NEURONES AND TEMPERATURE REGULATION

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FOREWORD

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This technical report has been reviewed and is approved.

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ABSTRACT

An attempt has been made to ascribe the regulation of body temperature in homeotherms to the hypothalamus and the preoptic region. Results of measurements of hypothalamic temperature and regulatory responses in the normal dog in hot, neutral and cold environments and, at various times, in the resting, waking, sleeping, exercising and fevered state, are interpreted on the assumption that the hypothalamus responds to changes in its own temperature like a proportional controller with an adjustable set point. For each thermal regulatory response, the response was as if its magnitude were proportional to the deviation of the actual hypothalamic temperature from a set point temperature, and as if the set point temperature were to increase in the cold environment, decrease in the hot environment, decrease at the onset of sleep, decrease at the onset of exercise and increase in fever. A model based on known characteristics of neurones is proposed which appears to function like a proportional controller with an adjustable set point.

INTRODUCTION

Without the central nervous system, (CNS), regulation of body temperature is no more than an equilibrium between heat loss and heat production where heat production is some basal metabolic state. Under this condition the body temperatures passively adjust such that the core to skin surface temperature difference times the body tissue conductance, and the skin surface to ambient temperature difference times the cooling coefficient become equal to heat production. A thermal stress imposed upon such a system passively affects the body temperatures and indirectly, through the activation energy of chemical reactions, alters the heat production so that a new equilibrium occurs at a new level of body temperatures and heat production.

In normal homeothermic mammals, the CNS intervenes by way of its thermal sensing elements, afferent pathways, integrative components and effector pathways to activate responses which modify rates of heat production and heat loss such that the core temperature does not vary beyond narrow limits when thermal stress is imposed upon the system. Many of the relationships between thermal regulatory responses and body temperatures for many species are well known and have been reviewed from time to time throughout the history of Physiology; recent reviews are those of: (Bazett, 1949; Hensel, 1952; von Euler, 1961; Hardy, 1961; and Andersson, Gale & Sundsten, 1963). Without exception, each reviewer has recognized the sensing, integrative and effector roles of the CNS, and using the information available has constructed a highly simplified "black box" model, identifying inputs, outputs, and feedback loops, as well as important anatomical sites represented by the "black box" components.

Almost without exception, no one has dared to detail the properties and interconnections between neurones required to achieve the known characteristics of the black box and for a very good reason, namely, that little is known about the neurones in those parts of the CNS known to be essential for the accomplishment of temperature regulation. Consequently, it is not difficult to construct models unhampered by facts about how neurones act and interact upon each other to yield regulation. Such models can give the impression that they accomplish the job at hand and account for the known relationships between thermoregulatory responses and body temperatures and other inputs. After we have reviewed the phenomenon of temperature regulation as we understand it, we, too, will suggest a working model composed of neurones which we think could accomplish the job.

THE CLOSED LOOP SYSTEM

We shall attempt an analysis of temperature regulation on the assumption that the system behaves like a closed loop control system involving negative feedback as an essential feature. Thus the basic black box representation of temperature regulation can be diagrammed as in Figure 1.

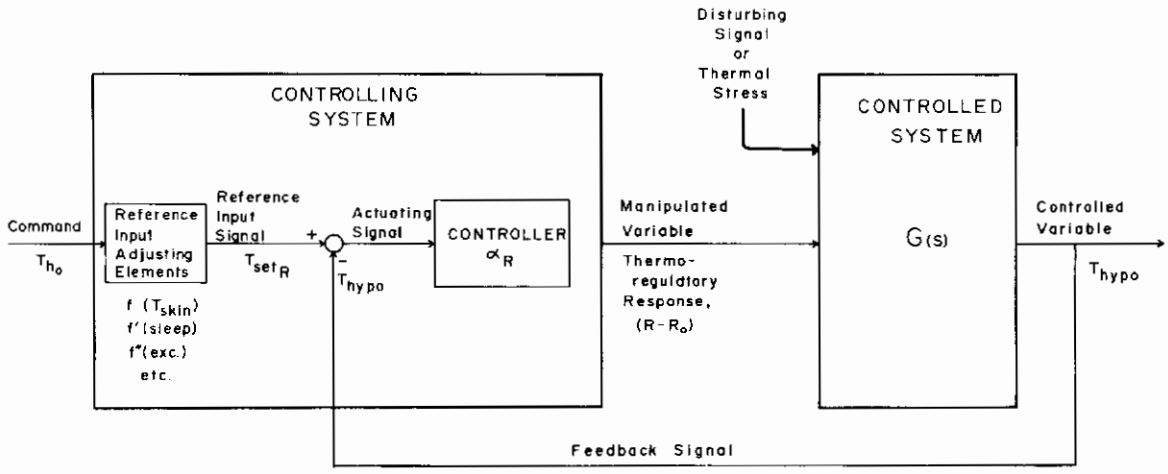

Figure 1. Block diagram for regulation of hypothalamic temperature.

We shall assume that the controlling system originates within the hypothalamus and in the preoptic region between the optic chiasm and the anterior commissure, and extends by way of the CNS to thermal

effector organs within the body. The output of the controlled system is assumed to be the temperature of the body as it is represented by the temperature of the hypothalamus, T_{hypo}. The control system serves to keep the output signal T_{hypo} equal to or at least close to the reference input signal, T_{set_R}, at all times in the face of varying environmental disturbances, changing properties of the controlled system, other inputs, etc. Since the transfer function G(s) for the controlled system is defined by the laws of heat transfer from within the body to its surface and from the surface to the environment, and does not directly involve the CNS, no further attention will be given to it. The controlling system, on the other hand, depends upon the CNS in an essential way, i.e., without the CNS there could be no controlling system.

There is abundant evidence in any current review of temperature regulation (Andersson, et al., 1963; von Euler, 1961; & Hardy, 1961) that the preoptic region of unanesthetized mammals responds to local heating by inducing panting and vasodilatation, and to local cooling by evoking shivering and vasoconstriction. Electrical stimulation and ablations in and around the hypothalamus leave no doubt that this region is involved in and, in fact, is essential for the regulation of body temperature.

Figure 2 is, in a sense, a summary of the evidence that the rostral hypothalamus is sensitive and responsive to small displacements of its own temperature.

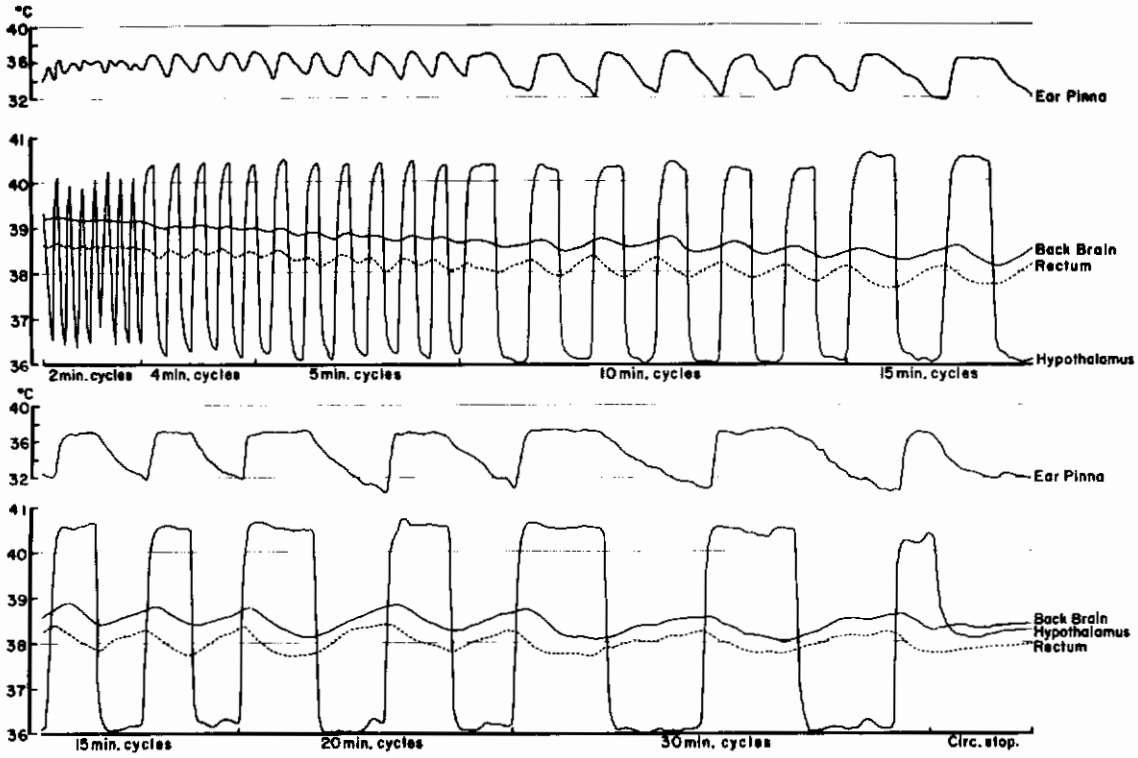

Figure 2. Cyclic heating and cooling of hypothalamus with water perfusing thermodes at alternately 41.0°C and 35.0°C. Ambient temperature = 25°C. 30 min. cycle = 15 min. heating and 15 min. cooling. Hammel, Strømme & Cornew (1963).

The widely swinging temperature (from 36.0 to 40.5°C) in this record is that of a thermocouple in the middle of the anterior hypothalamus while the hypothalamus is alternately heated and cooled at several frequencies. The low amplitude traces in the middle of the widely swinging trace are those of the cerebellar ("back brain" in Figure 1) and rectal temperatures swinging in consonance with the hypothalamic temperature. Above these

temperature traces is the trace of the ear pinna temperature of the dog in an ambient temperature of 25°C. When the hypothalamus was alternately cooled and heated, the blood vessels of the ear pinna were alternately constricted and dilated resulting in an alternately falling and elevated ear pinna temperature. Likewise, the rectal and cerebellar temperatures were alternately rising and falling at the same rate and by about the same magnitude while the hypothalamic temperature was displaced below and above its unperturbed level by equal amounts.

