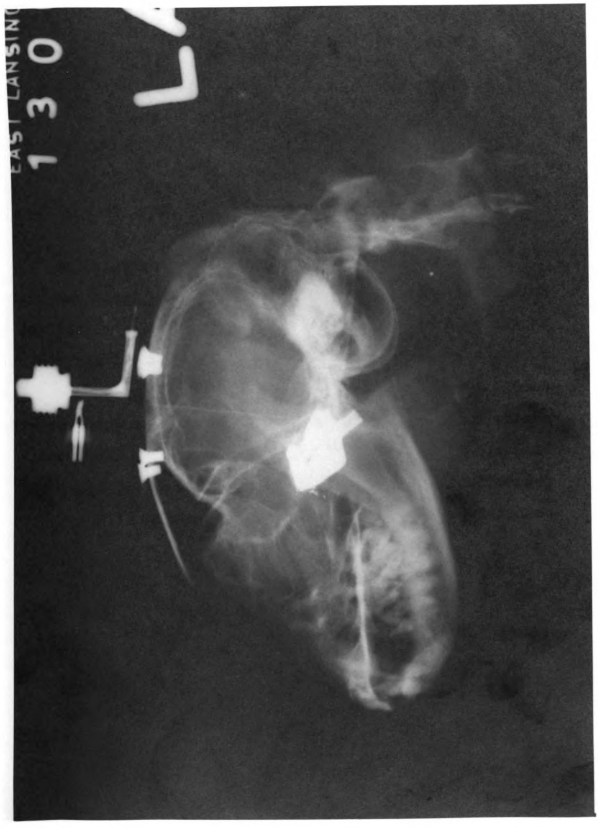

EAST LANSING
130

FIGURE 7

Circuit diagram for skin thermocouples

Each thermocouple (TC-1 to TC-12) was connected by welding its constantan (CO) lead to a common point. The copper (CU) thermocouple leads ran to a stepping relay within the recorder (adapted from Adams, 1962).

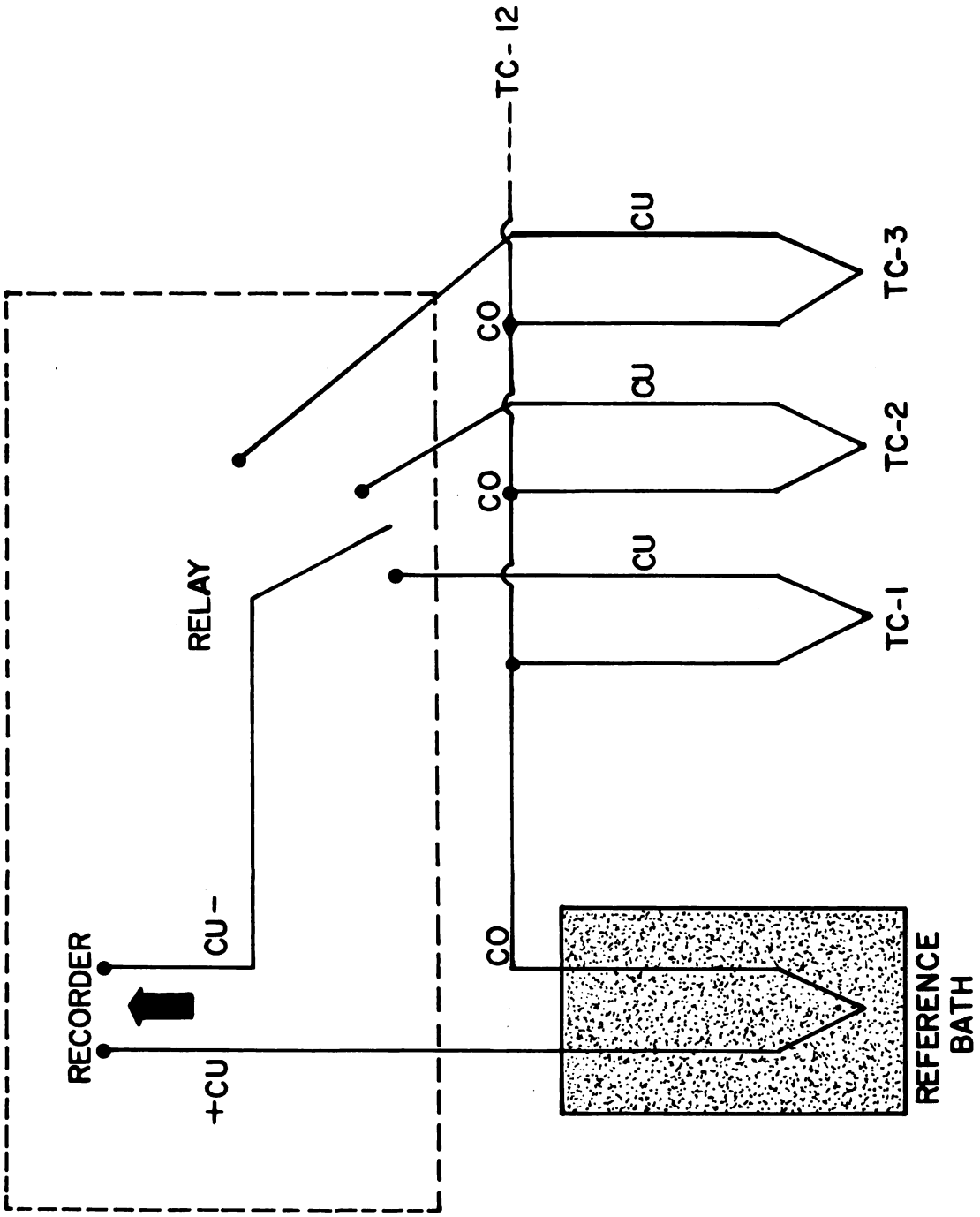
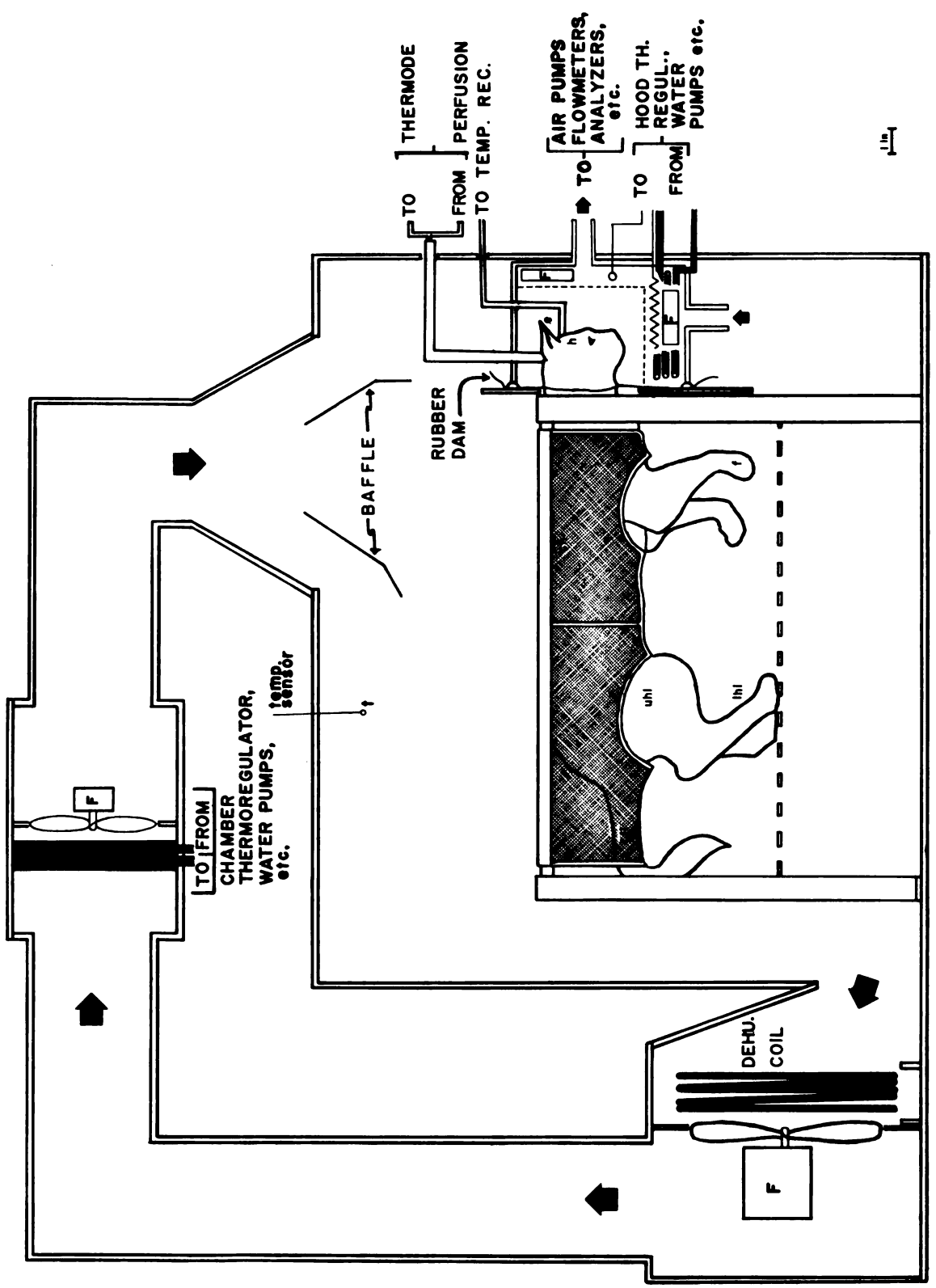

TC-12
CU
TC-3
CO
CU
TC-2
CO
CU
TC-1
CO
RELAY
CU-
RECORDER
+CU
REFERENCE
BATH

FIGURE 8

Exposure Apparatus

This semidiagramatic scale drawing indicates the relationship of the animal to components of the exposure chamber and hood, sites of thermocouple attachment (f, h, uhl, etc. see section 4.8.1), fans (F), dehumidifier unit, air flow direction (arrows), chamber temperature control, heat exchanger (HE), and restraint device.


TO
FROM
THERMODE
PERFUSION
TO TEMP. REC.
TO
FROM
AIR PUMPS
FLOWMETERS,
ANALYZERS,
etc.
HOOD TH.
REGUL.,
WATER
PUMPS etc.
RUBBER
DAM
BAFFLE
temp.
sensor
TO
FROM
CHAMBER
THERMOREGULATOR,
WATER PUMPS,
etc.
DEHU.
COIL
F
uhl
thl

V. RESULTS

1. Thermode Evaluation.

Temperature effects induced by the thermode systems were evaluated by determing isotherms around the thermode embedded in a block of agar, and in the brains of anesthetized cats as described in section IV 4.3 Isotherms reported in Figure 9 are representative of results in a series of tests on animals, and analogous to similar measurements made in agar. Isotherms were first determined with the thermode implanted in the animal, but not being perfused ("Control" Figure 9). After normal resting values were determined, measurements were made while the thermode was being perfused, and those representative isotherms are presented in Figure 9. "Heating" supports the suggestion that the thermode system can be effective in altering the temperature of basal brain areas.

Figure 10 presents data indicating the degree of brain temperature adjustment and control possible in the unanesthetized cat chronically implanted with the thermode system as described in section IV. For data presented in Figure 10, thermode perfusion ranged between 0-15 ml/min at a pressure gradient of approximately 5 psi to provide an average maximal temperature change of approximately $2^{o}C$/min, and

stability of about 0.1°C at a controlled level of brain temperature adjustment.

1.1 Effects of the Thermode on Body Thermal Load.

Tests on two of the animals used in the present study indicate that if all the heat lost or gained between the water inlet and outlet of the head mount were transfered to the central body, a net gain or loss of approximately 0.25°C/hr in internal body temperature (T_{re}) would result. Measurements of rectal temperature (Figures 11, 12, and 13) indicate that at $T_a = 23^{\circ}$ internal body temperature generally varied inversely as T_{hy} for both hypothalamic heating and cooling. Experimental variation of hypothalamic temperature when $T_a = 29^{\circ}$ resulted in essentially no change in T_{re} when T_{hy} was increased, and T_{re} increased as T_{hy} was decreased (Figure 12). A direct relationship between T_{re} and T_{hy} at $T_a = 35^{\circ}$ is demonstrated by data presented in Figure 13.

2.1 Relationship Between T_a and $\bar{T}_s$.

Data presented in Figure 14 demonstrate that the previously reported (Adams et al., 1970) linear relationship between average skin temperature ($\bar{T}_s$) and ambient temperature (T_a) was also represented in the present experiments when the animal was "resting", i.e. when the thermode was not being employed to alter brain temperature. The following section (2.2) described the relationship between T_a and $\bar{T}_s$ when T_{hy} was experimentally varied.

2.2 Relationship Between ΔT_{hy} and $\Delta \bar{T}_s$.

At steady state conditions, the relationship between

hypothalamic temperature (T_{hy}) and average skin temperature ($\bar{T}_s$) became more predictable at increased ambient temperature (T_a), (see Table 1). For $T_a = 23^o$, data reported in Figure 15 show no predictable change, from resting level, of $\bar{T}_s$ in response to either positive (heating) or negative (cooling) experimentally induced change in T_{hy}. Data for $T_a = 29^o$ (Figure 16) indicate a more predictable increase ($0.1<1.0^oC$ in 10 experiments) or no change in $\bar{T}_s$ as T_{hy} was increased, and pronounced decrease ($0.2<0.75$ in 11 experiments), no change, or slight in increase ($0 <0.3$ in 5 experiments) in $\bar{T}_s$ as T_{hy} was experimentally decreased. At the highest T_a used in the present study (35^oC) an increase in $\bar{T}_s$ subsequent to increased T_{hy} was observed in 19 of 20 experiments involving 5 cats (Figure 17), and decrease in $\bar{T}_s$ with decreased T_{hy} was noted in all of 20 experiments.

2.3 Relationship Between T_{hy} and $\bar{T}_E$.

When $T_a = 23^oC$, there was no consistent response for change in average extremity temperature ($\Delta\bar{T}_E$; see section IV. 8.1) as a function of change in T_{hy} (Figure 18). A significant relationship was observed for T_E as a function of T_{hy} when T_{hy} was either increased (regression coefficient $b = 1.15$) or decreased ($b=0.87$) at $T_a = 29^oC$ (Figure 19). With T_a held at 35^oC (Figure 20), an increase in T_{hy} was met with a small, but statistically significant, increase in $\bar{T}_E$ ($b=0.10$, $P<0.01$). Cooling the hypothalamus elicited a stronger response than did heating. Regression of $-\Delta\bar{T}_E$ on

$-\Delta T_{hy}$ revealed a slope much greater than 0 statistically ($b=0.38$, $P<0.001$).

2.4 Relationship Between T_{hy}, Average Central Skin Temperature ($\bar{T}_C$) and Rectal Temperature (T_{re}).

Central skin temperatures were seen to vary more in association with rectal temperatures (T_{re}) than with T_{hy} at different T_s's (Figures 21-22). As T_{hy} was increased when $T_a = 23^o$ (Figure 21 bottom), $\bar{T}_C$ generally decreased ($b= -0.24$ $P<0.001$); $\bar{T}_C$ also decreased as a function of rectal temperature (Figure 22) at $T_a = 23^oC$. A slope near 0 (0.0099), but significantly different from 0 ($P<0.001$), was determined for data recorded when $T_a = 29^o$ (Figure 21 middle). Similarly there was little alteration of T_{re} or $\bar{T}_C$ with T_{hy} (Figures 12 and 22) at $T_a = 29^oC$.

When T_a was set at 35^oC, $\bar{T}_C$ as a function of T_{hy} showed a slope significantly different from 0($b=0.24$ $P<0.001$) and increasing slightly with both T_{hy} and T_{re} (Figure 21 top).

3. Respiratory Responses.

Data reported in Figure 23 show the "resting" values for respiratory frequency (f). This relationship is in general agreement with data reported earlier. (Adams et al, 1970). Lowest respiratory frequencies were generally observed at 29^oC, with slightly higher values at $T_a = 23^oC$. At $T_a = 35^o$ values 3-4 times higher than those at 29^oC were observed. Regression lines for f on T_{hy} at 23, 29, and 35^oC are presented in Figure 24. A negative slope ($b=-2.54$; $P<0.001$) is identifiable as T_{hy} is increased over the range $36-41^o$ when $T_a =$

23^{o}. At 29^{o}, a negative slope (b=-0.29; P<0.001) considerably nearer 0 than for T_a = 23^{o}C was obtained, while at T_a = 35^{o}, the responses of f to hypothalamic heating or cooling fell along a line with slope b = 35.99 (P<0.001). Similar results were obtained when Δf was viewed as a function of ΔT_{hy} (Figure 25).

3.1 Changes in Evaporative Heat Loss.

Respiratory evaporative heat loss generally varied in the same manner as did f when hypothalamic temperature was changed at T_a = 35^{o} (Figure 28). However, data reported for T_a = 23^{o}C (Figure 26) and T_a = 29^{o}C (Figure 27) indicate that E was not related to T_{hy} when the hypothalamus was cooled, but increased slightly as T_{hy} was increased.

3.2 Metabolic Heat Production.

Metabolic heat production (M) was facilitated as a function of hypothalamic cooling, and inhibited as a function of hypothalamic heating when T_a was maintained at 23^{o}C (Figure 29). However, at 29^{o}, no significant metabolic changes occurred in response to change in T_{hy} (Figure 30). At T_a = 35^{o}, large changes in ΔM occurred, but were apparently not related to corresponding changes in ΔT_{hy} (Figure 31).

4. Relationship Between Hypothalamic, Rectal and Ambient Temperature.

Figure 32 illustrates the relationship of "resting" T_{hy} to T_a. Generally, lowest resting hypothalamic temperatures were observed when T_a = 29^{o}C; adjusting to a slightly higher

and less variable ($\bar{x}$ = 38.47, SEM = +0.14 at 29°; $\bar{x}$ = 38.54 SEM = +0.05 at 23°) level at T_a = 23°C. Average resting T_{hy} was approximately 0.4°C higher when T_a = 25° than at 29°C.

Comparison of data for T_{re}, T_{hy}, and T_a are presented in Figure 32. The difference between hypothalamic and rectal temperatures is essentially unchanged at T_a = 23°C or 29°C (Figure 32). However, when T_a = 35°, the gradient between T_{hy} and T_{re} is markedly increased. Although both T_{hy} and T_{re} increase as a function of increased T_a, T_{hy} increases slightly less than T_{re} when respiratory rate (Figure 23) is elevated.

5. Experimental Shifts in Hypothalamic Temperature and Thermal Balance.

The difference between metabolic heat production and evaporative heat loss (M-E) is plotted as a function of the difference between average skin temperature and ambient temperature ($\bar{T}_s - T_a$) in Figure 33. For resting values of T_{hy}, M-E was found to be a linear function of $\bar{T}_s - T_a$, confirming measurement accuracy for the parameters involved (i.e. convective [C], metabolic [M], evaporative [E], and radiative [R] heat exchange) in this study (Gagge et al., 1936). For average values of hypothalamic heating or cooling in all experiments of the present study, the balance of C, M, E and R heat exchange is not influenced by hypothalamic temperature when $\bar{T}_s$ is high (i.e. $\bar{T}_s$ = 35°, Figure 33). At T_a = 35°C, an implied maximum vasomotor response is in evidence, resulting in a minimal $\bar{T}_s$ to T_a gradient. While at

29°C, the influence of hypothalamic temperature upon $\bar{T}_s - T_a$ (and inferentially upon $\bar{T}_s$, since T_a was held constant) was greater than at either 23°C or 35°C. Convective exchange (indexed by $\bar{T}_s - T_a$) was not affected by hypothalamic temperature when T_a = 23°, as is also indicated by data for $\bar{T}_s$ (Figure 12). When T_a = 23°C and 29°, these data show that M is facilitated and/or E is inhibited; the converse occurs for experimental elevation of T_{hy}.

Figure 9

Intracranial Isotherms

Isotherms at 0.1°C intervals below the highest temperature (RT), dorsal (D; ordinate; mm) and lateral (L; abscissas; mm) in the brain of the anesthetized cat are shown at 2 levels (10.5 mm and 14.5 mm) anterior to the stereotaxic ear bar reference before (control) and during heating with the thermode in the sphenoid sinus. At 14.5 mm, heating, RT = 40.04°C; control, RT = 38.36°C. At 10.5 mm, heating, RT = 37.97°C.

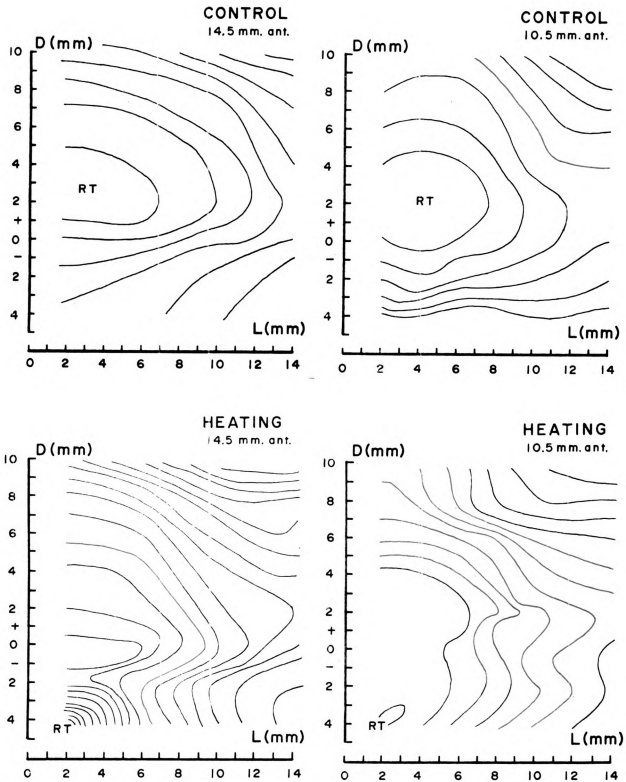
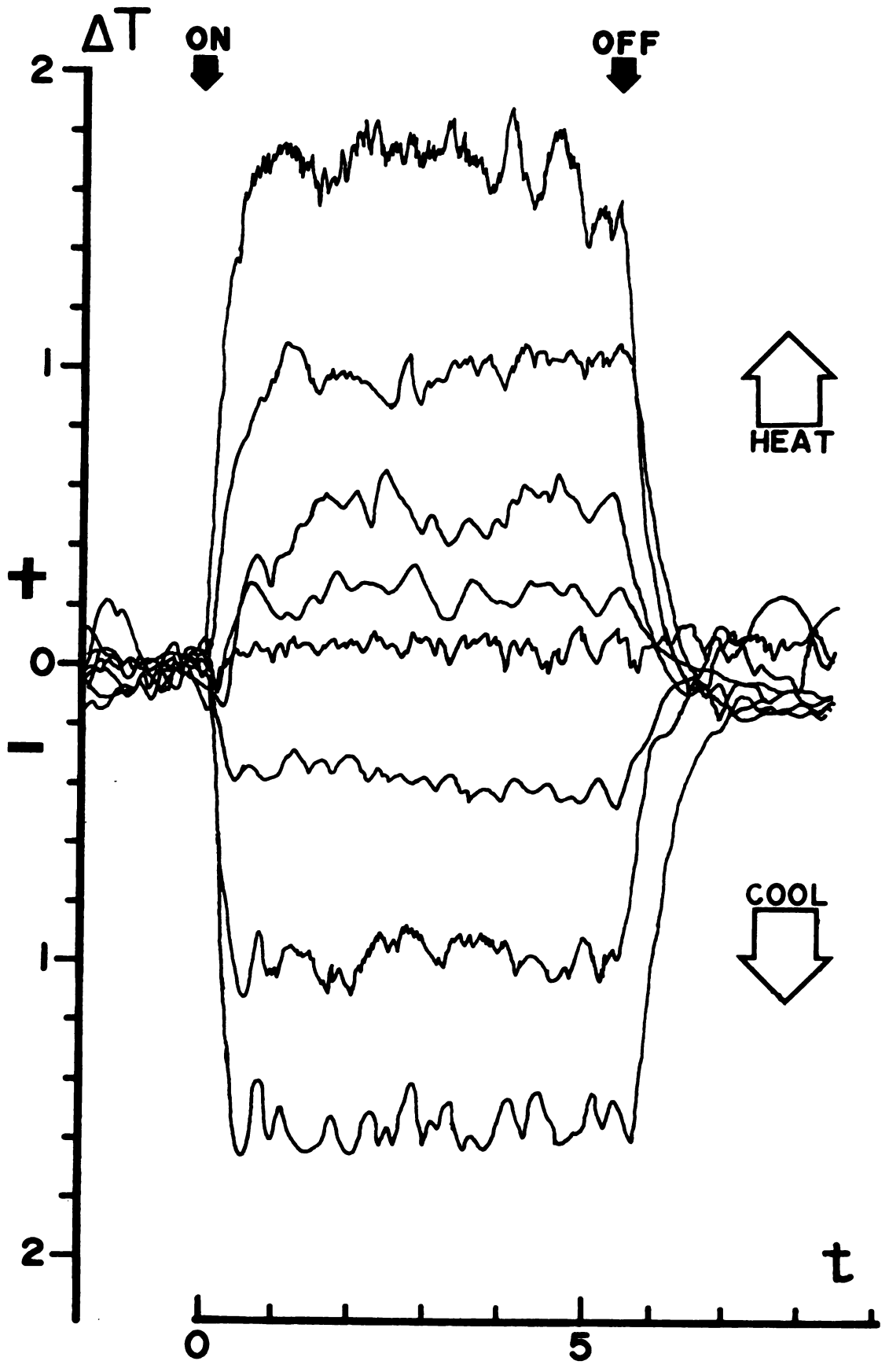

CONTROL
14.5 mm. ant.
D (mm)
RT
L(mm)
CONTROL
10.5 mm. ant.
D (mm)
RT
L(mm)
HEATING
14.5 mm. ant.
D (mm)
RT
L(mm)
HEATING
10.5 mm. ant.
D (mm)
RT
L(mm)

Figure 10

Hypothalamic Temperature Control

Change in hypothalamic temperature in an unanesthetized cat (T; ordinate; ^{o}C) is shown as a function of time (t, abcissa; min.) during three levels of cooling and four of heating of 5 min each using the thermode in the sphenoid sinus and thermistor at 14.5 mm anterior, 0.0 mm lateral, and 4 mm below stereotaxic reference.


ΔT
ON
OFF
2
1
+
0
−
1
2
HEAT
COOL
t
0
5

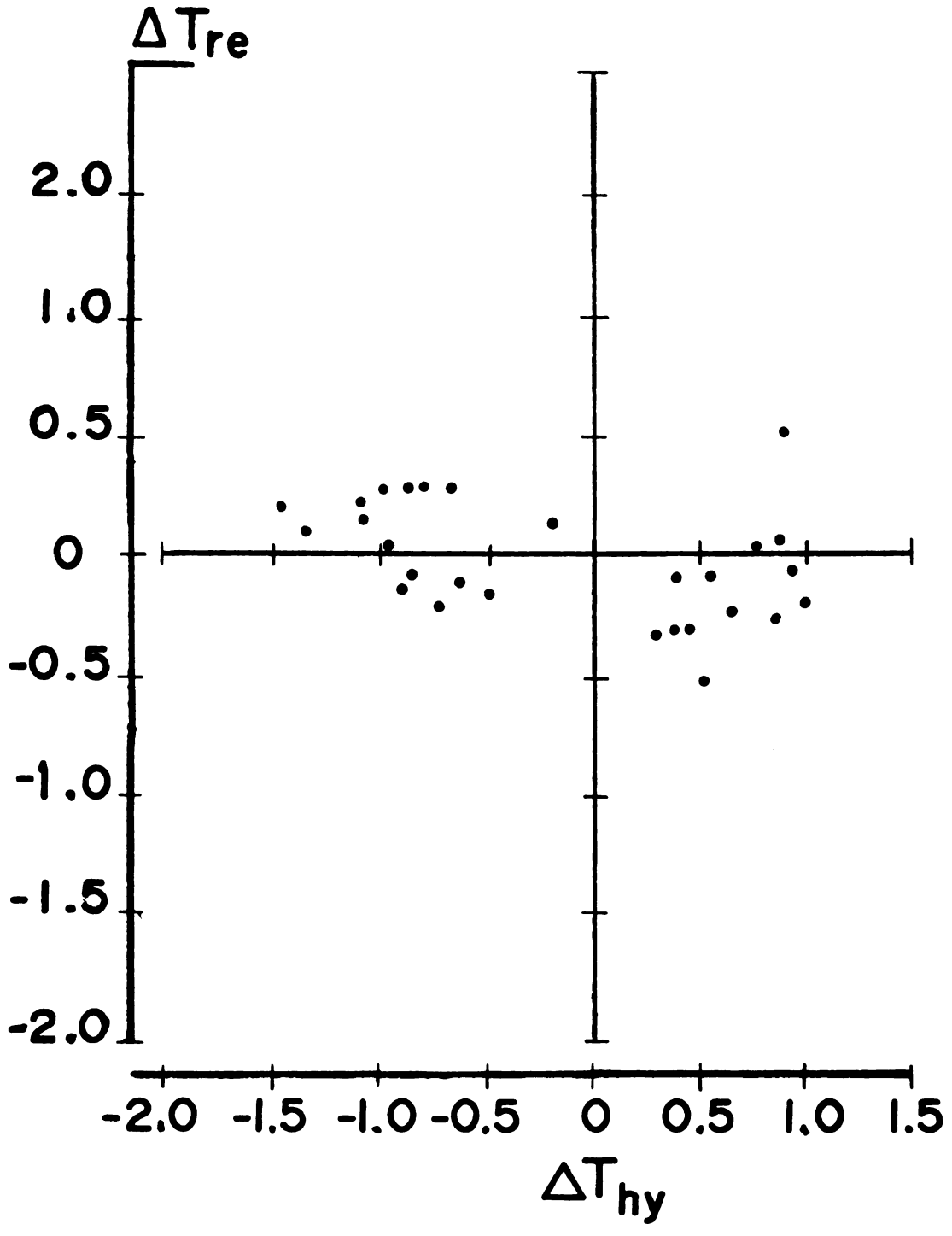


Figure 11. Change in rectal temperature (T_{re}) as a function of change in hypothalamic temperature when T_a = 23°C.

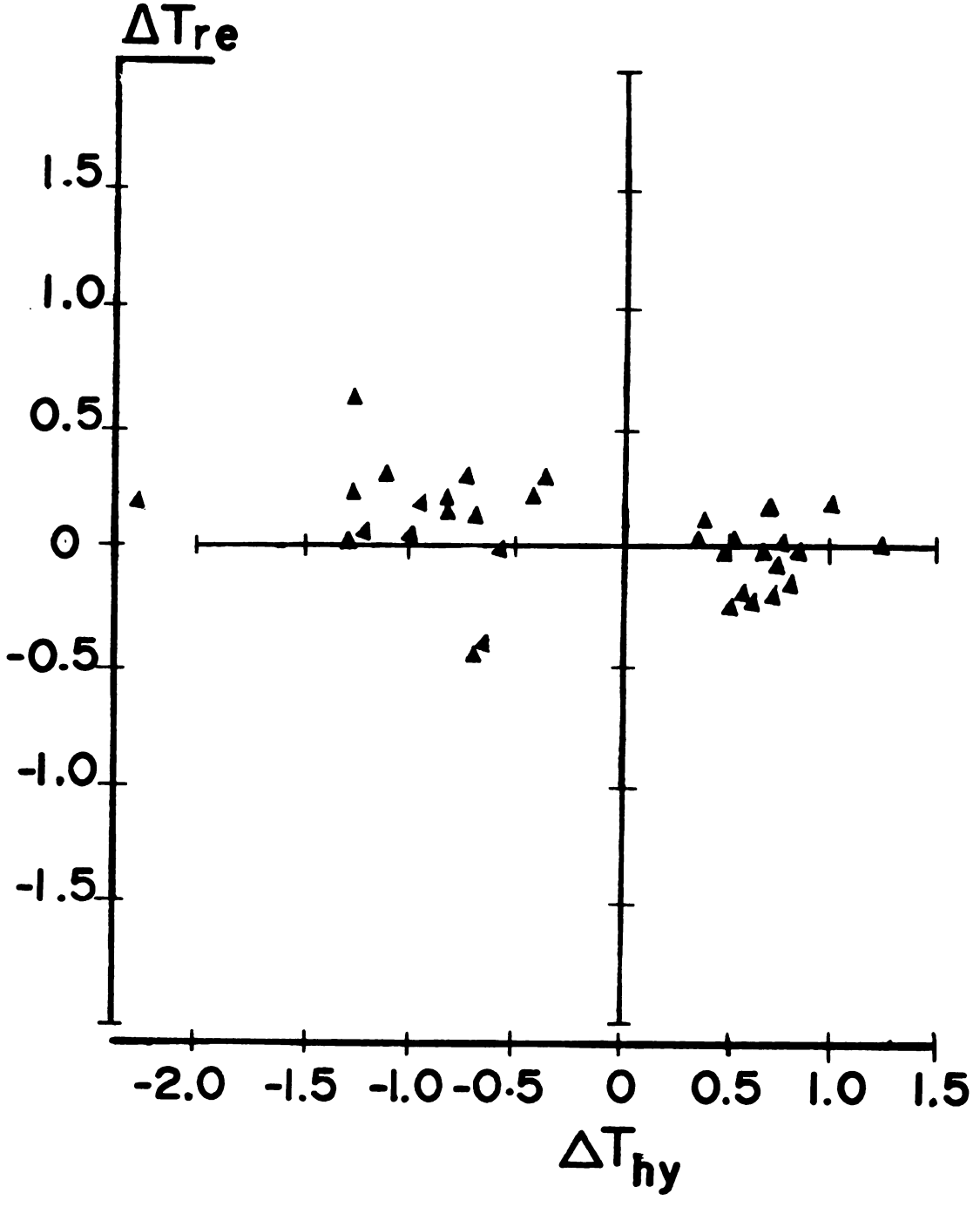


Figure 12. Change in rectal temperature as a function of change in hypothalamic temperature when T_a = 29°C.

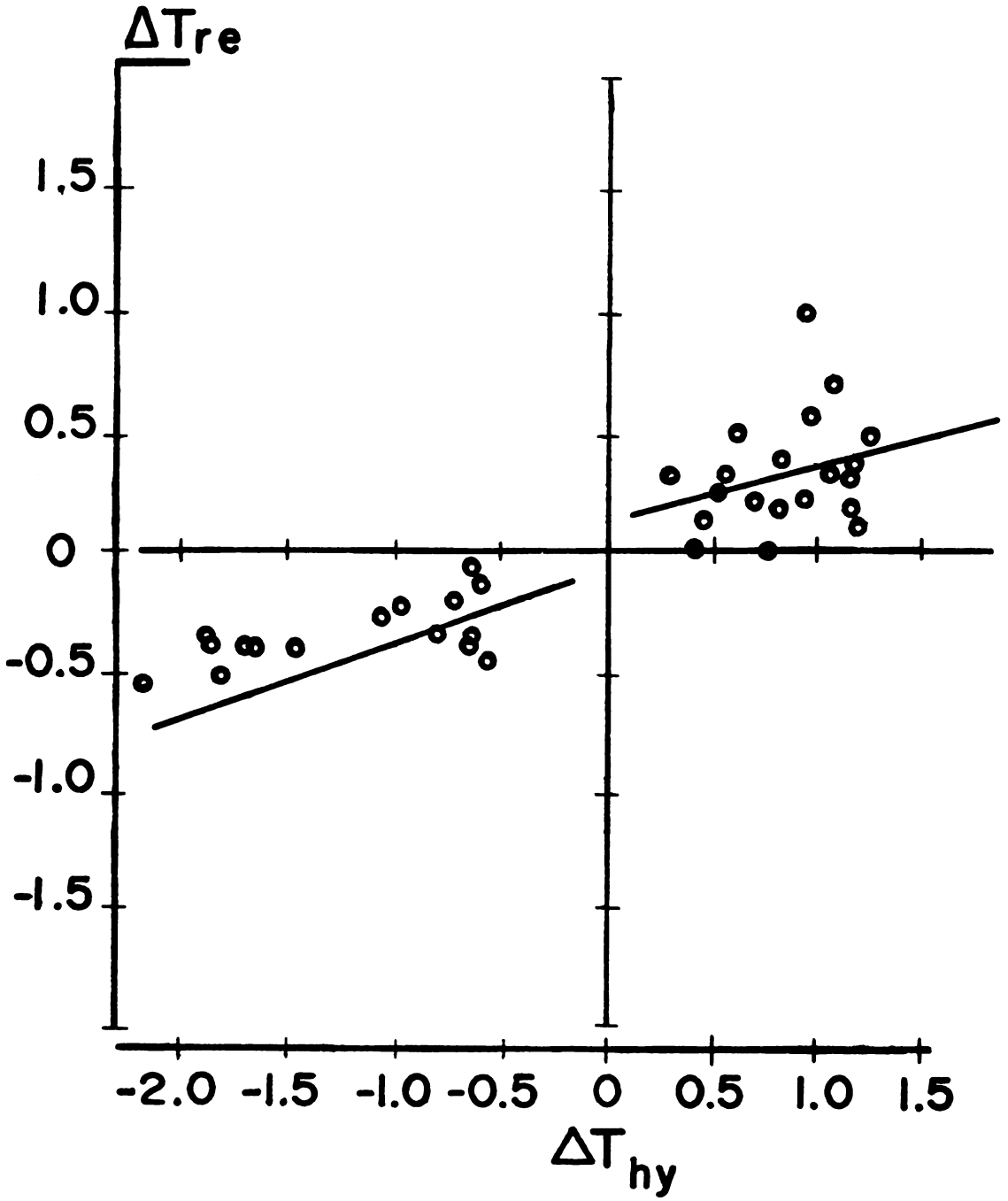


Figure 13. Change in rectal temperature as a function of change in hypothalamic temperature when T_a = 35°C.