We conclude from this that the anterior hypothalamus is responsive to both heating and cooling and with equal sensitivity to moderate heating and cooling.

THE LAW OF THE CONTROLLING SYSTEM

An important next step in elucidating the nature of the system is to obtain the so-called "law of the controlling system," that is, the relationships between the inputs and the outputs of the controlling system.

We shall assume that the law of the controlling system is an equation* of the form

$$R - R_o = \alpha_R (T_{hypo} - T_{set_R}) \qquad R - R_o \geq 0$$

where $R - R_o$ is the thermoregulatory response (metabolism, vasomotor activity, sweating, panting, etc.),

R_o is the basal level when $T_{hypo} = T_{set_R}$,

T_{hypo}, the actual hypothalamic temperature, is the feedback signal,

T_{set_R}, the functional** set temperature for response R, which is the reference input signal,

$(T_{hypo} - T_{set_R})$ is the actuating signal, and

α_R is the proportionality constant for the response $(R - R_o)$.

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* Ed. Note: Observe that R and R_o are quantitatively undefined except in the very general sense of having the dimension of heat flow, cal/hr.

** Ed. Note: The word functional is apparently intended to convey the meaning "effective in determining the level of function at the selected time."

Although the evidence is scanty, it is adequate for proposal of this law as a working hypothesis. It says that a given thermoregulatory response is proportional to an actuating signal which is the difference between the actual hypothalamic temperature and some functional set temperature for that response. It should be recognized at once that the properties of the system, a_R and T_{set_R}, may be different for each type of thermoregulatory response R.

Change of the Set Point versus Change of Hypothalamic Temperature.

This hypothesis suggests that if we could design an experiment whereby we could maintain the functional set temperature unchanged while displacing the hypothalamic temperature over a range of values, the response, say shivering, would occur as follows: $(M - M_o)$, the increase in metabolic rate above the basal level, would be zero for hypothalamic temperatures above T_{set_M}, while for T_{hypo} below T_{set_M} it would increase in proportion to the difference between the two temperatures. The results obtained from one attempt to perform this ideal experiment are shown in Figure 3.

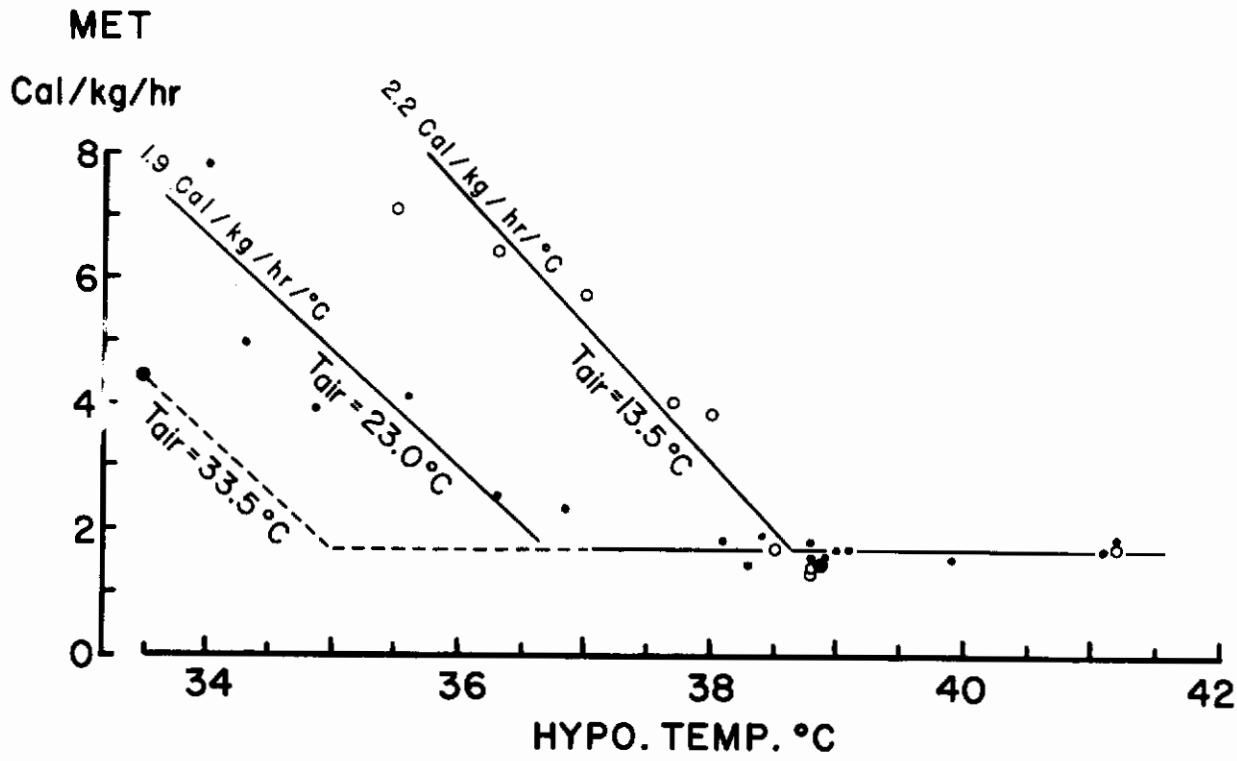

Figure 3. Heat production as a function of hypothalamic temperatures for a quiet, resting, wakeful dog at three air temperatures, 13.5°C, 23°C, and 33.5°C. Hammel, Strømme & Cornew (1963).

In our hypothetical statement of the law of the system, we intended to imply that the reference input signal T_{set_R} is not an invariant term, but may be adjusted by a variety of factors including skin temperatures, core temperatures, exercise, sleep, pyrogens and possibly humoral agents which excite, inhibit or depress hypothalamic neurones. Therefore, in our experiment conducted at a neutral environment of 23°C, we attempted to maintain the dog in a resting state by training, to prevent excitement by isolating the animal in the environmental chamber, to prevent sleep by occasional conversation through a speaking tube, to maintain constant environmental temperature and to initiate a test of metabolism at each hypothalamic temperature only after the rectal temperature had returned to 38.1°C. To obtain the results shown in Figure 3 at 23°C and 13°C, the hypothalamic temperature was artificially displaced by varying amounts above and below its normal level by perfusing six thermodes surrounding the preoptic region with water at suitable temperatures. The period of artificial hypothalamic temperature displacement was limited to about ten minutes and the corresponding metabolism was taken as the average over a two minute interval of the period of highest oxygen consumption during each period of thermal stimulation. The need to relate the hypothalamic temperature to the peak metabolism during a short interval was obvious since any artificial shivering or panting caused by the thermal stimulation changed the core temperature and in turn reduced the magnitude of the response. For example, with prolonged hypothalamic cooling, initial shivering is vigorous resulting in a rising rectal temperature and eventually in an elevated steady rectal temperature with shivering decreasing to zero. In a neutral environment, only vasoconstriction is sustained with prolonged hypothalamic cooling. Similarly, panting cannot be sustained by prolonged hypothalamic heating. Referring back to Figure 2, the rising or falling rectal temperature is seen to level off during the 30 minute hypothalamic heating-cooling cycle.

From these studies it does seem possible to represent the shivering response of a resting, wakeful dog in a neutral environment by a proportional equation of the form we have hypothesized where the properties of the system are:

$$a_M \simeq 2 \text{ kcal (kg. hr. °C)}^{-1}$$

and $$T_{set_M} \simeq 36.8°C \text{ in a } 23° \text{ environment.}$$

The properties of the system for the same quiet, resting, wakeful dog in a cold (13.5°) environment as determined by the same method, are:

$$a_M \simeq 2 \text{ kcal (kg. hr. °C)}^{-1}$$

and $$T_{set_M} \simeq 38.8°C \text{ in a } 13.5°C \text{ environment.}$$

By measurement of the water loss from the respiratory tract in the same experiments from which Figure 3 was drawn, the functional set temperatures for panting in the neutral and cold environments were found to be

$$T_{set_p} \simeq 38.8°C \text{ in } 23°C \text{ environment}$$

and

$$T_{set_p} \simeq 41°C \text{ in } 13.3°C \text{ environment.}$$

We have suggested that the law of the control system for temperature regulation is a zero order proportional equation, that is to say, the response of the controlling system is a function of T_{hypo} but not a function of the time derivative, $\dot{T}_{hypo}$. Although the evidence is meager, this assumption is based on an experiment such as that illustrated in Figure 4.

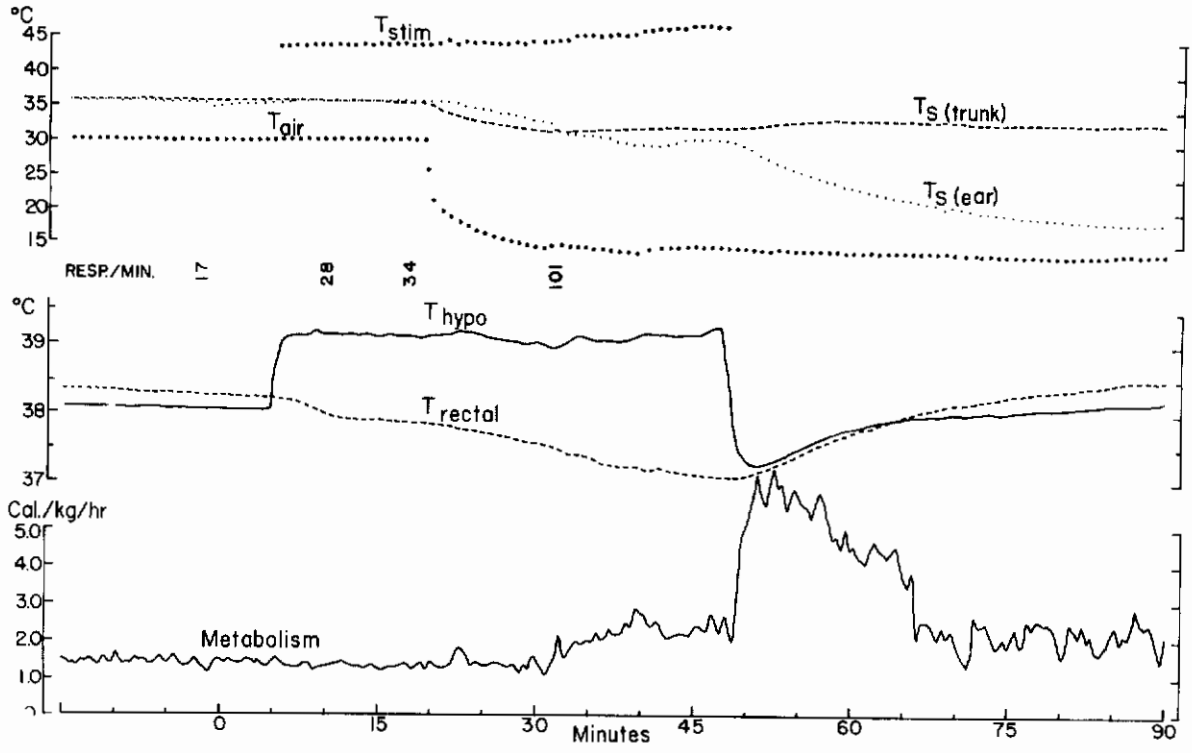

Figure 4. Body temperatures and heat production of resting, fasting dog exposed to neutral and cold environment while manipulating its hypothalamic temperature. Hammel, Jackson, Stolwijk, Hardy, & Strømme (1963).