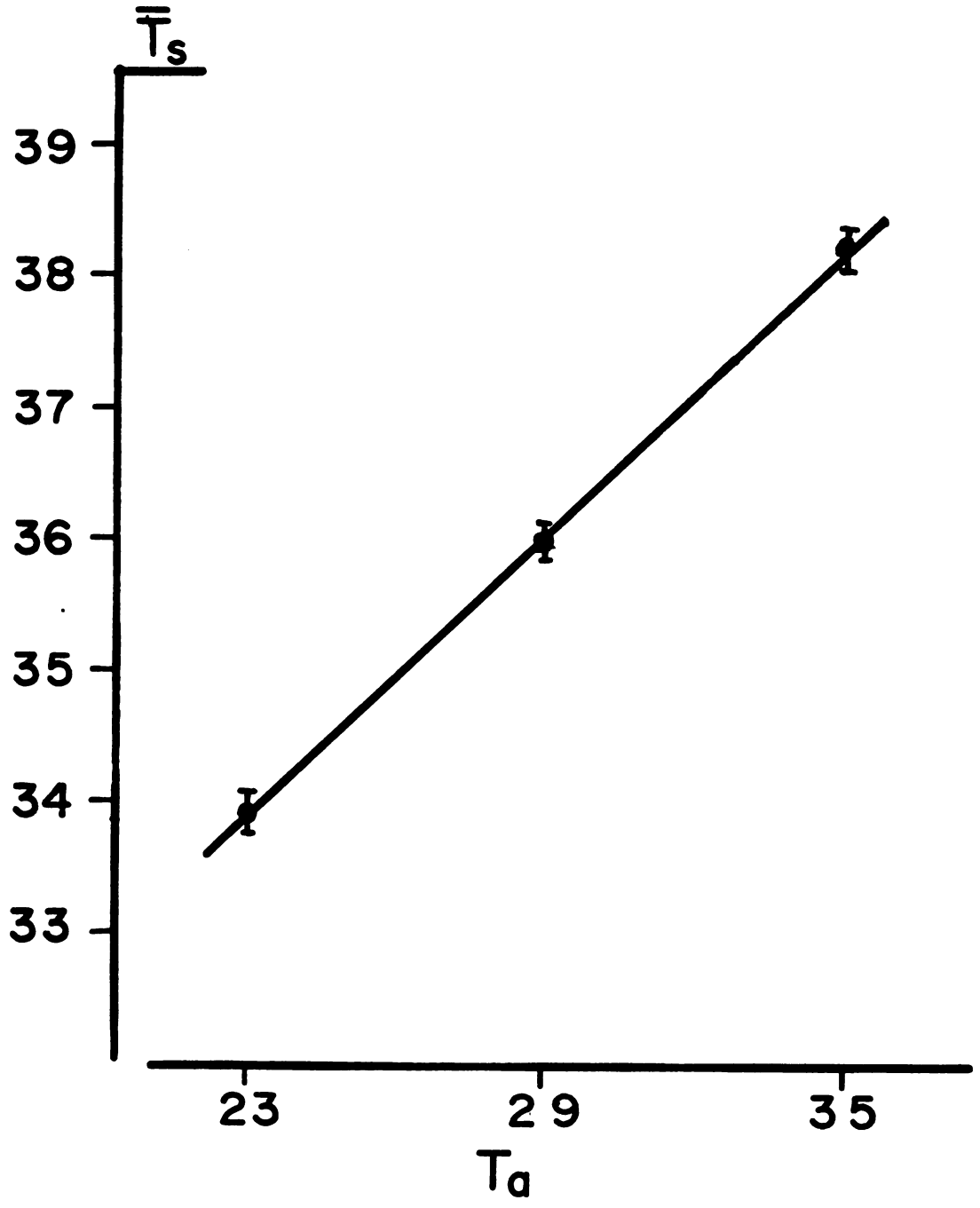


Figure 14. Average skin temperature as a function of ambient temperature. Vertical lines indicate SEM.

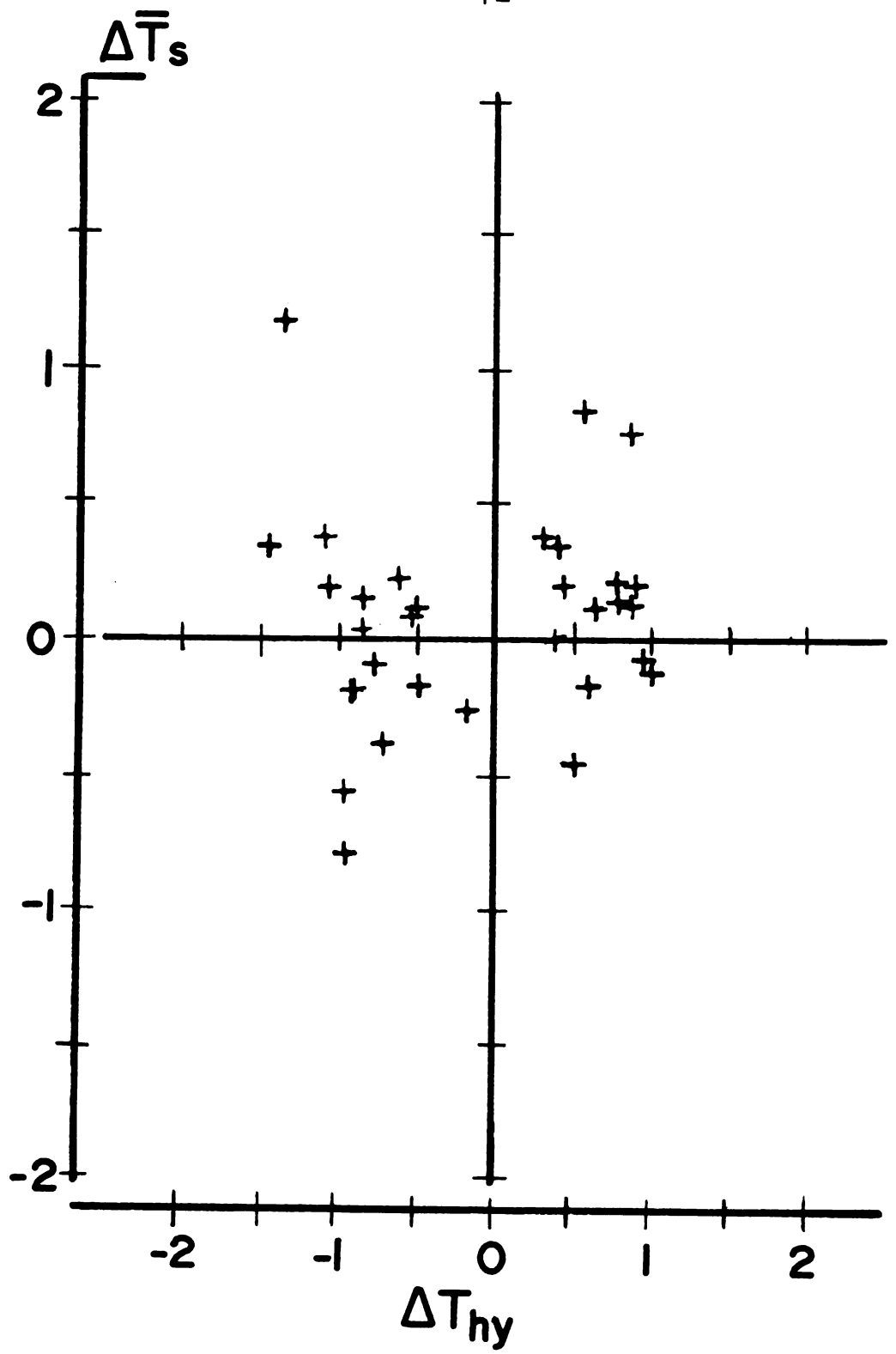


Figure 15. Change in average skin temperature as a function of change in hypothalamic temperature when T_a = 23°C.

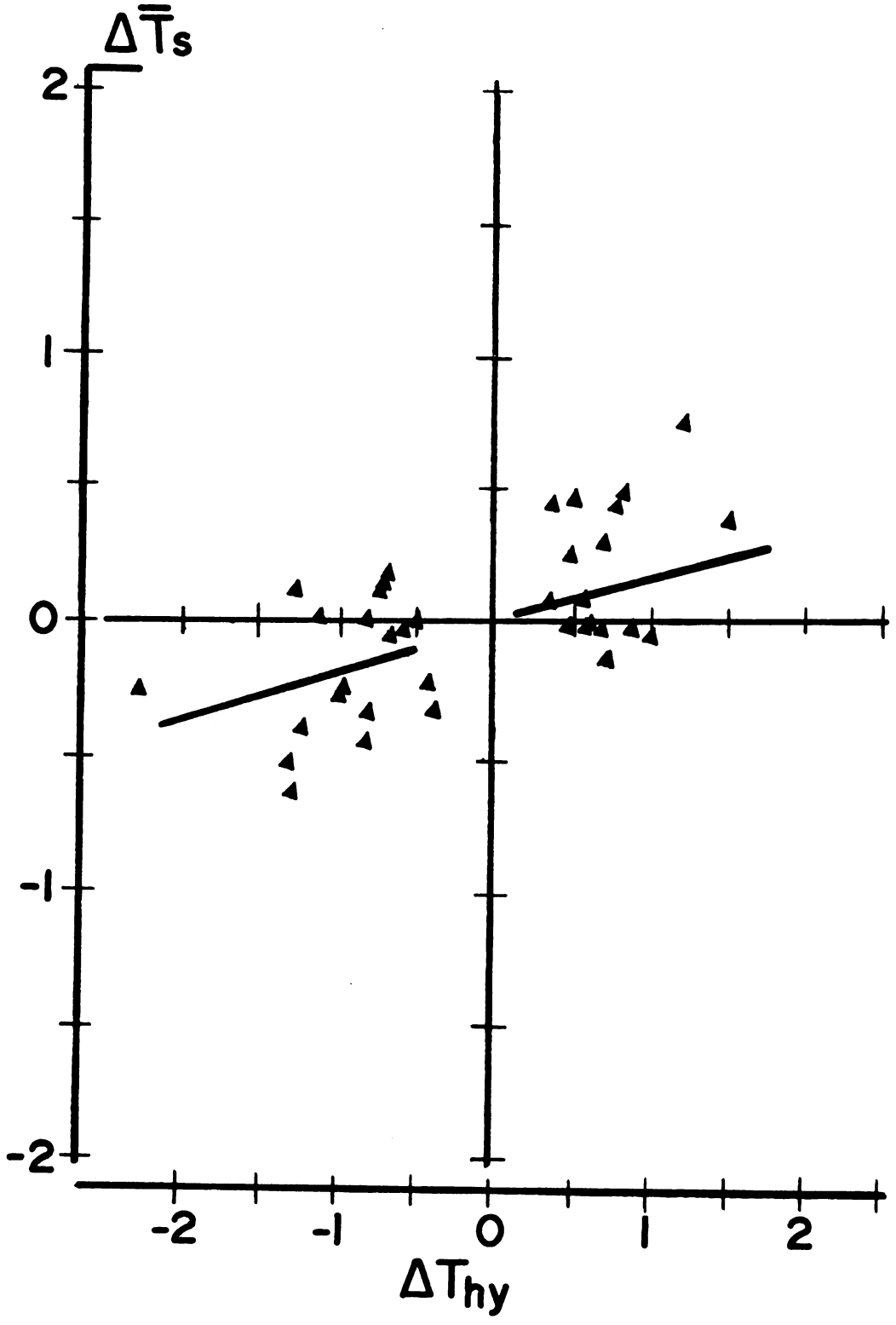


Figure 16. Change in average skin temperature as a function of change in hypothalamic temperature when T_a = 29°C.

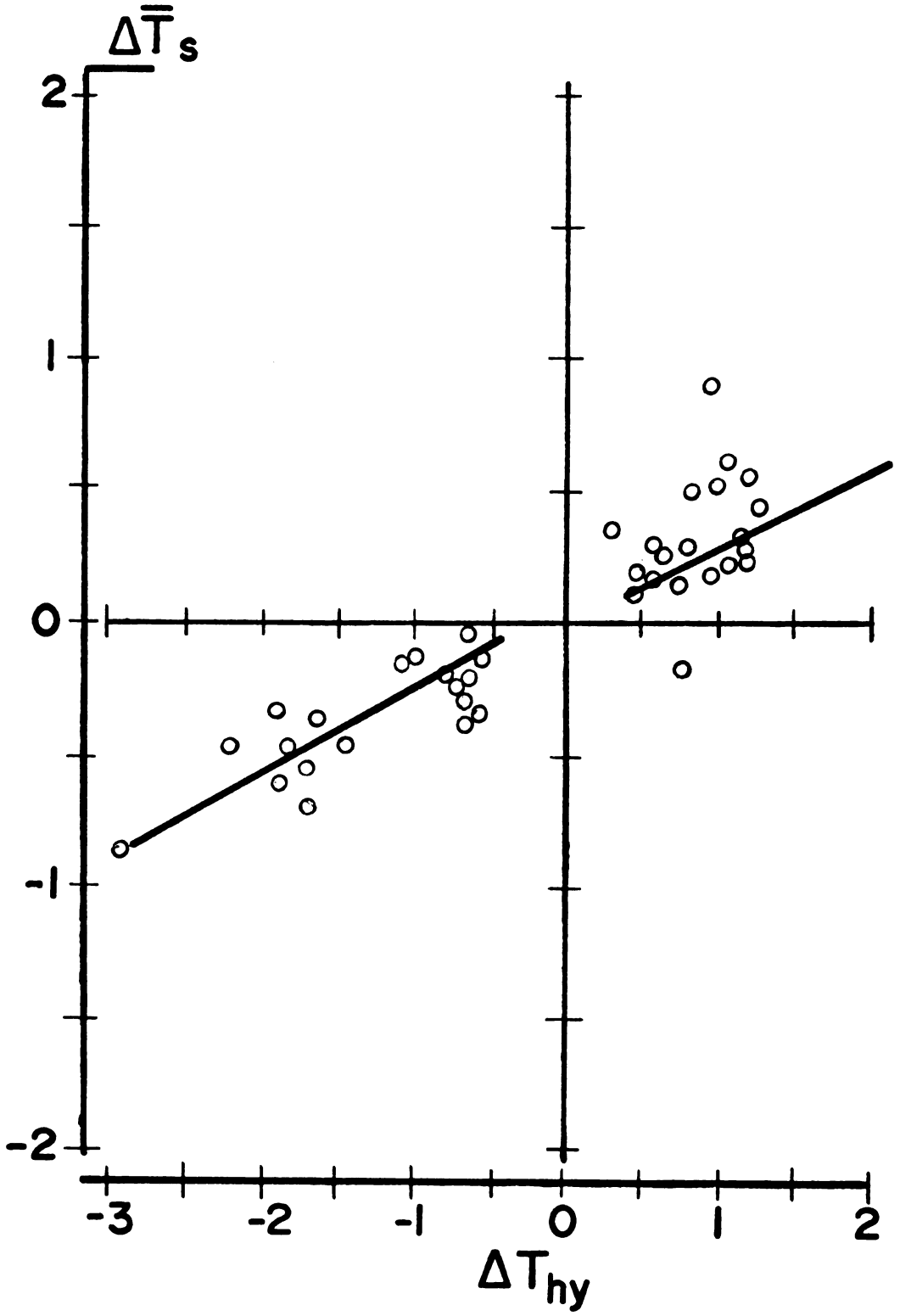
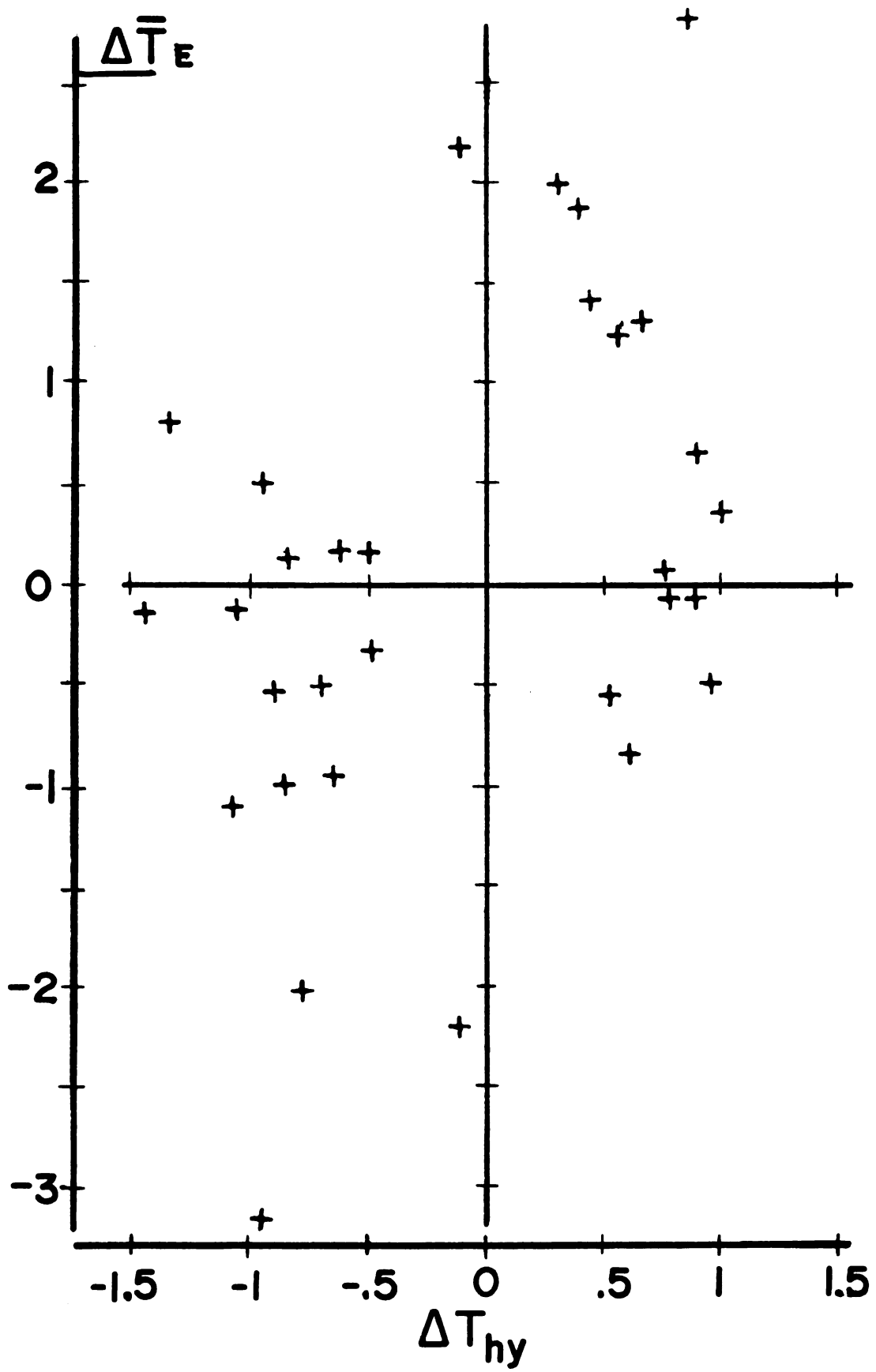


Figure 17. Change in average skin temperature as a function of change in hypothalamic temperature when T_a = 35°C.

Figure 18. Change in average extremity temperature as a function of change in hypothalamic temperature when T_a = 23°C.


$\Delta\bar{T}_E$
2
1
0
-1
-2
-3
-1.5
-1
-.5
0
.5
1
1.5
ΔT_{hy}

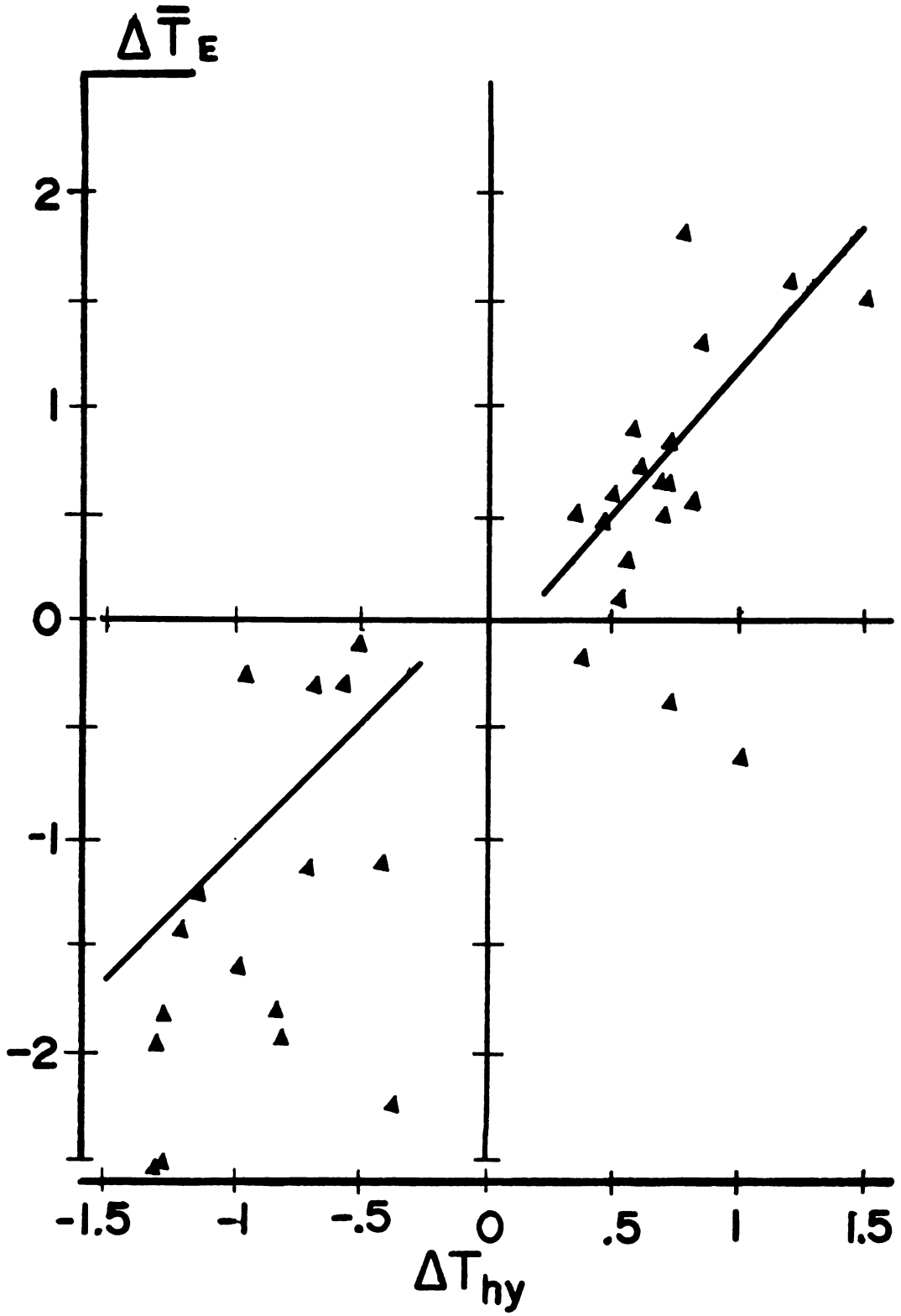


Figure 19. Change in average extremity temperature as a function of change in hypothalamic temperature when T_a = 29°C.

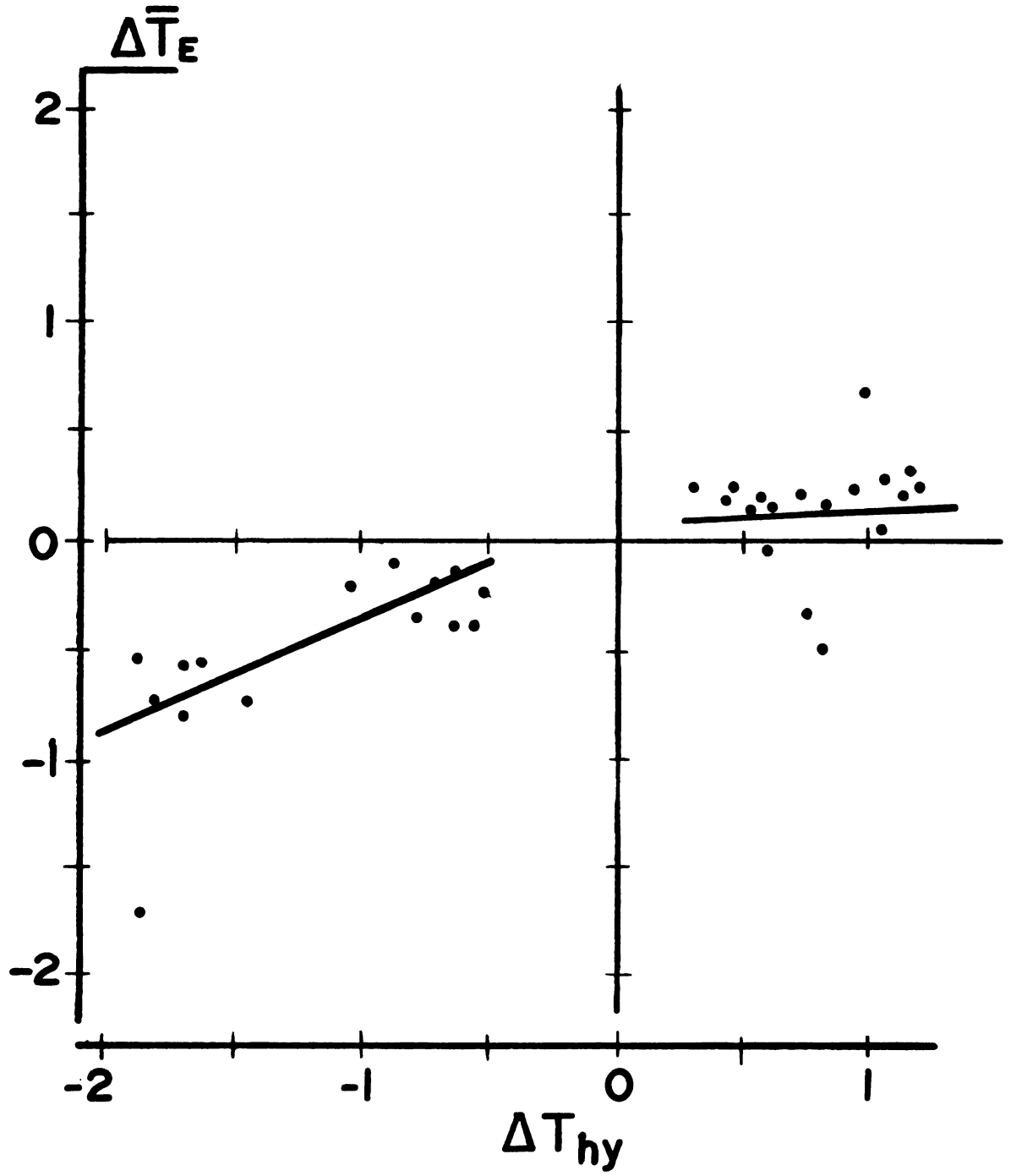


Figure 20. Change in average extremity temperature as a function of change in hypothalamic temperature when $T_a = 35^{\circ}C$.

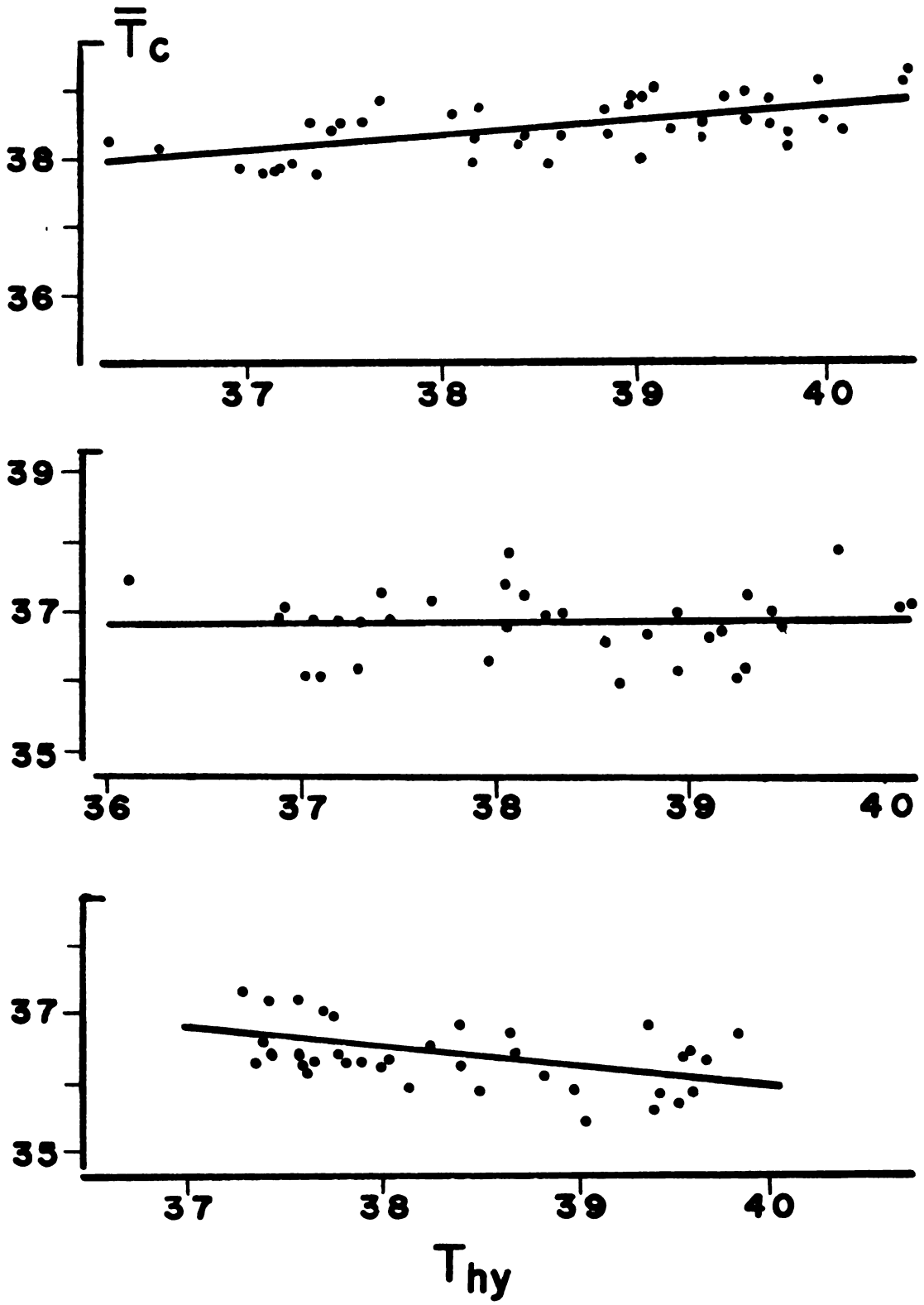


Figure 21. Average central skin temperature as a function of hypothalamic temperature at 3 different ambient temperatures; upper, T_a = 35°C; middle, T_a = 29°C; lower, T_a = 23°C.

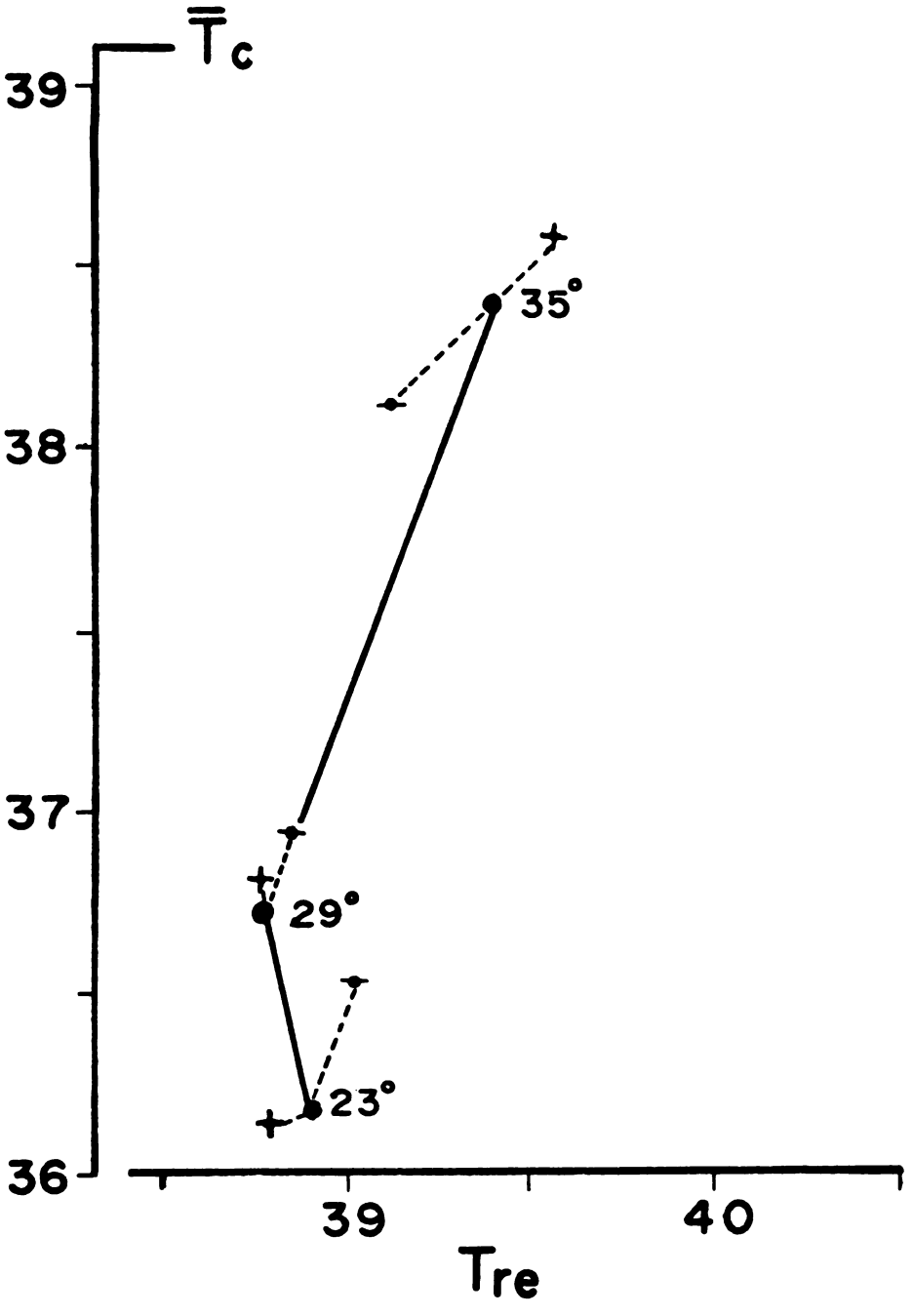


Figure 22. Average central skin temperature as a function of rectal temperature. Numbers beside points indicate T_a.
● = resting values; + = average values for hypothalamic heating; -●- = average values for hypothalamic cooling.