For this experiment the hypothalamic temperature of a dog was held at an elevated temperature (39.3°C) for one-half hour while the ambient temperature was maintained at 15°C with the result that the core temperature steadily decreased. When the artificial elevation of the hypothalamic temperature was discontinued, it fell very rapidly by about 2°C to a level just above the core temperature. There followed a large increase in metabolism, but the increased metabolism appeared to be due to the low hypothalamic temperature and not due to the very rapid rate of decrease in hypothalamic temperature. If the shivering response were a function of $\frac{dT_{hypo}}{dt}$, we would have expected to see a large burst of shivering during the interval when the temperature was falling. There was not. An additional value can be drawn from this experiment. By comparing the metabolism and the hypothalamic temperature just before the drop in T_{hypo} with the metabolism and hypothalamic temperature just after the drop, and assuming that there was no change in the functional set temperature in the short interval between, the proportionality constant for shivering was computed to be $\alpha_M = 2.0\,\text{kcal}\,(\text{kg.hr.°C})^{-1}$, or the same as was obtained in Figure 3.

We have reviewed evidence which suggests that the regulation of body temperature may be described as if the hypothalamus were responsive to changes in its own temperature and as if the set temperature for each response were adjusted by the environmental temperature, i.e., by its effect upon the skin temperature. Next we ask, what changes in hypothalamic temperature do actually occur when a resting animal is placed in a hot, neutral or cold environment and do these changes contribute to the thermoregulatory response? The answer may be found in Figure 5 which illustrates that the hypothalamic temperature changes very little, if at all, when the environmental temperature is changed from neutral (27°C) to cold (12°C) to hot (44°C).

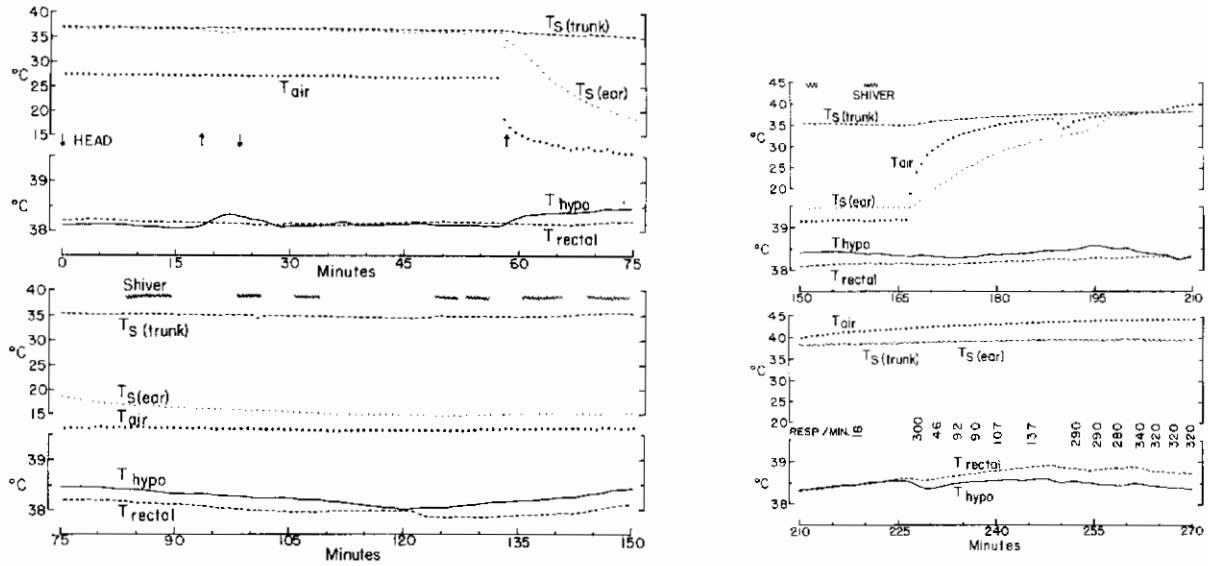

Figure 5. A continuous record of hypothalamic temperature, T_{hypo}, and other body temperatures of a resting, fasting dog exposed to neutral, cold, and hot environments. Shivering and respiration rates are noted. Hammel, Jackson, Stolwijk, Hardy, & Strømme (1963).

At time 60 minutes the air temperature was dropped to 12°C. The immediate increase in hypothalamic temperature seen here was due to awakening of the animal as the air temperature fell. At time 85 minutes the dog was shivering vigorously with a hypothalamic temperature of 38.4°C. Intermittent shivering continued for the next 80 minutes while the hypothalamic temperature varied between 38.0 and 38.4°C. At time 165 minutes the air temperature was increased up to 44°C. After an hour in the hot environment the dog began to pant, and for 40 minutes panted vigorously even though its hypothalamic temperature was between 38.4 and 38.5°C; that is no higher than it was when shivering vigorously. We have often observed the same dog to shiver vigorously when its hypothalamus was as much as 0.3°C higher than when panting vigorously.

Since the hypothalamic temperature may not change in a useful way in response to external thermal stress, we may suppose that either the hypothalamus is needlessly sensitive to changes in its own temperature and that the entire regulatory response is initiated by and regulated by a signal derived from the skin temperature, or that the actuating signal for driving the regulatory response may be achieved by off-setting the set point according to the thermal needs of the animal. By the latter thesis, which we prefer, when the skin temperature falls in a cold environment, the steady state and phasic firing rate of cold receptors in the skin increase and elevate the set point so that the hypothalamic temperature, without changing, is below the set point and drives heat conservation or increases heat production. Conversely, when the skin temperature rises in a hot environment, the steady state firing rate from the cold receptors diminishes to zero and the steady state and phasic firing rate from the warm receptors may increase and may, thereby, lower the set point temperature below the hypothalamic temperature so as to drive mechanisms that promote heat loss.

Even though the hypothalamic temperature may change very little from a cold to a hot environment or even increase in a cold environment or decrease in a warm environment so that the hypothalamus may appear to be insensitive or needlessly sensitive to its own temperature, it is, nevertheless, essential that it be responsive to changes in its own temperature and probably equally sensitive to warming and to cooling.

Next we shall attempt to show that other factors such as exercise, sleep and fever have an effect upon temperature regulation which may also be interpreted as if there is an adjustment of the set temperature. In the explanation of the experiments to follow, the emphasis will be to show that the results may be plausibly interpreted as if there had been an adjustment of the set temperature. No one can believe that these results exclude all other interpretations.

Adjustments of the Set Point in Normal Animals.

Measurements were made of respiratory heat loss, hypothalamic temperature, oxygen consumption, and rectal and skin temperatures on dogs resting and running on the level at 4 mph at several environmental temperatures. Figure 6 is a composite of results on three dogs showing the relationship between respiratory heat loss and hypothalamic temperature at rest and in exercise. Several conclusions may be drawn. a) In resting dogs C and D, there was only insensible respiratory heat loss for hypothalamic temperatures up to about 38.6 or 38.7°C. Above this temperature there was active panting. In resting Dog B there was also active panting at 38.7°C and higher, but there was somewhat more than the insensible amount of respiratory heat loss down to 38.3°C. b) In all exercising dogs, there was a several fold increase

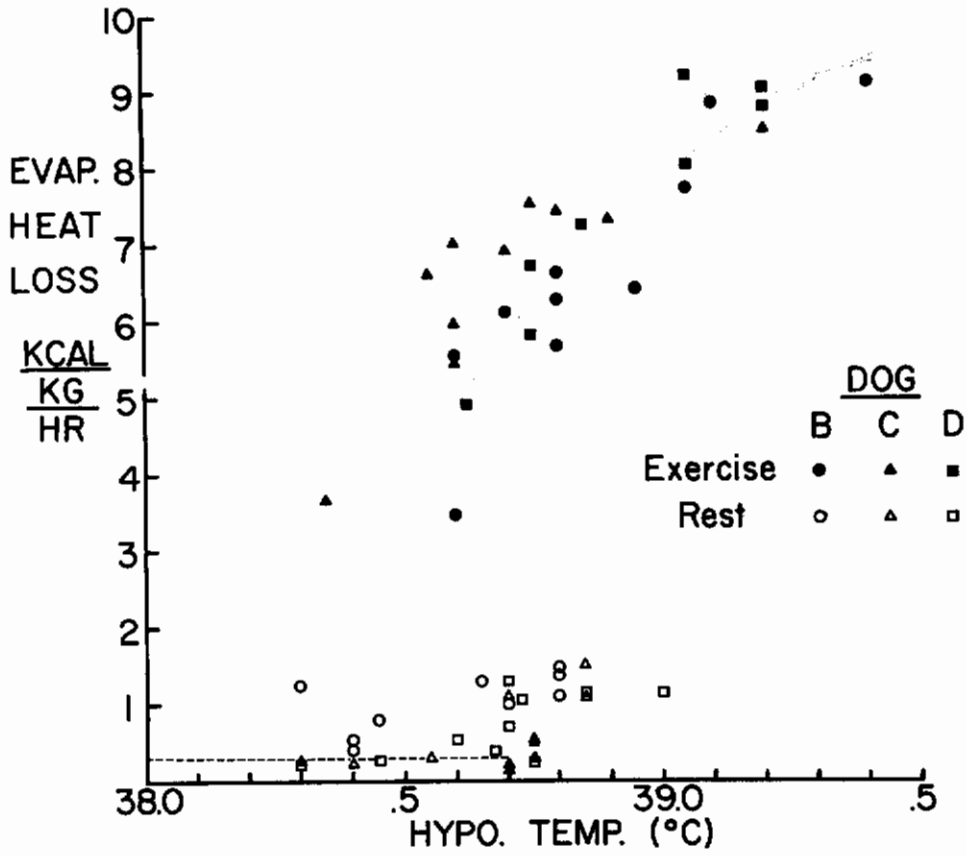

Figure 6. Evaporative heat loss as a function of hypothalamic temperature at rest and in exercise. Jackson & Hammel (1963).

in respiratory heat loss over the same range of hypothalamic temperatures as in the resting dogs. c) The respiratory heat loss increased with increasing hypothalamic temperature in the exercising dog. d) The exercise points lie on a line shifted to the left of the resting points. These results are consistent with the view that the functional set temperature has decreased by about 0.8°C for the level of exercise maintained in these experiments.

There is also no indication of an increase in the proportionality constant relating respiratory heat loss to hypothalamic temperature. From calorimetric data obtained in our laboratory some years ago on normal resting dogs, the proportionality constant for respiratory heat loss was found to be 3.8 kcal (kg. hr. °C)$^{-1}$ increase in rectal temperature. When a least square line is drawn to represent the data during exercise of Dogs B, C, and D, a proportionality constant, or slope, of 3.4 kcal (kg. hr. °C)$^{-1}$ increase in rectal temperature is obtained. Thus the major change in the rate of evaporative heat loss during exercise may be interpreted as if the set temperature were decreased at the onset of exercise.

Another situation where there is suggestive evidence that a shift in the set point occurs is in the transition from the wakeful state to sleep. The hypothalamic temperature of a rhesus monkey exposed for 24 hours to a hot environment (35°C), neutral environment (30°C) and a cold environment (20°C) is seen in Figure 7. On each of these three days the light in

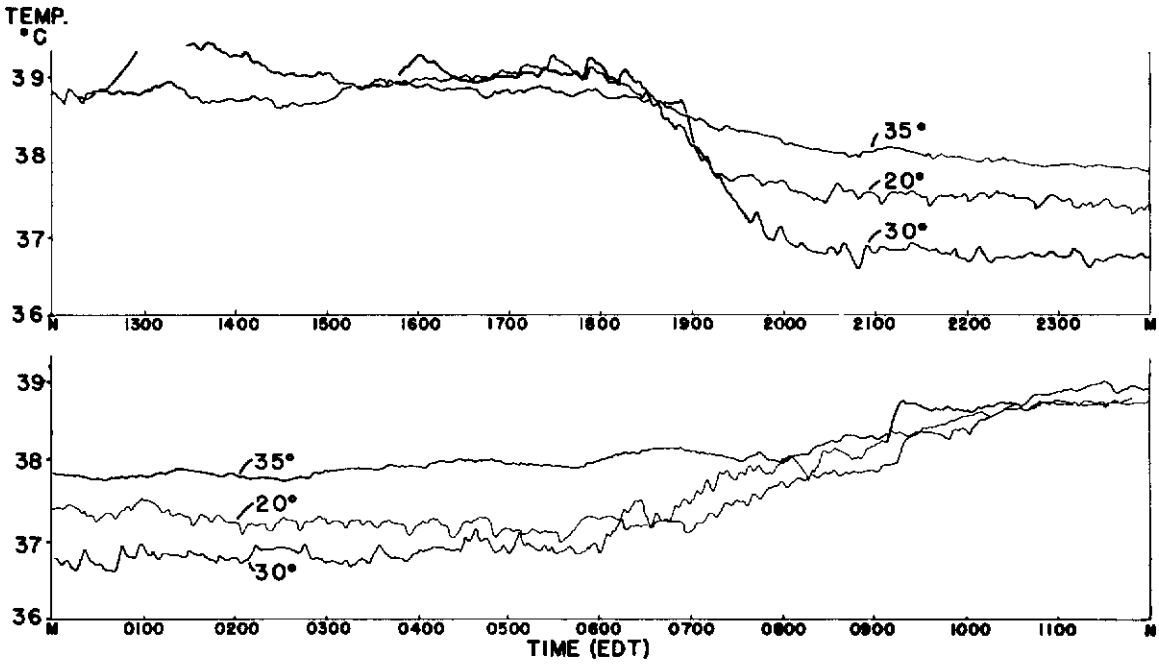

Figure 7. Hypothalamic temperatures of a rhesus monkey restrained in a primate chair in hot (35°C), neutral (30°C) and cold (20°C) environments (50% relative humidity) for 24 hr periods with normal day-night lighting. Hammel, Jackson, Stolwijk, Hardy & Strømme (1963).

the climatic chamber was turned off at 1800 hrs and turned on again at 0900 hrs. After 0615 hrs, daylight from the laboratory could also enter through a small uncovered window in the chamber. The monkey had been living in a primate chair for two months after the thermodes were implanted, and was trained to feed itself at will from a food pellet dispenser.

During the hours of light the hypothalamic temperature was regulated at 39.1 ± 0.2°C for all environmental temperatures. In each instance, soon after the light was turned out, the hypothalamic temperature fell to another level by an amount depending upon the ambient temperature. In the neutral 30°C environment, the hypothalamic temperature fell within two hours to 36.8 ± 0.2°C and remained so throughout the night. In the hot environment, the hypothalamic temperature fell to only 38.0 ± 0.1°C and remained so with only small fluctuations throughout the night. In the cold environment (20°C) which produced vigorous shivering day and night, the temperature fell to an intermediate level of 37.5 ± 0.2°C and stayed so throughout the night. In each instance, the hypothalamic temperature returned to the daytime level more slowly than it fell the evening before. The onset of the rising temperature occurred at about 0600 hrs, and the daytime temperature was achieved by about 1000 hrs.

The changes in the hypothalamic temperature that occur when an animal goes to sleep and the effect of these changes upon the thermoregulatory responses strongly suggests that a dramatic change has occurred in the regulation of body temperature. The only question is whether the change can better be described as a decrease in the set point temperature, or whether the responsiveness of the controller, α_R, has decreased. Suppose that the onset of sleep does not lower the set point, but that the gain of the regulatory mechanism is reduced. Then, in a hot (35°C) environment, a reduced gain at night would predict that the hypothalamic and core temperatures would passively increase to a level above the day temperatures. The fact is, the hypothalamic temperature is 1°C lower at night than in the day in the 35°C environment. Therefore, it appears that the observations of the hypothalamic temperatures in the monkey may be described by a set point shift at constant gain rather than by assuming that the set point is unchanged with the onset of sleep and only the gain of the thermoregulatory mechanism is reduced.

This conclusion receives further support in Figure 8. Here the hypothalamic temperature and the temperature of the ear pinna of a rhesus monkey exposed to a cool environment (22-24°C) during the day were recorded while noting whether his eyes were open or closed and also noting activity. This monkey was also confined to a primate chair for 5 weeks after implanting the re-entrant tubes. Its hypothalamic temperature was about 1.5°C lower at night than during the day in a neutral environment. When isolated in the climatic chamber but under continuous observation through a half-silvered mirror, the monkey's hypothalamic temperature fell several tenths of a degree each time it closed its eyes and conversely, its hypothalamic temperature increased each time its eyes opened during 7 hours of observation. Each time his eyes closed, he vasodilated so that the ear pinna temperature increased to 36°C. Likewise, each time he opened his eyes, he vasoconstricted causing the pinna temperature to fall down to as low as 30°C or lower. So with falling hypothalamic temperature, the animal increases heat loss and with rising hypothalamic temperature heat loss is decreased. These results may also be interpreted as if the temperature regulator is modified by a decrease in the set temperature at the

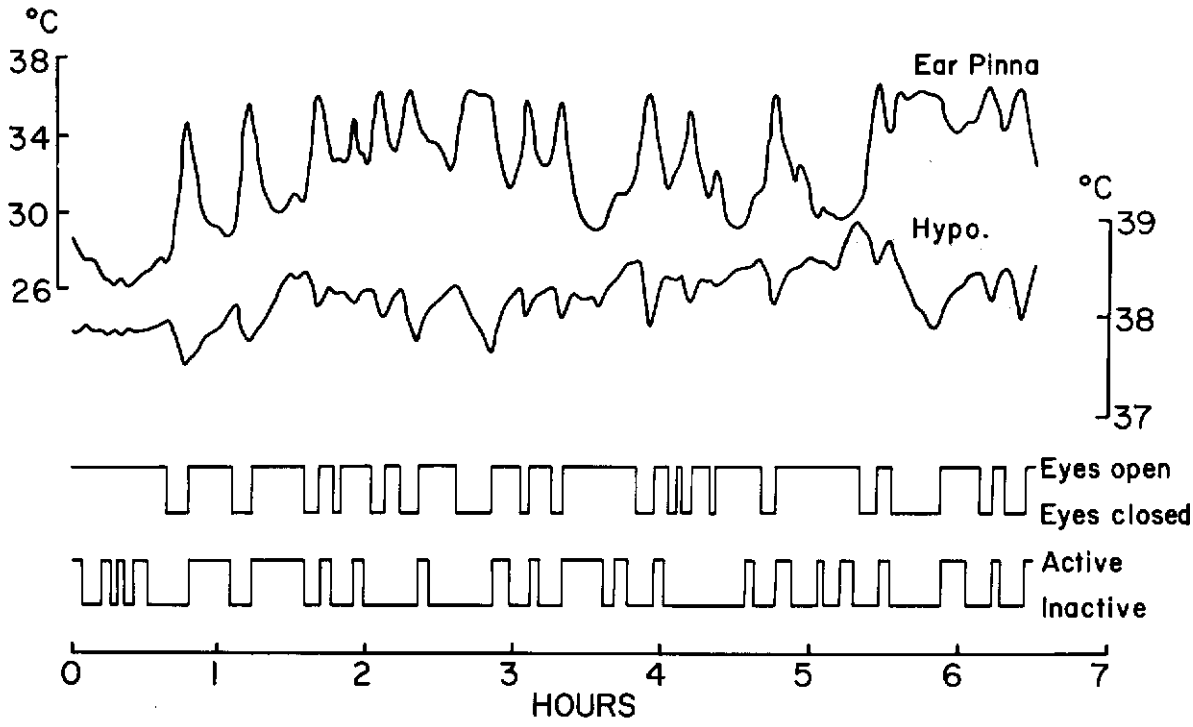

Figure 8. Hypothalamic and ear pinna temperatures of rhesus monkey in a primate chair in cool environment (22-24°C). Eyes open or closed and activity are noted. Hammel, Jackson, Stolwijk, Hardy & Strømme (1963).

onset of sleep and an increase upon awakening.