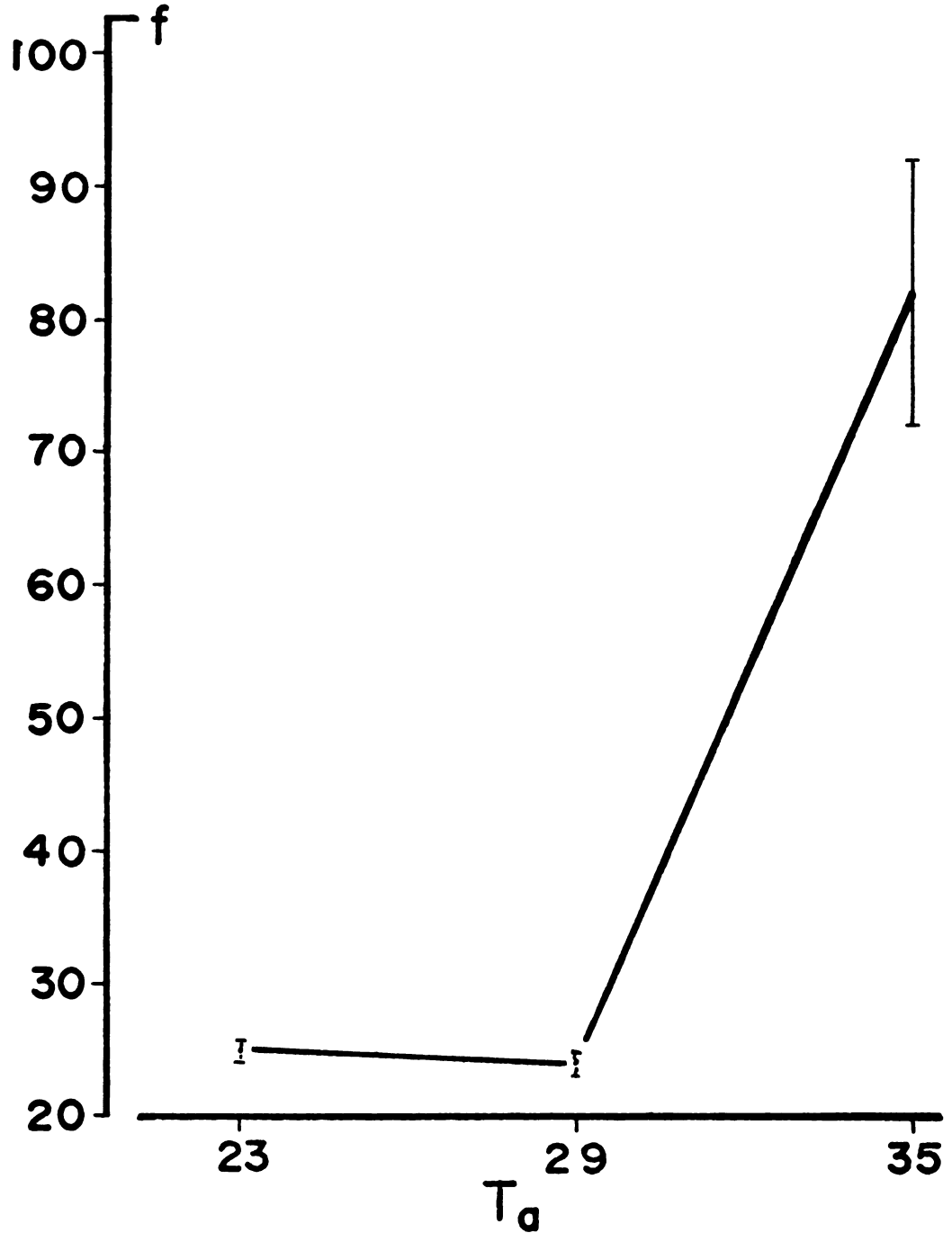


Figure 23. Respiratory frequency (resting) as a function of ambient temperature. Vertical lines indicate standard error of the mean (SEM) for f.

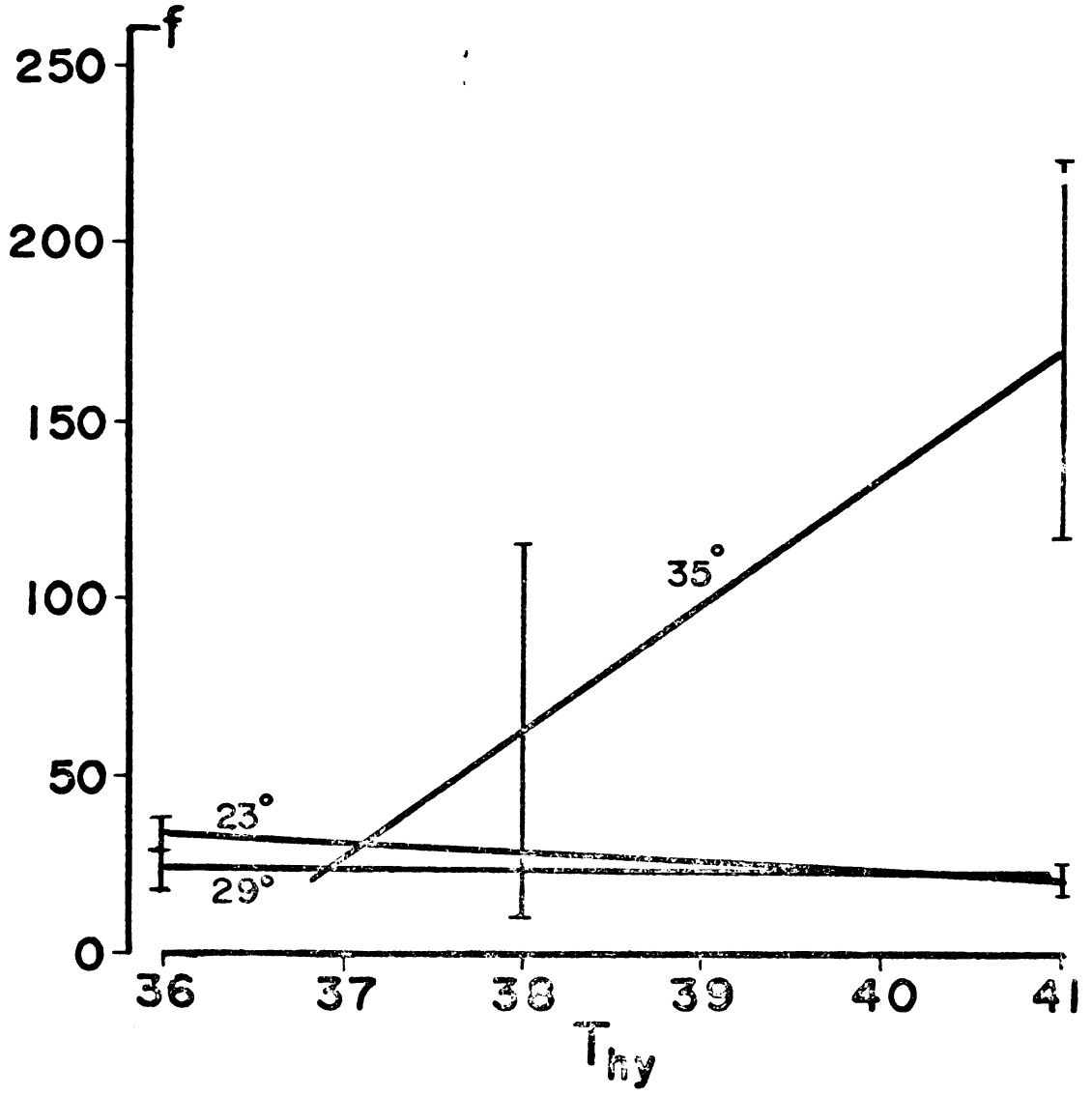


Figure 24. Respiratory frequency as a function of hypothalamic temperature. Curves were determined by linear regression of f on T_{hy}; vertical lines indicate SEM.

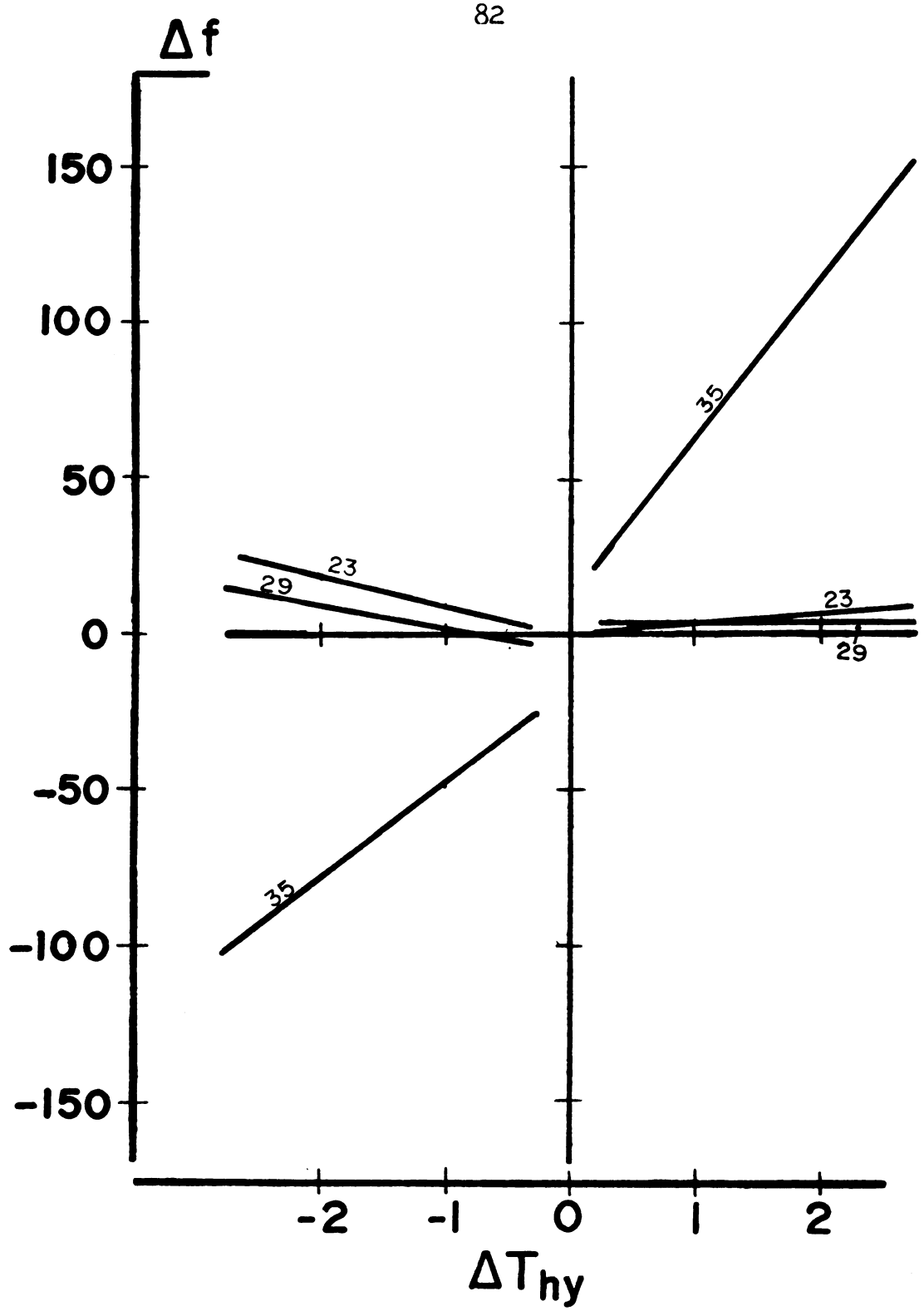


Figure 25. Regression lines for change in respiratory frequency (breaths/min) as a function of change in hypothalamic temperature when T_a's = 23, 29, and 35°C.

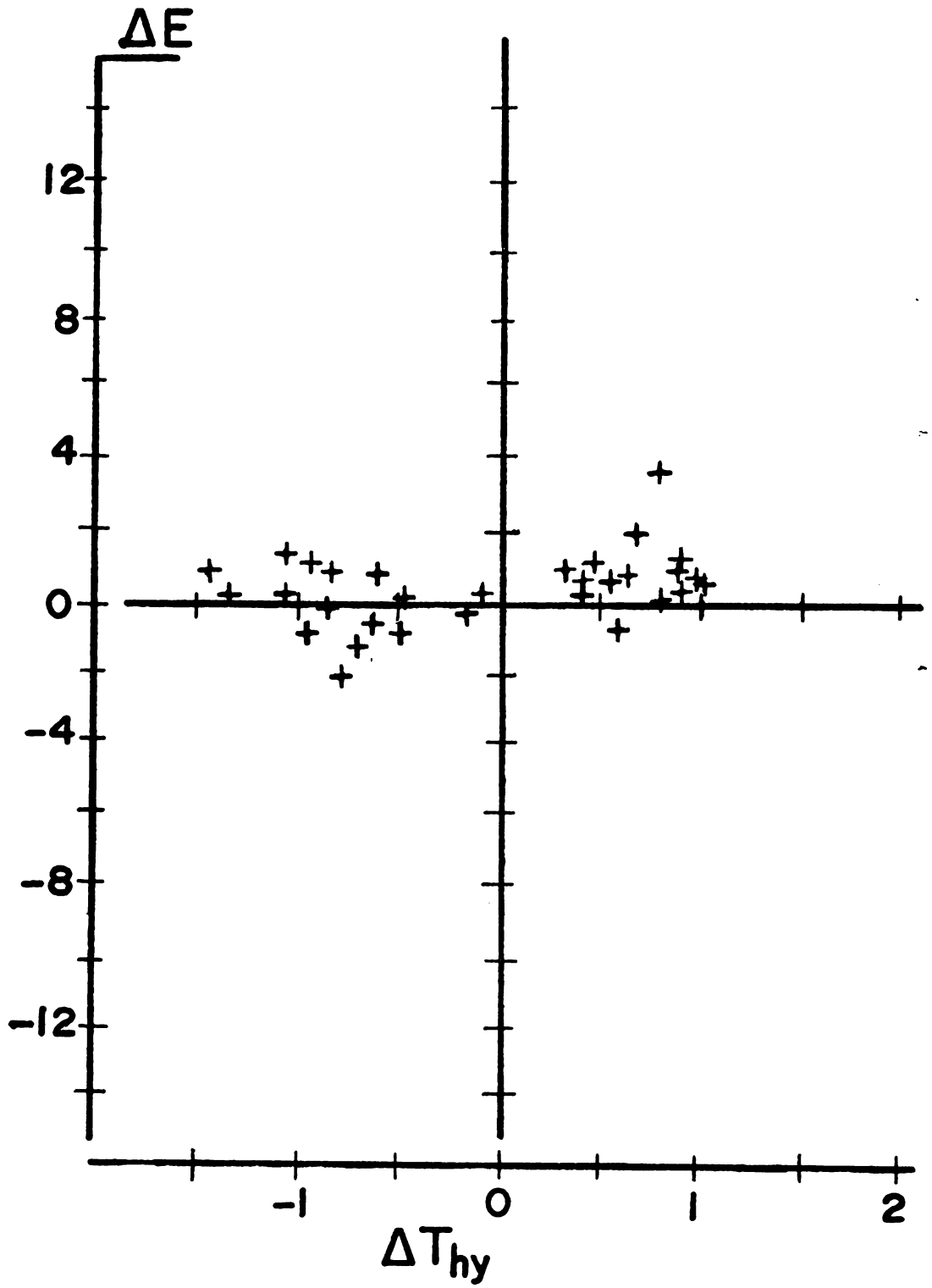


Figure 26. Change in respiratory evaporative heat loss (W/m^2) as a function of change in hypothalamic temperature when $T_a = 23^{\circ}C$.