Adjustment of the Set Point in Fever.

The transition from a normal to a fevered state provides another example illustrating how thermal regulation may be modified by a shift in the set temperature. This description of fever as involving an elevation in set temperature enjoys wide acceptance although a few still reject the concept. After waiting the usual latent period following administration of an exogenous pyrogen, hypothalamic cooling was instituted; its effect is shown in Figure 9. A "hyper-fever" was produced during the chill phase by vasoconstriction and shivering. While still in the fever phase the hypothalamic cooling was terminated, with the result that panting and

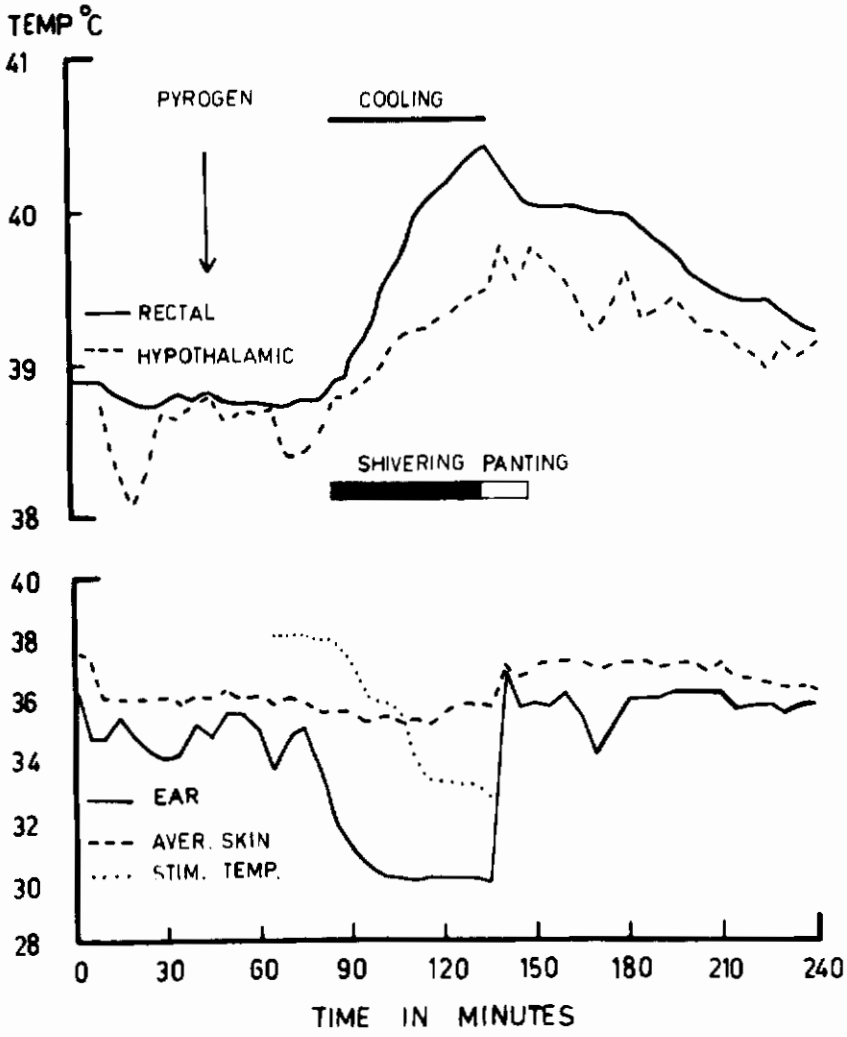

Figure 9. The additive effect of injected pyrogen and hypothalamic cooling. A "hyper-fever" was produced. Andersen, Hammel & Hardy (1961).

vasodilatation occurred and brought the "hyper-fever" down to the normal fever level. Again, the suggestion that a pyrogen acts to elevate the set temperature is plausible.

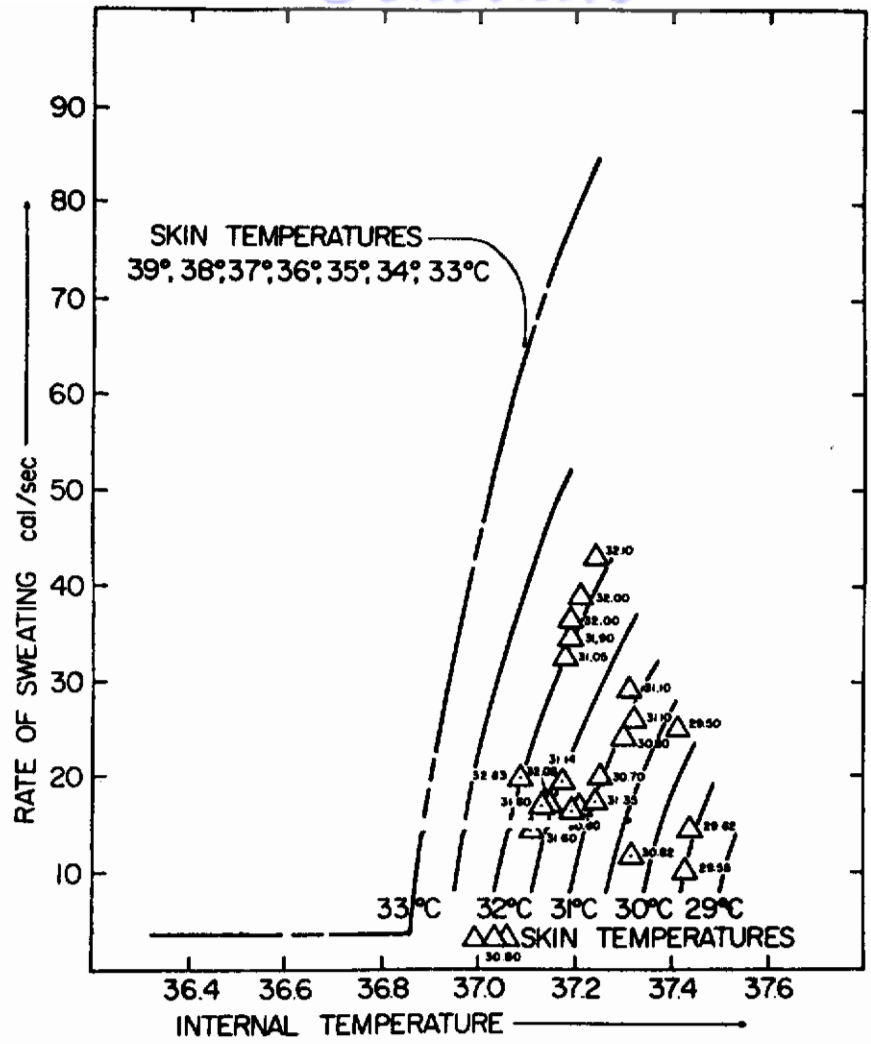

Figure 10. Intensity of thermoregulatory sweating during cold reception at the skin. Sweating rates were plotted against internal cranial temperatures. Measurements obtained at similar skin temperatures were connected with "best lines." At any given cranial internal temperature, sweating rates are seen to be diminished by approximately 40 cal/sec for every degree C decrease in level of skin temperature. The line for 33° skin temperature is from Figure 12. Figure 10 contains no resting observations as these paradoxical conditions cannot be produced in steady states at rest. Work rates were mechanically equivalent to 6 cal/sec (▲) or 11 cal/sec (Δ), respectively. Increase in work rate enlarges the range of observations to the right (low skin, with high internal temperature). (Experiments were carried out between April 4th and June 5th, 1961 with one subject, D.D., nude, age 26, weight 88.6 kg. height 176 cm.). Benzinger, Kitzinger & Pratt (1963).

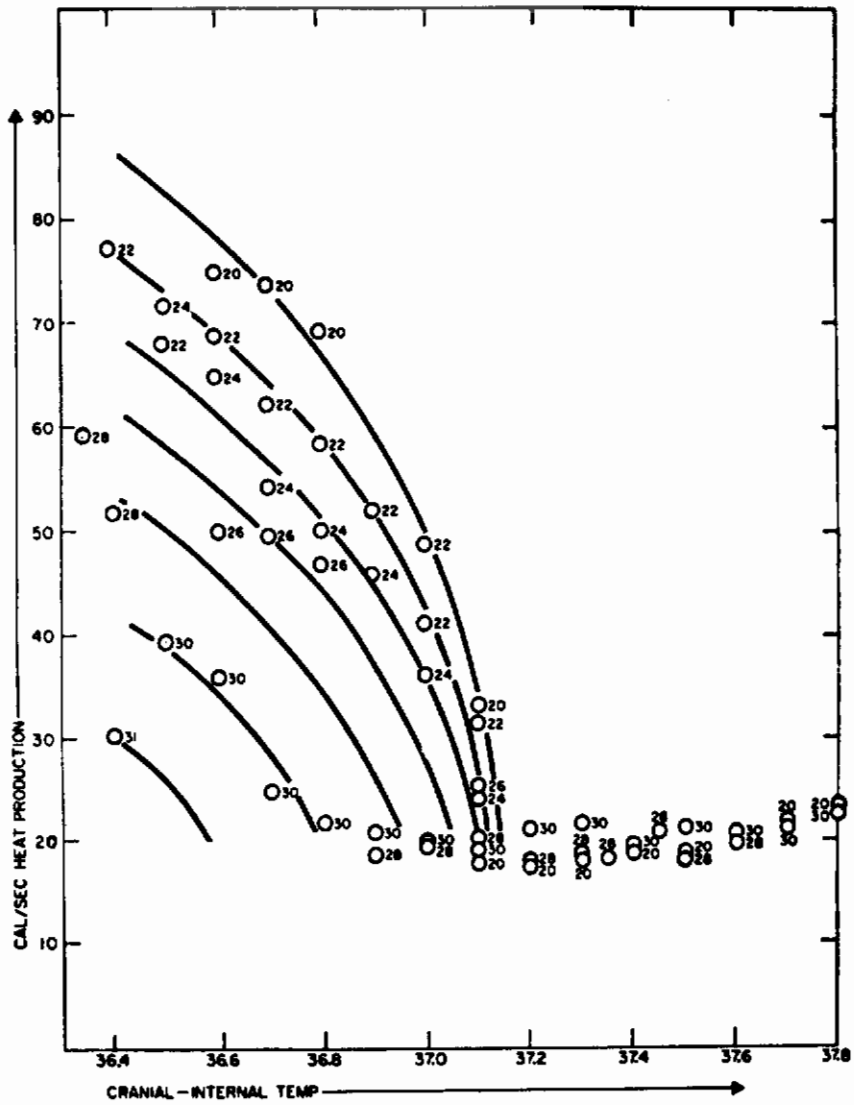

Figure 11. Quantitative resolution of "chemical" heat regulation. (cranial internal temperature plot). This figure gives the metabolic responses to almost any physiological combination of skin and cranial internal temperatures. The dependence of metabolic rate upon cranial internal and skin temperatures appears quantitatively from this graph. The thermostatic function of the internal thermoreceptive system is clearly visible: when cranial internal temperature falls below the set point, 37.1°C, the metabolic response to cold begins to rise with falling cranial internal and falling skin temperatures. Benzinger, Kitzinger & Pratt (1963).

The quantitative data from which we have derived a law of the controlling system for temperature regulation has been obtained from experimental animals in which hypothalamic temperature may be readily obtained and easily displaced by artificial means. Man is not to be neglected in developing a quantitative understanding of temperature regulation and need not be. The data from Benzinger's laboratory as summarized in Figures 10 and 11 may be interpreted by the same relationships between input and output which we have already described for experimental animals. We interpret the results in Figure 10 to mean that in a neutral environment when the skin temperature is 33°C, heat loss by sweating increases proportionally as the hypothalamic temperature rises above some functional set temperature for sweating $T_{set_{sw}}$ where the proportionality constant $a_{sw} \simeq 12$ kcal (kg. hr. °C)$^{-1}$ and $T_{set_{sw}} \simeq 36.85°C + \Delta$ where Δ is some small difference between hypothalamic and tympanic membrane temperatures. Figure 10 also suggests that the functional set temperature increases as the skin and ambient temperature decrease. Similarly, Figure 11 may be interpreted to mean that in a neutral or slightly cool environment when the skin temperature is 31°C, heat production by shivering increases proportionally as the hypothalamic temperature drops below some functional set temperature for shivering, $T_{set_{sh}}$, where the proportionality constant is $a_{sh} \simeq 4$ kcal (kg. hr. °C)$^{-1}$ and $T_{set_{sh}} \simeq 36.6° C + \Delta$. Again the functional set temperature is seen to increase as the skin and ambient temperatures decrease. It also appears that the proportionality constant a_{sh} increases to as high as 10 kcal (kg.hr.°C)$^{-1}$ for extremely low average skin temperatures. Assuming this to be true, then the apparent non-linear relationship between shivering and $(T_{set_{sh}} - T_{hypo})$ for very low skin temperature may be explained by suggesting that as the metabolism increases to 4 times basal there is a levelling off since it is difficult to shiver by more than 4 BMR no matter how cold the brain.

There appear to be some discrepancies between the results obtained from man and those obtained from dogs. For instance, Benzinger has interpreted his results obtained for a resting or exercising man, Figure 12, to mean that the set point temperature for sweating is the same in exercise and at rest. He notes that if the lower average skin temperature during exercise (1.5°C) were to have the same effect upon the sweat rate as a similar drop in skin temperature in a resting man as shown in Figure 10, this would have lowered the exercising man's sweat rate by 40 cal/sec at the same brain temperature. Perhaps these results may be interpreted

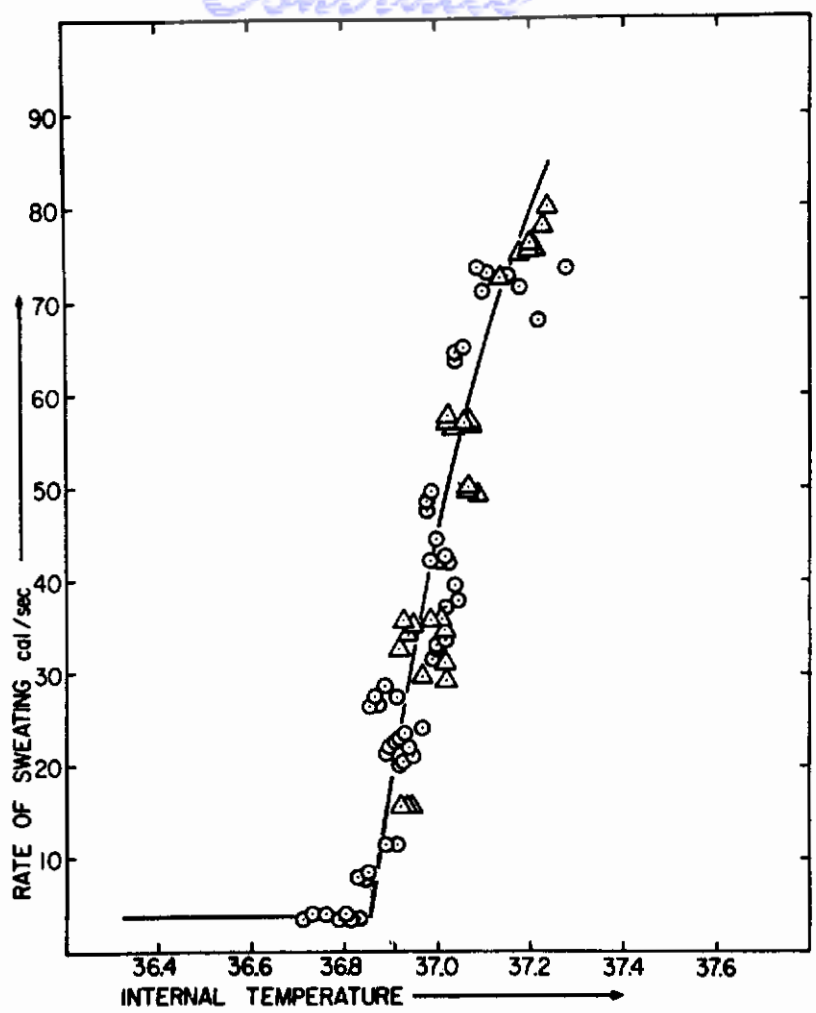

Figure 12. Intensity of thermoregulatory sweating during warm reception at the skin. Sweating rates were plotted against internal cranial temperatures in steady states of rest (0) or exercise (▲ 6 cal/sec and △, 11 cal/sec). Sweating began at a sharply defined internal cranial temperature, the "set point" of the human thermostat, a result reproduced over a period of two months. The intensity of thermoregulatory sweating was inseparably related to the level of internal cranial temperature. There was no visible effect of the drastic differences in skin temperature (average, 2°C) between the resting and the working observations. This difference (average, 2°C) would have lowered the triangles by an estimated 80 cal/sec in comparison with the cycles measured at the same internal cranial temperature, if the inhibiting effect of cold observed in Figure 10 extended with similar intensity into the range of warm reception. (Experiments were carried out between April 4th and June 5th with one subject, D. D., nude, age 26, weight 88.6 kg, height 176 cm.). Benzinger, Kitzinger & Pratt (1963).

to mean that the lower skin temperature during exercise does in fact raise the functional set temperature for sweating, as in Figure 10, and at the same time the exercise per se lowers the set temperature, so that there is no apparent change in the set temperature in Figure 12. Recent data do suggest that the functional set temperature decreases during exercise in man (Minard, 1963).

Other apparent differences between the results on man and dog are the larger proportionality constants in man than in dog (twice or more) and the smaller effects of ambient temperature (and exercise) upon the functional set temperatures in man. It cannot now be stated whether these differences are more apparent than real because there are important differences in the methods by which the brain temperatures were manipulated in order to relate response to brain temperature, and differences in the way skin temperatures were affected by the environment; moreover, there is some uncertainty in relating hypothalamic temperature to tympanic membrane temperature. If the differences are real, then we might suppose the greater thermal capacity, and consequently greater thermal inertia, of man enables him to enjoy a more sensitive control mechanism without the risk of an unstable system.

NEURONES IN THE CONTROL SYSTEM

Having guessed our way this far in our effort to arrive at a formal statement or a "law of the controlling system" for temperature regulation, we feel there will be only an imperceptible transition in our story if we attempt to offer at least one plausible scheme showing how neurones may be connected so as to achieve the relationships stated in the formal equations.

Our model will be based on the following assumptions:

1) There are neurons in the rostral hypothalamus having spontaneous firing rates which are strongly temperature dependent, i.e. $Q_{10} >> 1$, over the range of normal deep body temperatures. These are designated as hi-Q_{10} primary sensory neurones.

2) Axons of these sensory neurones synapse with neurones within the hypothalamus which ultimately activate thermoregulatory responses. These latter are designated as first stage or primary motor neurones.

3) The primary motor neurones may or may not have spontaneous firing rates depending upon the choice of models to be preferred. Their firing rates are assumed to have little or no temperature dependence except as influenced by the sensory neurones.

4) Synaptic terminations on cell bodies of both primary sensory and primary motor neurones may either facilitate or inhibit the neurones.