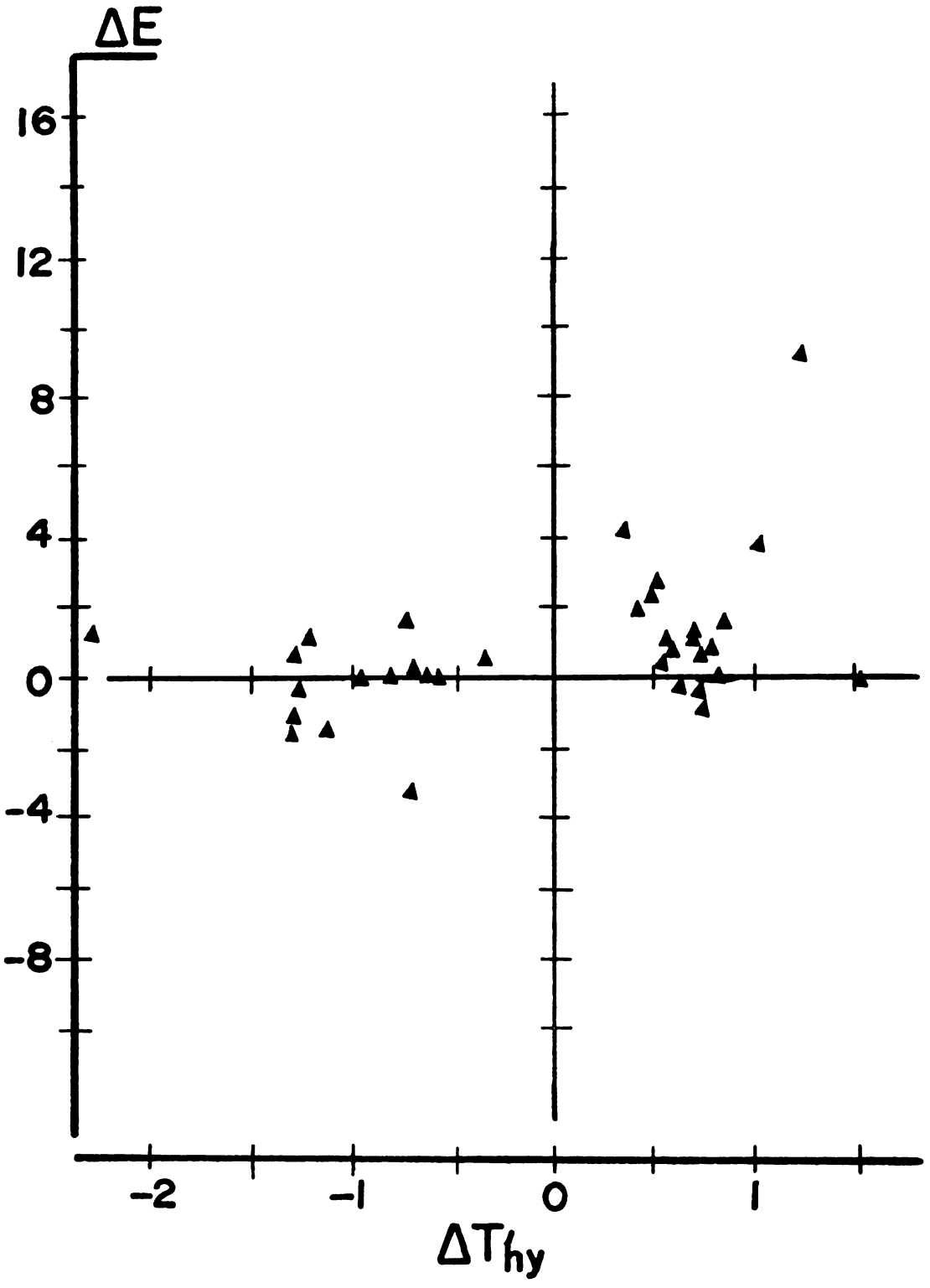


Figure 27. Change in respiratory evaporative heat loss (W/m^2) as a function of change in hypothalamic temperature when $T_a = 29^{\circ}C$.

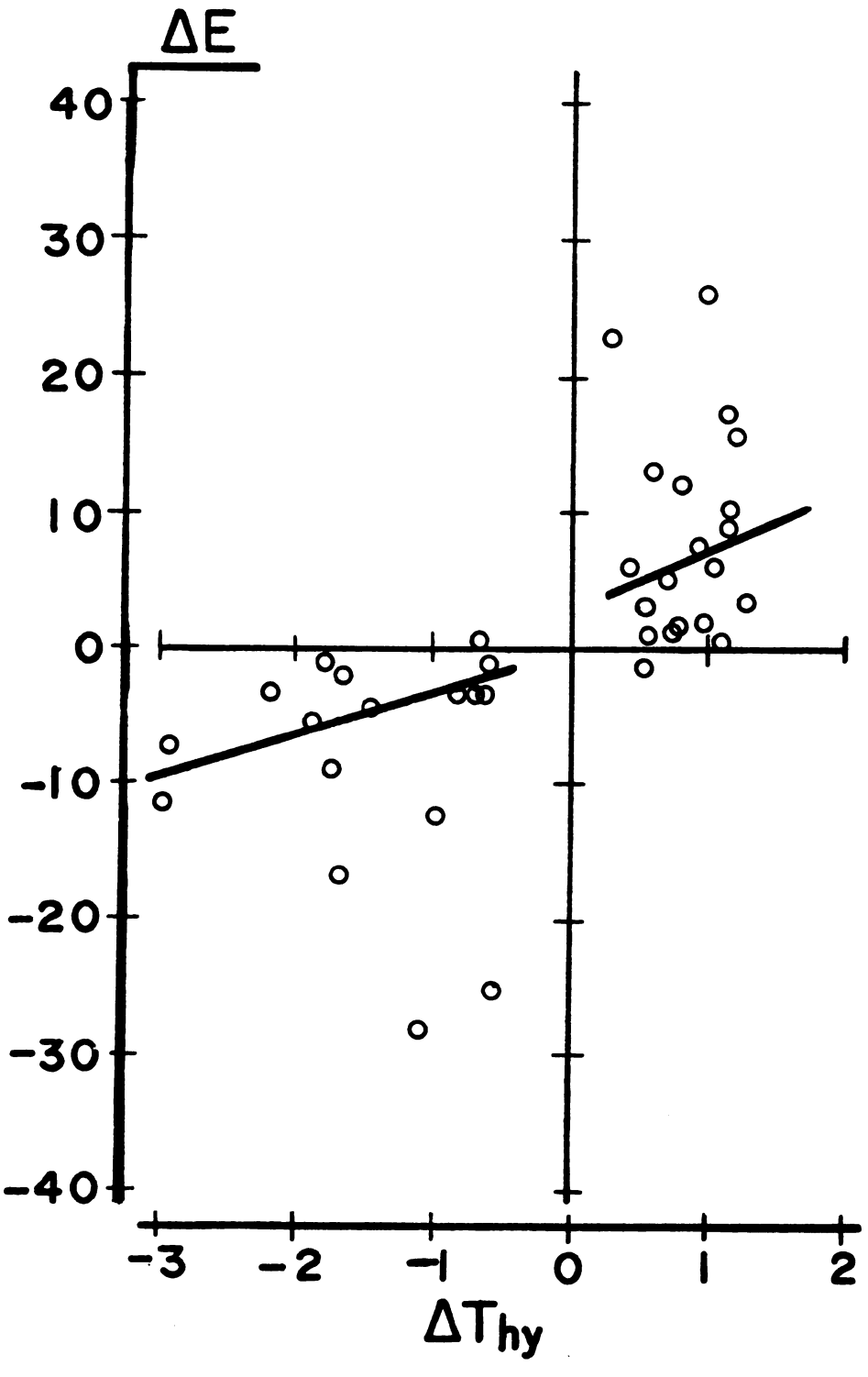


Figure 28. Change in evaporative heat loss (W/m^2) as a function of change in hypothalamic temperature when $T_a = 35^{\circ}C$.

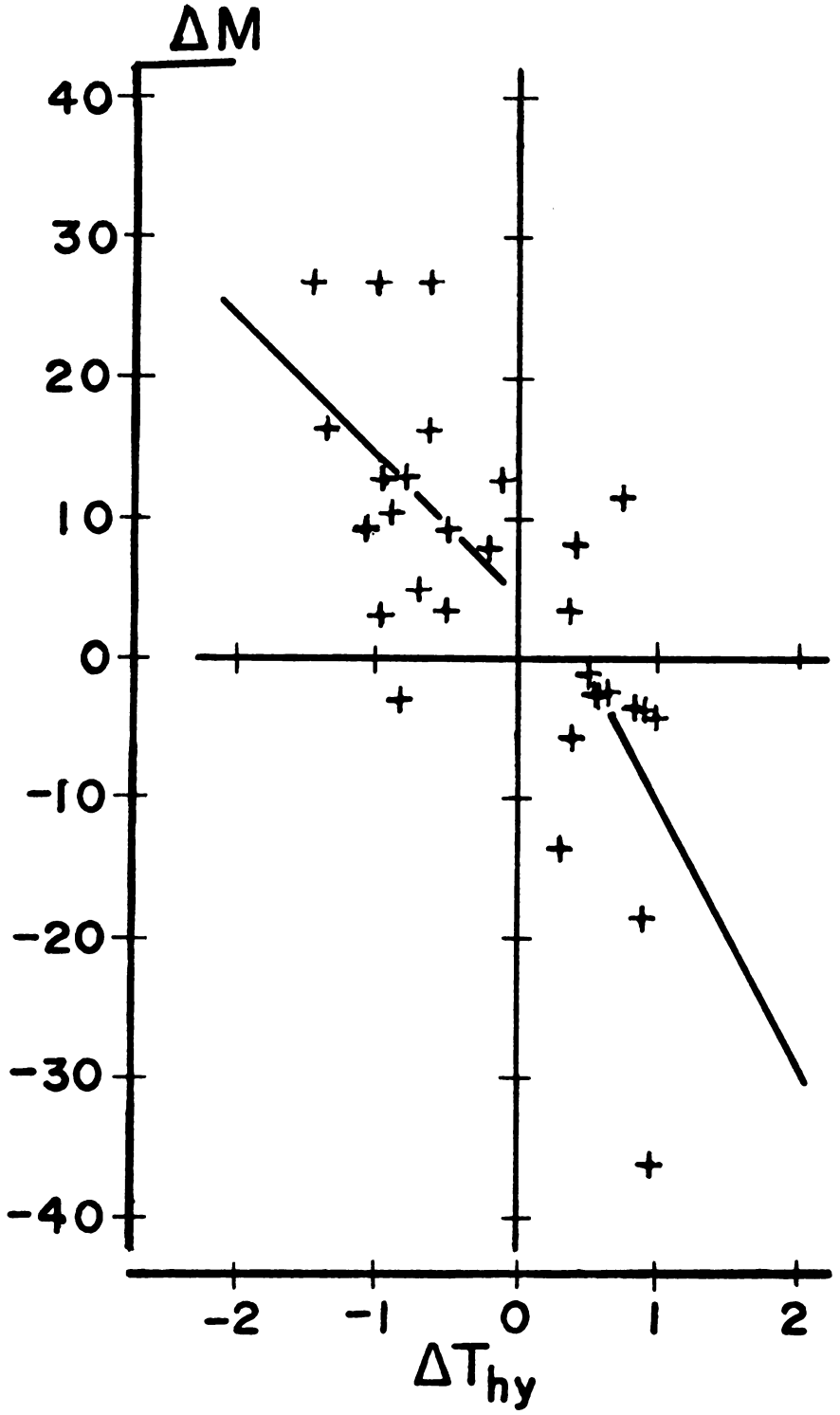


Figure 29. Change in metabolic heat production (W/m^2) as a function of change in hypothalamic temperature, when $T_a = 23^{\circ}C$.

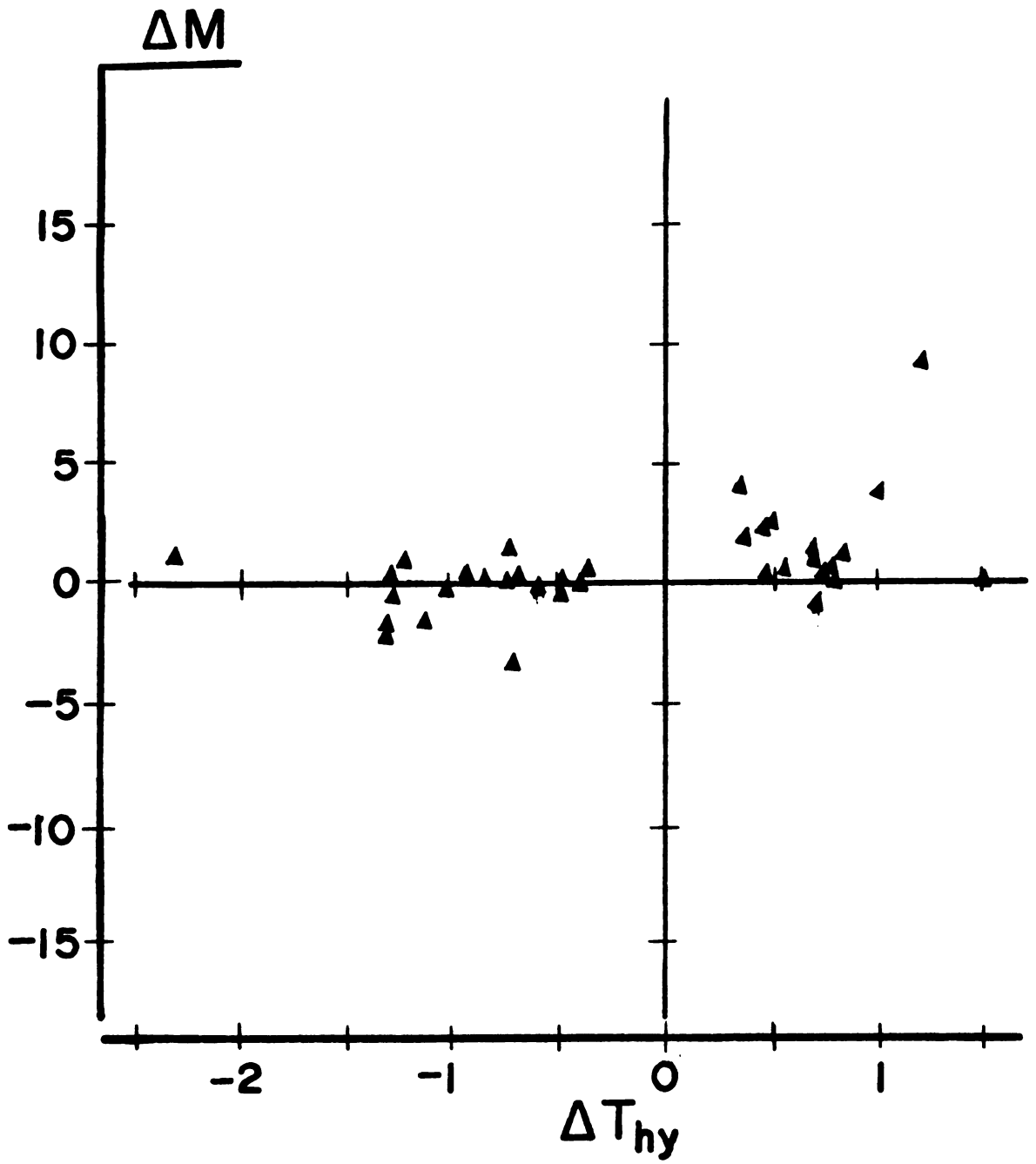


Figure 30. Change in metabolic heat production (W/m^2) as a function of change in hypothalamic temperature when $T_a = 29^oC$.

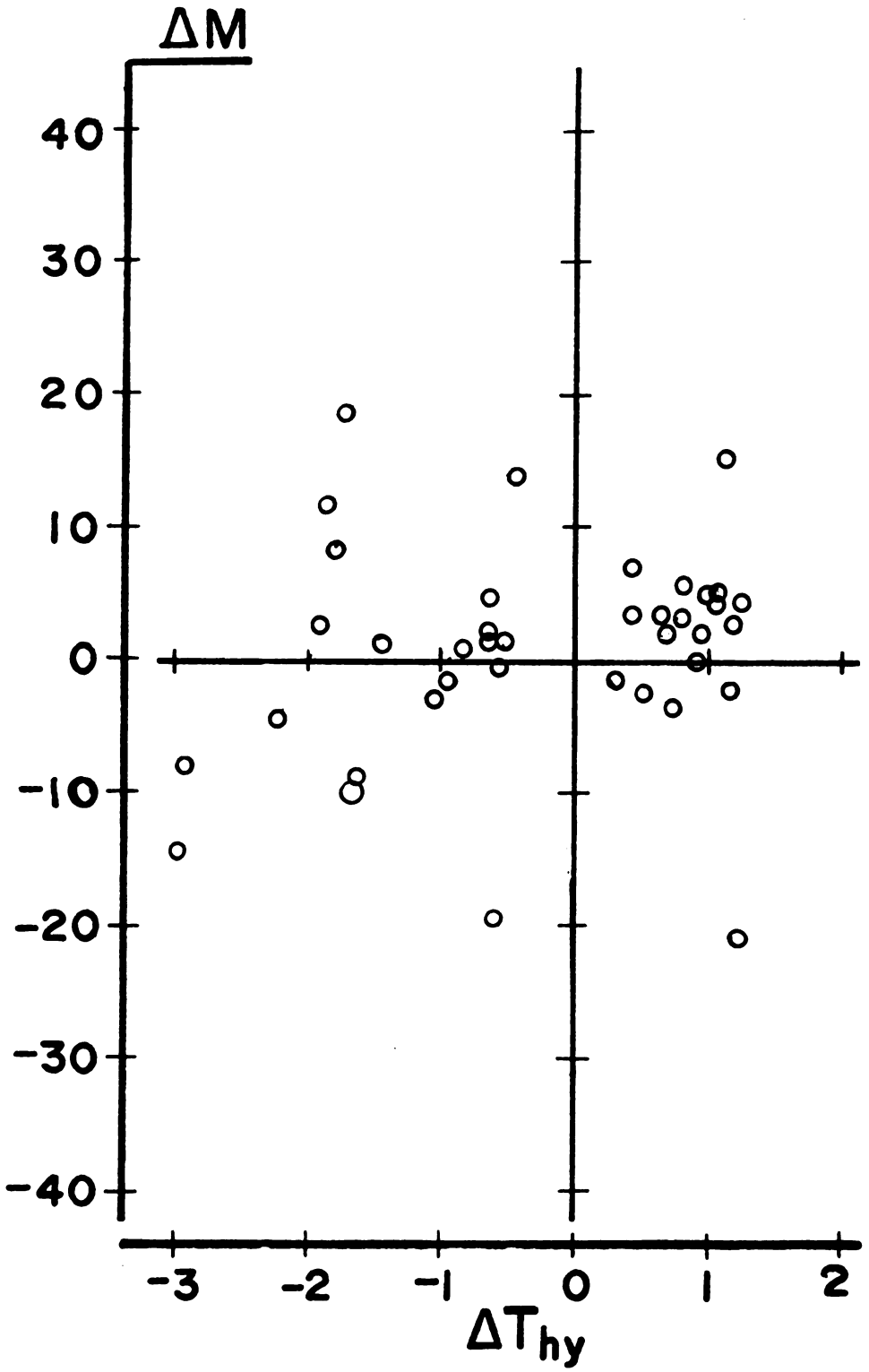


Figure 31. Change in metabolic heat production (W/m^2) as a function of hypothalamic temperature when T_a = 35°C.

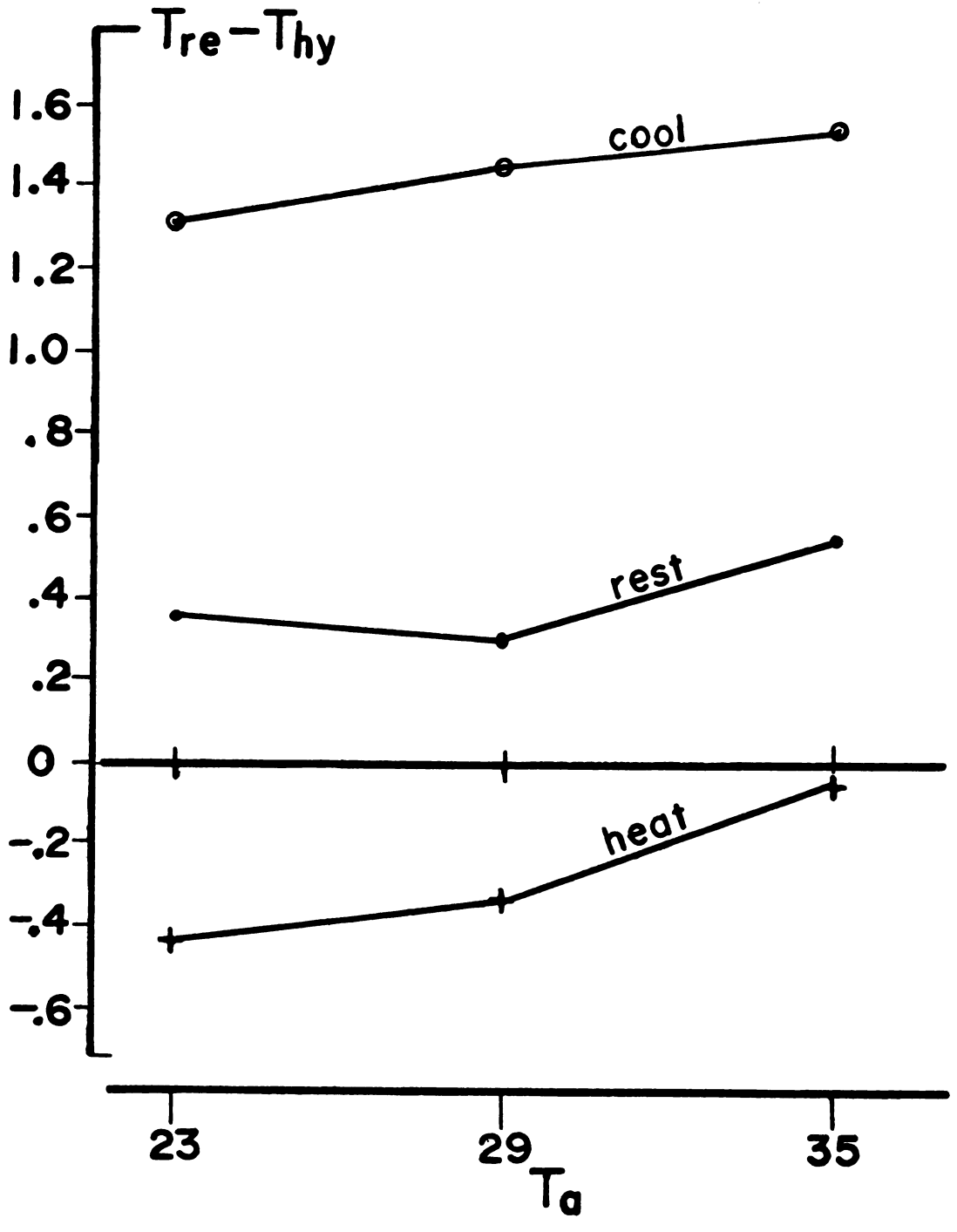


Figure 32. Rectal-hypothalamic temperature differences as a function of ambient temperature for grand means of all hypothalamic heating, cooling, and resting periods.

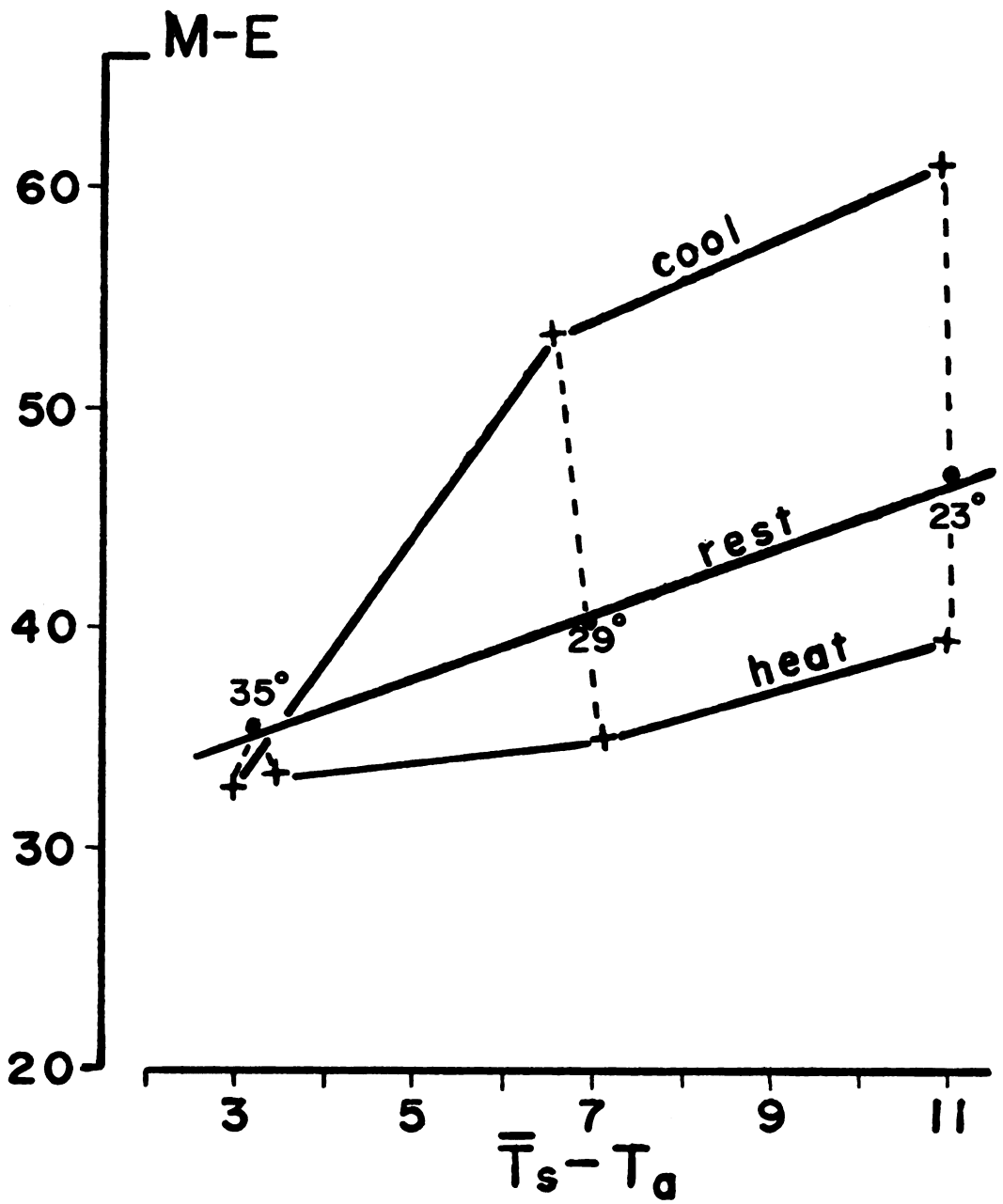


Figure 33. Difference between metabolic heat production and evaporative heat loss (W/m^2) as a function of difference between average skin temperature and ambient temperature (^oC) for grand means of M-E and $T_s - T_a$ during hypothalamic heating, cooling, and resting periods. Numbers next to points indicate ambient temperature.

TABLE 1. Resting values for measured and calculated parameters at Low, Thermoneutral, and High ambient temperatures.

	23°C			29°C			35°C		
	n	$\bar{X}$	SEM	n	$\bar{X}$	SEM	n	$\bar{X}$	SEM
T_{hy}	34	38.54	0.048	45	38.47	0.14	41	38.85	0.14
T_h	34	33.48	0.2789	45	34.75	0.1667	43	37.46	0.0894
T_e	34	24.31	0.3822	45	33.42	0.4269	43	38.13	0.0774
T_f	34	29.20	0.6713	45	34.73	0.2310	43	38.01	0.0678
T_{ch}	34	36.92	0.0812	45	37.43	0.0953	43	38.69	0.0741
T_{lhl}	34	25.95	0.4747	45	32.88	0.2202	43	37.64	0.0754
T_{uhl}	34	36.23	0.1726	45	36.87	0.1291	43	38.34	0.0685
T_t	34	25.16	0.3388	45	33.38	0.3762	43	37.80	0.1224
T_{re}	32	38.90	0.0600	38	38.65	0.1407	41	39.38	0.0728
f	32	24.65	0.72	37	23.67	0.76	40	82.02	10.05
T_s	32	33.79	0.14	37	35.94	0.10	40	38.28	0.14
T_E	32	26.25	0.4331	38	33.37	0.2647	41	37.84	0.0761
T_C	32	36.18	0.0793	38	36.62	0.1334	41	38.38	0.0655
M	31	50.71	2.5107	38	43.75	1.2966	41	41.96	2.8561
E	32	3.90	0.3697	37	3.59	0.2231	39	10.33	1.7519
M-E	31	46.70	2.4005	37	40.20	1.3659	35	35.39	3.2553
T_s-T_a	32	10.79	0.1349	38	6.86	0.1260	40	3.29	0.0624
T_{re}-T_{hy}	32	0.41	0.0670	37	0.41	0.0830	40	0.54	0.0685

VI. DISCUSSION

1. Thermode Function.

Isotherms presented in Figure 9 (upper) support earlier evidence (Serota and Gerard, 1932; Hunter and Adams, 1966) that for the anesthetized cat with deep body temperature maintained within normal limits, the warmest portion of the brain is located centrally. Progressively cooler temperatures were observed at sites nearer the dorsal, lateral and ventral brain surfaces.

Although the dense vascularity and high perfusion rate of brain tissue (Lierse and Horstman, 1965) provide a great degree of convective thermal exchange within the brain, thermal gradients resultant to convective, radiative, and evaporative heat exchange at oro-nasal and outer head surfaces persist. These gradients may produce differences of $1^{o}C$ or more between the brain surface and warmer central regions.

Data reported in Figure 9 (lower) indicate that thermal gradients within the brain can be substantially modified by the chronically implanted thermode designed for this study (see section IV. 2.1). These data also indicate that in contrast to temperature effects produced by a thermode chronically implanted within the brain tissue (Fusco, 1963;

Hammel et al., 1960; Forster and Ferguson, 1952; Adams, 1964), the thermal influence of a heat exchanger located extracranially in the sphenoid sinus involves the entire ventral diencephalon, not just tissue immediately surrounding the thermode. Since whole body thermal stress in the unanesthetized animal probably involves more than a punctate central temperature stimulus (Hunter and Adams, 1971) the present technique seems to be the best one currently available for the type of physiological testing undertaken for this study, namely, experimental alteration of brain temperature simulating the effects of thermal stress (both heat and cold) on brain tissues, but independent of thermal involvement with body regions such as skin or deep visceral regions. Data reported in Figure 9 indicate that small irregular variations in hypothalamic temperature were seen both at rest and during experimental change in brain temperature (Figure 10). This phenomenon in the cat has been reported previously by Forster and Ferguson (1952), and Adams (1963). In the present study, the amplitude of these variations appeared to increase as hypothalamic temperature levels warmer or cooler than at rest, were induced by the thermode. This increase could be due either to changes in intrathoracic pressure which are reflected in variations of venous return from the head, or to intracranial or extracranial vasomotor activity affecting brain blood flow. Since convective thermal exchange is probably the most important avenue for thermal exchange in the brain, variations

with relatively short time constants (i.e. fraction of a second to several minutes), would be due to differences in the temperature of incoming blood, and/or the rate of blood flow through the brain (assuming a temperature difference between the blood and the brain tissue). Baker and Hayward (1967) reported that the temperature of cerebral arterial blood of the cat can be altered by countercurrent heat exchange between blood in the carotid rete, and that returning from the oral and nasal mucosa. Blood flow in the basal portion of the brain overlying the thermode, could vary by either or both of these mechanisms. Temperature variations would increase with heat exchange between the thermode and basal cerebral arterial and venous blood.

1.1 Effects of the Thermode on Body Thermal Load.

Measurements in two animals (see Results, section 1.1) indicate that at high water flow rates through the thermode, body temperature (T_{re}) can be affected by heating or cooling the brain. The effect is graded as a function of ambient temperature (Figures 11-13). At $T_a = 23^{o}$, there was an inverse relationship between T_{re} and T_{hy} during hypothalamic heating and cooling, as reported earlier (Strom, 1950; Lim and Grodins, 1952; Freeman and Davis, 1959) (Figure 11). At $T_a = 29^{o}C$, T_{re} remained constant as T_{hy} varied (Figure 12), and at $T_a = 35^{o}C$ T_{re} varied directly with T_{hy} (Figure 13).

A possible explanation for the effect of the thermode on T_{re} can be suggested based on the demonstration (Baker

and Hayward, 1967) that vasomotor activity of the oral and nasal mucosa, and the warm (or cool) venous return from those areas can change brain temperature. Vasomotion of the mucosal vessels could be set by skin temperature or the direct effects of the temperature of inspired air on mucosal vessels. Because of oral and nasal mucosal venous flow into the cavernous sinus, the amount of heat delivered to (or removed from) the central body by the thermode might be expected to vary directly with mucosal vasomotor activity. At high $\bar{T}_s$'s (e.g. $T_a = 35^oC$), vasodilated mucosal vessels could increase the flow of blood, warmed or cooled by the thermode, back into the central body. At low T_a's (e.g. $T_a = 23^oC$), with mucosal, and cavernous sinus flow decreased, warmed or cooled blood returning to the central body would be reduced. When T_a was high and the thermode perfused with warm water, central body heat load could rise faster than it could be dissipated. With high T_a, and thermode cooling, central body temperature could decrease due to the direct effects of the thermode on whole body heat load in spite of the effect of its initiation of physiological heat conservation responses to cooling of the hypothalamus. Were T_a low, the mucosal and cavernous sinus flow would be decreased, thereby decreasing the effects of the thermode on whole body heat load, and allowing rectal temperature to be influenced more by physiological responses to thermode effects than by the direct physical effects of thermode heat loading. Data presented in Figures 11, 12, and 13 are consistent with this postulation.

2. Peripheral Vasomotion.

Data presented in Figures 15-17 indicate that $\bar{T}_s$ is influenced more strongly by changes in T_{hy} as T_a is set at progressively higher levels. Hammel (1965) suggested that input from peripheral sensors could act on hypothalamic neurons in such a manner that the neuronal activity normally expected at a given brain temperature would be modulated to provide a signal, initiating thermoregulatory responses. This would effectively change the set point for a given response or set of responses. The question of whether the concept of variable setpoint (or of setpoint in general) is well founded remains open; however, evidence in addition to that reported herein is accumulating, and tends to support the concept of reciprocal modulating effects between thermosensory inputs from the skin and hypothalamus. Hellon (1970), recording from thermally sensitive units in urethane anesthetized cats and rabbits, obtained evidence that the firing rate of temperature sensitive anterior hypothalamic neurons can be influenced by T_a. These findings are consistent with data presented in Figures 15-17, as are those of Wit and Wang (1968), who reported that some units in the hypothalamic region of cats are stimulated by rise in T_{hy}, while others are activated by afferent impulses from the skin.

It may be inferred that as the inhibitory influence of a low $\bar{T}_s$ ($\bar{T}_s \prec T_a$ for resting T_{hy}) is removed during whole

body response to warm T_a, T_{hy} is more influential as a drive for peripheral thermoregulatory vasomotor activity. Cold receptors from the skin may provide an inhibitory influence on central thermoregulatory drives to vasomotor activity.

2.1 Hypothalamic Influence on Extremity Vasomotion.

The action of peripheral thermal receptors on central thermoregulatory drives is further demonstrated in the relationship of $\bar{T}_E$ and T_{hy} as shown in Figures 11-13. Under steady state conditions, the relationship between T_{hy} and $\bar{T}_E$ is more predictable the higher the ambient temperature.

As shown in Figure 19, at $T_a = 29^oC$ for $-\Delta\bar{T}_E/-\Delta T_{hy}$, $b = 0.87$ as compared with $b = 0.38$ for $T_a = 35^oC$; the difference between the two slopes is significant statistically ($P<0.001$). If T_{hy} is increased at $T_a = 35^oC$, only a slight increase in b for regression of $\bar{T}_E$ on T_{hy} was found ($b = 0.07$; $P<0.001$ that $b = 0$). The lack of increase in $\bar{T}_E$ with T_{hy} was presumably due to the limited capacity for further peripheral vasodilation when $\bar{T}_s$ was high. At $T_a = 29^oC$, however, the slope for $\bar{T}_E$ as a function of T_{hy} is different from that at 35^oC ($b = 1.15$, $P<0.001$), indicating a peripheral vasomotor response to changes in T_{hy}, unaffected by skin thermosensory input. This effect was probably eliminated with skin temperature (set by $T_a = 29^oC$) at thermoneutrality.

The absence of a predictable relationship between T_{hy} and $\bar{T}_E$ when $T_a = 23^oC$ (Figure 18) can be explained in that

an inhibitory input from the skin at below-thermoneutral temperatures eliminates the hypothalamic influence on peripheral vasomotor activity. This allows vasomotor state of the extremities to vary more in response to nonthermoregulatory cardiovascular demands than would occur when central drives were facilitated by those from the periphery as influenced by a high T_a. Alternatively, the effects of conflicting sensory information could evoke nonthermoregulatory effects on vasomotor activity through the sympathetic system.

2.2 Central Skin Temperature.

$\bar{T}_c$ has a linear relationship with T_{re} for heating, cooling, and thermoneutral exposures. Similar results have been reported by Hammel et al. (1960) for the unanesthetized dog. When $T_a = 35^oC$ (Figure 22), $\bar{T}_c$ varied directly as T_{re}, and both T_{re} and $\bar{T}_c$ increased with T_{hy}; some of the implications of this relationship between T_{re} and T_{hy} were discussed in section VI, 1.1; others are discussed in section VI 5.