5) Although studies employing experimentally induced lesions and electrical and thermal stimulation may indicate that primary sensory and motor neurones are found in high concentrations in certain hypothalamic sites, these results cannot be interpreted to mean that neurones of a given type are located only in a small circumscribed region.

These are not unreasonable assumptions to make regarding neuronal activity and are generally accepted as working assumptions on the limited evidence available (Hardy, 1961; von Euler, 1961). An additional assumption will be made at this time; its justification, or rather its desirability, will become apparent later.

6) We shall assume that another set of primary sensory neurones designated as lo-Q_{10} sensory neurones are located in the rostral hypothalamus in the same region with the hi-Q_{10} sensory neurones. The lo-Q_{10} sensory neurones are assumed to have spontaneous firing rates over the range of deep body temperature. Further suppose the cells are either not strongly temperature dependent, i.e. $Q_{10} \simeq 1$ or, as suggested by Bazett, 1949, increase their firing rate with decreasing temperature, i.e. $Q_{10} \ll 1$. Like the hi-Q_{10} sensory neurones, the lo-Q_{10} sensory neurones are assumed to synapse with and facilitate or inhibit the primary motor neurones which activate regulatory responses.

In Figure 13, we are suggesting one way in which the hi-Q_{10} and lo-Q_{10} sensory neurones are connected with three classes of primary motor neurones which respectively activate panting, vasoconstriction and shivering. In this figure we have slipped in two more assumptions, one essential and the other trivial. It is essential to assume that the hi-Q_{10} sensory neurones facilitate primary motor neurones increasing heat loss, e.g., panting, and at the same time inhibit primary motor neurones which lead to vasoconstriction and shivering. Conversely, the lo-Q_{10} sensory neurones must inhibit panting and at the same time facilitate vasoconstriction and shivering. The other assumption is that the panting and shivering primary motor neurones in Figure 13 have no spontaneous firing rates by themselves. In order to obtain different set temperatures for panting and shivering, we have shown more inhibition than facilitation from the sensory neurones synapsing with the

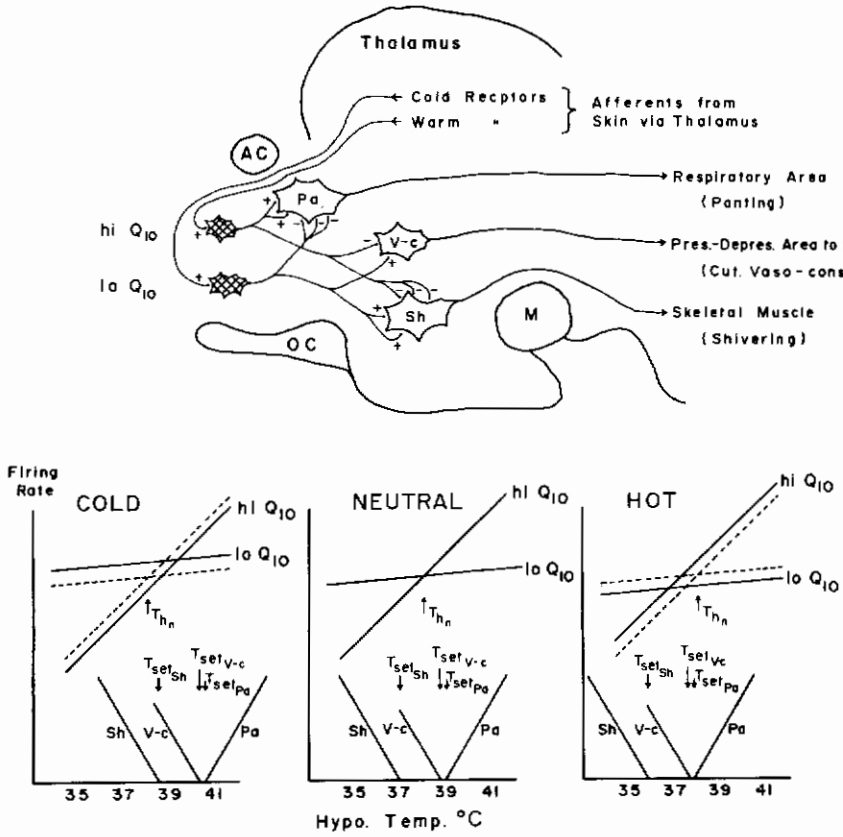

Figure 13. A physiological model for establishing a set point temperature and illustrating possibilities for adjusting the set point. AC, anterior commissure; OC, optic chiasm; M, mammillary body; Pa, primary panting neurone; Sh, primary shivering neurone; v.c., primary vasoconstriction neurone; cross hatched cell bodies, low-Q_{10} and high-Q_{10} primary sensory neurones.

panting and shivering neurones. The same condition could also be achieved by assuming these motor neurones to have low but not zero thresholds so that more facilitation than inhibition would be required to activate panting and shivering.

Reference to the activity curves of each of the sensory and motor neurones below the diagram of Figure 13 will indicate how the controlling system is presumed to function. First, examine the set of activity curves for the neutral environment. For the temperature at which the

firing rate curves of the hi-Q_{10} and lo-Q_{10} sensory neurones are equal, i.e., intersect, the facilitation and inhibition from these sensory neurones upon the vasoconstriction (v.c.) motor neurones nullify each other so that v.c. motor neurone is active at its own spontaneous firing rate. The temperature at which the firing rate curves of the hi-Q_{10} and lo-Q_{10} neurones intersect in a neutral environment for a resting, wakeful, normal animal is designated to be T_{h_n}*. If the hypothalamic temperature drops below T_{h_n} in the neutral environment, then the v.c. motor neurone is more facilitated than inhibited and vasoconstriction is increased. If the hypothalamic temperature rises above T_{h_n} then vasoconstriction decreases. The temperature at which vasoconstriction becomes zero is designated as the functional set temperature for vasoconstriction in a neutral environment.

As shown in the activity curves for the neutral environment, when the hypothalamic temperature equals T_{h_n}, both the panting and shivering motor neurones are more inhibited than facilitated so there is no panting or shivering. As the hypothalamic temperature increases, facilitation of panting increases faster than inhibition. For temperatures above $T_{set_{pa}}$, facilitation exceeds inhibition and panting results in proportion to $(T_{hypo} - T_{set_{pa}})$. Similarly, as the hypothalamic temperature drops below T_{h_n}, inhibition of the shivering motor neurone decreases more rapidly than does facilitation. For hypothalamic temperatures below $T_{set_{sh}}$, facilitation exceeds inhibition and shivering increases in proportion to $(T_{set_{sh}} - T_{hypo})$.

So far, we have considered a neuronal model of temperature regulation located within the hypothalamus and have considered how it may function without any input from outside itself, i.e., no input from peripheral receptors in the skin, from extra-hypothalamic core receptors, from the reticular

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* T_{h_n} may differ from the intrinsic hypothalamic set temperature T_{h_o} of Figure 1, since in the wakeful dog in a neutral environment there may be and very likely are afferent inputs into the hypothalamus from the thermal receptors in the skin and from the reticular activating system.

activating system or from any other source. The model postulates that the primary sensory and primary neurones alone can activate thermoregulatory responses and to do so requires only an appropriate displacement of the hypothalamic temperature from the functional set temperature for each response. The model, thereby, conforms with our experimental results obtained from displacing the hypothalamic temperature and finding that the response is proportional to the difference between the actual hypothalamic temperature and the functional set temperature for that response. Our results then went on to show that placing the animal in hot or cold environments did not actually lead to a useful displacement of the hypothalamic temperature although there were appropriate regulatory responses. We did not choose to interpret this to mean that the hypothalamus is therefore needlessly sensitive to changes in its own temperature but rather that afferent input into the hypothalamus from thermal receptors in the skin somehow shifts the functional set temperatures for each regulatory response. Our results obtained by displacing the hypothalamic temperature with the dog in neutral, cold, and hot environments, Figure 3, support this interpretation. They also suggest that the environmental temperature shifts only the functional set temperatures and not the proportionality constants.

The effects of afferent inputs into the hypothalamus consistent with our experimental results may be readily and simply achieved by running afferent fibers to the primary sensory neurones where they either facilitate (or inhibit) the spontaneous and temperature dependent activities of these sensory neurones. In Figure 13, afferents from the cold receptors in the skin are shown to facilitate the lo-Q_{10} sensory neurones and afferents from the warm receptors in the skin are shown to facilitate the hi-Q_{10} sensory neurones. In the cold environment, the activities of the primary sensory and motor neurones are presumed to be as shown in the lower left graph of Figure 13. The increased firing rate from the cold receptors in the skin is shown to facilitate the activity of the lo-Q_{10} sensory neurones, and the decreased firing rate from the warm receptors in the skin is shown to reduce the activity of the hi-Q_{10} sensory neurones with the combined effect of raising all functional set temperatures. Thus, although there may be no change in the actual hypothalamic temperature---and, in fact, it may increase a little---it is below the functional set temperatures for vasoconstriction and shivering and will drive these responses in proportion to the differences.

In like manner, the activities of the primary sensory and motor neurones in the hot environment are presumed to be as shown in the lower right graph of Figure 13. Reduced firing rates from cold receptors in the skin are shown to reduce the activity of the lo-Q_{10} neurones, and increased firing rates from warm receptors in the skin are shown to increase facilitation of the

hi-Q_{10} neurones with the combined effect of lowering all functional set temperatures. The hypothalamic temperature, without changing, still drives panting and reduces vasoconstriction.

Simply by suggesting that all afferent connections to the temperature regulatory mechanism within the hypothalamus act by facilitating either the hi-Q_{10} or lo-Q_{10} sensory neurones, it is possible to account for the apparent shifts in the functional set temperatures that occur in the transition from wakefulness to sleep or in exercise, and without any apparent adjustment of the proportionality constants. For example, we may visualize that connections from the reticular activating system terminate on the lo-Q_{10} sensory neurones and facilitate these during the waking hours. At the onset of sleep, the facilitation may rapidly diminish with a resultant immediate drop in all functional set temperatures--without changing any of the a_R's.