When $T_a = 29^oC$, $\bar{T}_c$ increased slightly with T_{re} (during hypothalamic cooling), but $\bar{T}_c$ as a function of T_{re} did not change in relation to resting values while the hypothalamus was being heated. This relationship is consistent with data presented in Figure 12, and that which was discussed in relation to the effects of the thermode on whole-body thermal loading (section VI, 1.1).

An opposite relationship to that reported for $T_a = 35^oC$ was observed when $T_a = 23^oC$. Although $\bar{T}_c$ changes with T_{re}, $\bar{T}_c$ and T_{re} are increased with hypothalamic cooling, and

decreased with hypothalamic heating.

3. Respiratory Responses.

Thermoregulatory respiratory responses appear as the limits of cardiovascular defenses to heat stress are reached. Peripheral vasomotor responses are most related to T_{hy} at $T_a = 29^{\circ}C$, and their limits of effectiveness are reached at $T_a = 35^{\circ}C$. These findings are in agreement with those of Adams et al. (1970). Respiratory frequency is essentially unaffected by experimental variation of T_{hy} when $T_a = 23$ or $29^{\circ}C$ (Figures 24 and 25).

Much emphasis has been put on the thermoregulatory involvement of respiratory rate in different species (Magoun et al. 1938; Andersson et al., 1956; Findlay and Hales, 1969; Hemingway and Hemingway, 1966), however, it is obvious that respiratory frequency per se provides only a rough index of the actual evaporative and convective thermal exchange between the respiratory surfaces and the environment. A much more reliable and quantitative index of respiratory thermoregulatory function is provided by measurement of respiratory evaporative heat loss (E), discussed in section VI, 3.1 below.

3.1 Evaporative Heat Loss.

Data presented in Table 1 indicate only a general relationship of increased E as a function of increased f. No clear relationship between E and f was evident, probably because of the unevaluated influence of tidal volume. The animal may use variations among respiratory frequency, tidal

volume and (possible) water availability at the respiratory surfaces to meet thermoregulatory demands for evaporative heat loss.

Data presented in Figures 26-28 indicate a relationship between T_{hy} and E which is similar to that for T_{hy} and f. However, E did not always vary (in the case of one cat) as a function of f. A general relationship between E and f is suggested in that both E and f exhibit a markedly stronger relationship to T_{hy} at $T_a = 35^{\circ}C$ than when $T_a = 23$ or $29^{\circ}C$ (Figures 24-28). The implication is that high $\bar{T}_s$ facilitates hypothalamic drives to increased E and f, and low $\bar{T}_s$ inhibits those drives.

3.2 Metabolic Heat Production.

M was inversely related to T_{hy} at $T_a = 23^{\circ}C$ (Figure 29), indicating that when $\bar{T}_s$ is low, (near or below shivering threshold) hypothalamic drives to increased M are facilitated. Conversely, at a higher $\bar{T}_s$ (when peripheral vasomotor activity or E is the primary thermal defense), the effects of hypothalamic drives (i.e. local cooling) for increased M are inhibited. These findings generally support those reported by Jackobson and Squires (1970).

4. Relationship Between Hypothalamic, Rectal, and Ambient Temperatures.

Resting hypothalamic temperature did not parallel T_a, but was minimal when $T_a = 29^{\circ}C$ (Figure 32) and increased when $T_a = 23$ and $35^{\circ}C$. This observation supports earlier

data (Adams et al., 1970) indicating that the cat controls internal temperature at different levels depending on T_a (Figure 32).

Data presented in Figure 32 indicate that $T_{re} - T_{hy}$ increases between $T_a = 29^{\circ}C$ and $T_a = 35^{\circ}C$. This increase may be attributed to the level at which the cat regulates internal body (rectal) temperature during heat stress. The increase in internal body temperature leads to an increased resting hypothalamic temperature (Figure 32). T_{hy} does not rise by the same amount as does T_{re} because the cat provides a degree of brain temperature control through heat exchange mechanisms involving the carotid rete (as discussed in section VI, 1.1). Further, the data in this study are consistent with data reported by Hunter and Adams (1966); describing the change in relationship of T_{hy}, and T_{re} after the onset and cessation of panting in cats exposed to whole body heating and cooling. Additional evidence that the brain of cats is normally cooled by the carotid arterial blood was supplied by Randall et al. (1963) who observed that bilateral carotid occlusion resulted in prompt elevation in both anterior and posterior hypothalamic temperature.

The type of control which allows central body temperature to increase more than brain temperature is not unique to the cat, and has been described for various other species possessing a carotid rete system (Daniel, et al. 1953; and Taylor, 1969).

Data for T_{re}-T_{hy} as a function of T_a during hypothalamic heating and cooling (Figure 32) indicate that thermode cooling forced T_{hy} even farther below T_{re} than at resting levels, and that thermode heating elevated T_{hy} to levels exceeding T_{re}, the inverse of the normal relationship between T_{hy} and T_{re}.

There is no evidence from the present study to indicate that there are drives to maintain a constant temperature difference between deep body regions and the brain, or that changes in T_{hy}, T_{re} difference *per se* triggers responses which act to regulate body temperature. However, there is evidence that sensory input from deep visceral regions can act to modify respiratory rate when T_a is high and constant, $\bar{T}_s$ is constant, and T_{hy} is constant. On two occasions each in two cats (4 kg male, and a 2.3 kg female), T_{re} rose as much as 1°C during periods of hypothalamic heating. During the following rest period (thermode off, T_a = 35°C) respiratory rate, E, extremity temperatures, and T_{hy} (after it has returned to a resting level lower than that induced by the thermode) remained constant, but T_{re} began to decline. As T_{re} declined reductions in f were also noted; T_E and T_{hy} remaining constant. Analogous observations have been reported by Hammel (1960) for a dog which had a below-normal T_{re} following hypothalamic heating while skin temperature was set by a neutral T_a. With no input from skin (since it was at a thermoneutral temperature) or hypothalamus,

the dog shivered, presumably because of thermal stimulus from visceral regions. Rawson and Quick (1970) have obtained strong evidence for thermoregulatory drives as a function of intraabdominal heating in the ewe.

5. Thermal Balance in Relation to Experimental Shifts of Hypothalamic Temperature.

The balance of C, M, R, and E for the cat is not influenced by a change in hypothalamic temperature when $\bar{T}_s$ is high (i.e. $T_a = 35^\circ$, Figure 33), but is when $\bar{T}_s$ is lower (i.e. when $T_a = 23$ or $29^\circ C$). M-E for hypothalamic heating and cooling indicates not only a modification of convective and radiative exchange due to peripheral vasomotor changes, but also a change in the relationship between M and E.

The different slopes for M-E as a function of $\bar{T}_s - T_a$ at 23 and $29^\circ C$ (Figure 33, dashed lines) are attributed to the effect of altered T_{hy} on $\bar{T}_s$, since T_a was held constant. Decreased T_{hy} reduces the difference between $\bar{T}_s$ and T_a when $T_a = 29^\circ C$, implying an influence of peripheral vasoconstriction; an increase in T_{hy} produces peripheral vasodilation as implied by an increase in the difference between $\bar{T}_s$ and T_a.

There are comparatively slight changes in $\bar{T}_s - T_a$ when T_{hy} is altered at $T_a = 23^\circ$, suggesting that reduced $\bar{T}_s$ produces inhibition of hypothalamic thermoregulatory drives to vasomotor activity.

Heating and cooling the hypothalamus also influenced the relationship between M and E, especially when $T_a = 23^\circ$ or $29^\circ C$. Cooling the hypothalamus at $T_a = 29^\circ$ and 23° results

in both increased M and decreased E, which appears in Figure 33 as an increase of M-E. Hypothalamic heating leads to decreased M and increased E at both T_a = 23 and 29°C which is represented in Figure 33 as a decrease of M-E.

The individual values of M and E (especially of E) vary as functions of T_{hy} when T_a = 35°C. The net effect of changes in T_{hy} produces little change in the value of M-E. Raising T_{hy} leads to slightly increased M (apparently due to the increased work of polypnea and panting) and an offsetting, or overriding, increase in E. Lowering T_{hy} results in decreased M paralleled by decreased E equal to, or slightly exceeding that of M.

VII. CONCLUSIONS

1. Hypothalamic heating or cooling did not affect the vasomotor state of the extremity (ears, feet, tail) or central (chest, upper hind legs) skin when $\bar{T}_s$ was low (T_a = 23°C); f and E were also unchanged, but M varied directly with T_{hy}. T_{re} varied inversely as T_{hy}.

2. When T_a (and consequently $\bar{T}_s$) was at thermoneutral level (29°C) hypothalamic heating and cooling produced peripheral vasodilation and constriction respectively, but f, E, M, and T_{re} were unchanged.

3. At high $\bar{T}_s$ levels (T_a = 35°C), hypothalamic heating produced little peripheral vasodilation in addition to the near maximal vasomotor state induced by high $\bar{T}_s$; hypothalamic cooling produced vasoconstriction in the extremities; f, E, and T_{re} varied directly as T_{hy}, while M was not affected by experimental alteration of T_{hy}.

4. The results of this study were interpreted as indicating that although both $\bar{T}_s$ and T_{hy} function as thermoregulatory control inputs, the influence of each is modulated by the other to a degree dependent upon the thermal environmental conditions.

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APPENDICES

APPENDIX A

FREQUENTLY USED SYMBOLS

T_a	Ambient Temperature
$\bar{T}_s$	Average Skin Temperature
$\bar{T}_E$	Average Extremity Skin Temperature
$\bar{T}_c$	Average Central Skin Temperature
T_h	Head Skin Temperature
T_e	Ear Temperature
T_f	Front Foot Temperature
T_{ch}	Chest Temperature
T_{lhl}	Lower Hind Leg Temperature
T_{uhl}	Upper Hind Leg Temperature
T_t	Tail Temperature
T_{re}	Rectal Temperature
M	Metabolic Heat Production
E	Respiratory Evaporative Heat Loss
T_{hy}	Hypothalamic Temperature
SEM	Standard Error of the Mean
W	Watts
m^2	Square Meter

APPENDIX B

PROPORTIONING FACTORS FOR AVERAGING SKIN TEMPERATURES

Skin Site	Weight* Range	Factor $\bar{T}_s$	Factor $\bar{T}_E$
ear	a	0.31	0.127
	b	0.34	0.128
Front foot	a	0.60	0.247
	b	0.66	0.250
lower hind leg	a	0.103	0.424
	b	0.113	0.428
tail	a	0.049	0.282
	b	0.051	0.194
			Factor $\bar{T}_c$
head	a	0.122	0.161
	b	0.110	0.150
chest	a	0.431	0.569
	b	0.405	0.550
upper hind leg	a	0.204	0.269
	b	0.221	0.300

* a = Body weight range 3501-6000 gm

b = Body weight range 2501-3500 gm

APPENDIX C

STATISTICAL FORMULAE

Grand mean, $\bar{\bar{x}} = \frac{\Sigma \bar{x}}{n}$

Where: $\Sigma \bar{x}$ = sum of individual means

n = number in sample

Standard error of mean (SEM)

$$SEM = \sqrt{\frac{\Sigma \bar{x}^2 - (\Sigma \bar{x})^2}{n(n-1)}}$$

Continuous Simple Linear Regression

(Program code #2.19 from: Statistical Analysis Manual for Olivetti Underwood Programma 101 Computer p.68)

Slope of Regression Line, $b = \frac{T}{\Delta}$ = regression coefficient

Where: $T = N\Sigma XY - \Sigma X \Sigma Y$

$\Delta = N\Sigma X^2 - (\Sigma X)^2$

Intercept of Regression Line of Y Axis,

$$a = \frac{\Sigma Y - b\Sigma X}{N}$$

Standard Error of Estimate (biased)

$$Sy.x = \frac{\sqrt{\Delta 1 - T^2/\Delta}}{N}$$

Test for Significance of Regression Coefficient, b. (Probability that slope is not different from zero)

Standard Error of the Regression Coefficient

$$S_b = \sqrt{\frac{s^2 y.x}{\Sigma x^2}}$$

Testing Significance of the Regression Coefficient

$$t_s = \frac{(b-0)}{S_b}$$

Where: t_s = critical value for Students t-distribution, and degrees of freedom = n-2.

P = probability that the slope b is not different from 0

APPENDIX D

REGRESSION STATISTICS AND EQUATION*

T_a	x	y	a	b	Sy·x	P <
35	ΔT_{hy}	ΔT_{re}	0.14	0.22	0.22	0.001
	$-\Delta T_{hy}$	$-\Delta T_{tr}$	0.06	0.36	0.29	0.001
29	ΔT_{hy}	ΔT_{s}	0.02	0.27	0.22	0.001
	$-\Delta T_{hy}$	$-\Delta T_{s}$	-0.06	0.16	0.22	0.001
35	ΔT_{hy}	ΔT_{s}	0.56	0.28	0.20	0.001
	$-\Delta T_{hy}$	$-\Delta T_{s}$	0.08	0.38	0.20	0.001
29	ΔT_{hy}	ΔT_{E}	-0.07	1.15	0.23	0.001
	$-\Delta T_{hy}$	$-\Delta T_{E}$	-0.62	-0.87	0.57	0.001
35	ΔT_{hy}	ΔT_{E}	0.15	0.10	0.19	0.05
	$-\Delta T_{hy}$	$-\Delta T_{E}$	-0.02	0.40	0.30	0.001
23	T_{hy}	T_{c}	45.73	-0.24	0.42	
29	T_{hy}	T_{c}	36.50	0.01	0.47	
35	T_{hy}	T_{c}	28.91	0.24	0.33	
23	T_{hy}	f	123.46	-2.54	3.56	
29	T_{hy}	f	35.64	-0.29	6.01	
35	T_{hy}	f	1305.56	35.99	63.90	
23	ΔT_{hy}	Δf	1.05	-2.28	2.56	0.02
	$-\Delta T_{hy}$	$-\Delta f$	-3.21	-5.27	2.07	0.001
29	ΔT_{hy}	Δf	1.32	-0.08	4.71	0.4
	$-\Delta T_{hy}$	$-\Delta f$	-5.90	-6.56	3.83	0.001
35	ΔT_{hy}	Δf	9.10	53.17	46.07	0.001
	$-\Delta T_{hy}$	$-\Delta f$	-17.33	31.23	38.86	0.001
23	ΔT_{hy}	$-\Delta M$	6.92	-18.23	10.50	0.001
	$-\Delta T_{hy}$	ΔM	3.60	-10.26	7.71	0.001

*$y = a + bx$

APPENDIX E

```
PROGRAM    BEAST   FORTRAN EXTENDED VERSION 2.0  (210) 4/27/71
      PROGRAM BEAST(INPUT,OUTPUT,TAPE60=INPUT,TAPE61=OUTPUT
      DIMENSION TBAR(12),T(6),CALC(17),CON(16,2),NAME(5,17)
      WRITE(61,827)
827   FORMAT(*9*)
       READ(60,800)((CON(I,J),I=1,16),J=1,2)
      READ(60,805)NAME
      READ(60,801)NDC
      DO 1 M1=1,NDC
      READ(60,802)ARNR,IDATE1,IDATE2,IDATE3,PB,TA,SA,WC,V,TV,NR
      WRITE(61,823)((CON(I,J),I=1,16),J=1,2)
      WRITE(61,826)
      WRITE(61,822)ANRN,PB,TA,SA,WC,V,TV,NR,IDATE1,IDATE2,IDATE3
      DO 2 M2=1,NR
      WRITE(61,825)
      DO 3 M3 =1,12
      NCC=M3
      READ(60,803)ANRN,NC,T
      IF(NCC,NE,NC)NCC=NC
      N=0
      TBAR(NCC)=0.
      DO 4 M4=1,6
      IF(TM4),NE.0.0)N=N+1
   4  TBAR(NCC)=TBAR(NCC)+T(M4)
      TBAR(NCC)=TBAR(NCC)/N
   3  WRITE(61,824)NCC,TBAR(NCC),(T(IHG),IHG=1,N)
      L=1
      IF(SA,GT,,2591)L=2
C     AVERAGE SKIN TEMPERATURE
      CALC(1)=TBAR(2)*CON(2,L)+TBAR(3)*CON(3,L)+TBAR(5)*CON(4
             ,L)+TBAR
     1(6)*CON(5,L)+TBAR(7)*CON(6,L)+TBAR(1)*CON(7,L)+TBAR(4)
             *CON(8,L)
C     AVERAGE EXTREMITY TEMPERATURE
      CALC(2)=TBAR(2)*CON(9,L)+TBAR(3)*CON(10,L)+TBAR(5)*
             CON(11,L)+TBAR
     2(7)*CON(12,L)
C     AVERAGE CENTRAL SKIN TEMPERATURE
      CALC(3) =TBAR(1)=CON(13,L)+TBAR(4)*CON(14,L)+TBAR(6)
             *CON(15,L)
```

```
C       HEAT PRODUCTION
        CALC(4)=(CON(1,L)*TBAR(11)*(PB/(273.0+TV)))/SA
C       EVAPORATIVE HEAT
        CALC(5)=(CON(16,L)*TBAR(12)*WC*V)/SA
        R=CALC(4)-CALC(5)
        G=CALC(1)-TA
C       INSULATION OF EXTREMITIES
        CALC(6)=((TBAR(8)-CALC(2))*G)/((CALC(2)-TA)*R)
C       INSULATION OF CENTRAL SKIN
        CALC(7)=((TBAR(8)-CALC(3))*G/((CALC(3)-TA)*R)
C       INSULATION OF TOTAL SKIN
        CALC(8)=(TBAR(8)-CALC(1))/R
C       EAR INSULATION
        CALC(9)=((TBAR(8)-TBAR(2))*G)/((TBAR(2)-TA)*R)
C       FOOT INSULATION
        CALC(10)=((TBAR(8)-TBAR(3))*G)/((TBAR(3)-TA)*R)
C       UPPER HIND LEG INSULATION
        CALC(11)=((TBAR(8)-TBAR(6))*G)/((TBAR(6)-TA)*R)
```

APPENDIX F

SAMPLE THERMISTOR PROBE CALIBRATION