We recognize that terminating all inputs into the hypothalamus upon the sensory neurones is not the only way to affect temperature regulation. It is possible that some or all of the peripheral inputs feed into the motor neurones directly and facilitate or inhibit these neurones. But to do so would require that the peripheral inputs would also have to exercise antagonistic control over the classes of primary motor neurones. For example, in order to shift all functional set temperatures in the cold environment, as occurs experimentally, it is necessary to suppose that the cold receptors in the skin not only facilitate the primary shivering neurones but at the same time inhibit the primary panting neurones. Similarly, the warm receptors in the skin must not only facilitate the primary panting neurones but also inhibit the shivering neurones. If the peripheral inputs do go directly to the primary motor neurones rather than to the primary sensory neurones, then the hypothalamus may be thought of as needlessly sensitive to changes in its own temperature because the hypothalamic temperature does not change in response to external thermal stress.

Since we know of no experimental evidence as to whether the afferent inputs go directly to the primary motor neurones* or go directly to the primary sensory neurones, we have favored the latter view because it is a more simple arrangement and because it does not render the hypothalamus as needlessly sensitive to changes in its own temperature.

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* Primary sensory and motor neurones in this context refer to the initial (Hi-lo-Q_{10}) and terminal cells of the model rather than cells of the spinal cord. Evidence does exist for thermoregulatory responses at cord level.

It is worth noting that whatever afferent connections are made with the hypothalamus, or for that matter any agent which acts upon the primary sensory or motor neurones within the hypothalamus, appears to affect regulation in the same way---namely, by adjusting the functional set temperatures rather than by changing the proportionality constants. Should a body of evidence accumulate demonstrating that the proportionality constants do change with thermal stress, (for example, $\alpha_{shivering}$ increasing in cold exposure or $\alpha_{panting}$ increasing in heat exposure), then it will be necessary to suggest that within a class of primary motor neurones there is a wide range of thresholds or a range of levels of spontaneous activity so that there is a range of functional set temperatures for each response. Thus, as the hypothalamic temperature deviates toward its extreme limits there would be recruitment of thermoregulatory response and therefore increasing α_R. At present, the evidence is too meager to speculate further on this possibility.

Benzinger has proposed that there are two central sites involved in temperature regulation and that they "differ basically in their main characteristics." The central site for regulation of vasodilation and sweating is placed in the anterior hypothalamus; it acts as a terminal sensory receptor organ for temperature and acts independently of heat stimulation of the skin. On the other hand, the central site for regulating metabolism is placed in the posterior hypothalamus and acts like a synaptic relay station for afferent impulses from cold (not warm) receptors in the skin. This synaptic relay station he supposed is not affected by its own temperature, but it may be influenced by the anterior hypothalamus which is responsive to its own temperature; that is to say, a warm anterior hypothalamus may diminish shivering by depressing the activity of the posterior hypothalamus which is relaying the impulses from the cold receptors in the skin to the muscles. In an opposite way, cooling the anterior center is said to release the normal depressing effect of the anterior upon the posterior hypothalamus. Thus, the function of the cold receptors in the skin is to "elicit (not to gradate and regulate) the metabolic response to cold," and the function of the central thermoreceptive system is to "either depress or release the metabolic response to cold receptor impulses from the skin precisely to such an extent as is required to maintain or restore homeostasis" (Benzinger, Kitzinger & Pratt, 1963). Andersson holds a similar view with regard to the role of the thermo-receptive center in controlling shivering (Andersson, et al., 1963).

If the posterior hypothalamus serves as a relay station for impulses from the cold receptors in the skin which are presumed to elicit the metabolic response to cold, and if the only role of the thermo-receptive center in the anterior hypothalamus is either to depress or release the metabolic response to cold receptor impulses from the skin, then it is difficult to understand how it is possible to elicit shivering in an animal when its skin temperature is normal as in a neutral environment, or when its skin temperature is high

as in a hot environment. It is, in fact, easy to elicit shivering in a neutral environment by dropping the hypothalamic temperature of the dog below about 37°C, and it is even possible to more than double the metabolism in a hot environment by dropping the hypothalamic temperature to about 34°C (Figure 2). Therefore, we are inclined to the view already expressed that there are two sets of primary sensory neurones with widely different firing rate Q_{10}'s, one set with $Q_{10} >> 1$ and the other with $Q_{10} \underset{\sim}{\sim} 1$ or possibly $<< 1$, and that the regulatory response is a result of the difference between these two antagonistic sets acting upon the primary motor neurones.

For want of information, we have had to ignore many relevant and interesting questions. We cannot elaborate upon the mechanism by which a primary sensory neurone achieves a $Q_{10} >> 1$ except to suggest that such a unit may be in fact a cascade of neurones each with a more normal Q_{10} of 2 or 3. We do not attempt to say how a given sensory neurone may facilitate on the one hand and inhibit on the other. It may be that one-half the class of hi-Q_{10} sensory neurones facilitates and the other half inhibits their respective target motor neurones. We are unable to say whether the thermal drive from the skin needs to be divided into regions with each region having a different effectiveness upon temperature regulation. Common experience does suggest that raised or lowered temperatures of the skin of the face, hands and feet yield sensations different from those derived from similar temperature changes of trunk surfaces.

We have assumed five basic classes of neurones in our model, two primary sensory and three primary motor neurones. The direct evidence for these is meager, indeed, and the indirect evidence from electrical stimulations, ablations and thermal stimulations was only partially reviewed here. Nakayama, Hammel, Hardy & Eisenman, 1963 have evidence that at least in the anesthetized animal there are neurones in the rostral hypothalamus whose firing rates increase with increasing temperature, and neurones whose spontaneous firing rates do not change with temperature (Nakayama, et al., 1963). But we can only suppose that at least some of these are involved in regulating temperature. They may not be, however. Furthermore, it cannot be stated whether those neurones with Q_{10} as high as 10 are primary sensory neurones or perhaps primary motor neurones for panting. However, microelectrode studies in this rostral region of the hypothalamus in the unanesthetized preparation should reveal a difference between a hi-Q_{10} sensory and a "panting motor neurone." The activity of the former should increase continuously over the range of a few degrees below body temperature to a few degrees above; whereas "panting motor neurones" should be silent at temperatures below body temperature and increase only at higher temperatures. Another useful microelectrode study would be an

attempt to record activity from "shivering motor neurones" in the posterior hypothalamus while cooling in the rostral hypothalamus in the unanesthetized animal.

A recent provocative study by Keller & McClaskey, 1964 has led them to conclude, "The neural integration of heat dissipation is wholly dependent upon the anatomical integrity of the subthalamic and cephalic midbrain level of the brain stem. Except for a possible permissive function, heat dissipation is quite independent of the hypothalamus." Also they conclude, "The neural integration of resistance-to-hypothermia is wholly dependent upon the anatomical integrity of the hypothalamic grey and is completely independent of tissues lying cephalad to the hypothalamus." These views are in stark contrast to those held by the author throughout this entire chapter.

Much thought and effort may be required to reestablish communication between those who seek insight into the nature of body temperature regulation by ablating or sectioning segments of the central nervous regulator and examining the fragments of normal physiological function that may be left and those who choose to molest the hypothalamus by no more than gently perturbing its temperature. A few suggestions are made which, hopefully, will be steps toward mutual understanding:

1) Keller and McClaskey found in the dog "that diencephalonectomized or high-midbrain preparations retain the ability to physiologically resist overheating in a sufficiently adequate manner to prevent a critical rise in body temperature." They believe this to be evidence "that not only the anterior but the entire hypothalamus is not essential for effective dissipation of heat" and that "the only permanent deviation from the normal which may be exhibited by these preparations is a 'raised heat-dissipation threshold'." These results seem rather to demonstrate that there are internuncial neurones which reside in the midbrain and which connect the regulatory neurones in the preoptic region with the respiratory neurones in the medulla and that these have thermal properties of their own which include a spontaneous firing rate with a not unlikely Q_{10} of 2 or 3. If this were the case then these midbrain neurones, when isolated from the rostral controller, may very well activate some panting if their temperature is elevated sufficiently. On the other hand, assuming reasonable values for the tissue conductance, cooling coefficient, and insensible evaporative heat loss for the dog, it may be shown that had Keller and McClaskey anesthetized their high-midbrain preparations they would have found the rectal temperature of these dogs in a 38 C environment

1) (continued)

to rise no more than a few tenths higher than that of the same preparation unanesthetized. We are unable to regard the residual capability of these preparations as regulation with a "raised heat-dissipation threshold" for it lacks the essential characteristics of regulation. Such a preparation makes no response at all to a greatly reduced body temperature.

2) Keller and McClaskey also found that dogs with high hypothalamic sections and even dogs with low hypothalamic sections from which "anterior hypothalamic tissue lying dorsal and cephalic to the mid-level of the chiasm was aspirated" were able to pant and shiver with threshold shifts of no more than 2 or 3 C. These results may demonstrate that although the primary neurones (including sensory and motor neurones) of the controlling system are found in the highest concentration in the preoptic region, they are also found more diffusely distributed. This being the case, we would expect a variety of bizarre results ranging from little to severe deficit depending upon assymetry in the ablation and on the presence of even small remnants of primary tissue.

It is only too plain at this stage that neuronal models for temperature regulation are to a high degree guesswork and that they may be justified on the grounds that making them is pleasurable. They might also lead to useful investigations.

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13. ABSTRACT

An attempt has been made to ascribe the regulation of body temperature in homeotherms to the hypothalamus and the preoptic region. Results of measurements of hypothalamic temperature and regulatory responses in the normal dog in hot, neutral and cold environments and, at various times, in the resting, waking, sleeping, exercising and fevered state, are interpreted on the assumption that the hypothalamus responds to changes in its own temperature like a proportional controller with an adjustable set point. For each thermal regulatory response, the response was as if its magnitude were proportional to the deviation of the actual hypothalamic temperature from a set point temperature, and as if the set point temperature were to increase in the cold environment, decrease in the hot environment, decrease at the onset of sleep, decrease at the onset of exercise and increase in fever. A model based on known characteristics of neurones is proposed which appears to function like a proportional controller with an adjustable set point.

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It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as *(TS)*, *(S)*, *(C)*, or *(U)*.

There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

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