Temperature regulation by hypothalamic proportional control with an adjustable set point

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HAMMEL, H. T., D. C. JACKSON, J. A. J. STOLWIJK, J. D. HARDY, AND S. B. STRÖMME. Temperature regulation by hypothalamic proportional control with an adjustable set point. J. Appl. Physiol. 18(6): 1146-1154. 1965.—The role of the hypothalamic and skin temperatures in controlling the thermal response of a resting animal was studied by measurements of 1) hypothalamic, rectal, ear skin, and trunk skin temperatures on the resting dog and rhesus monkey in hot, neutral, and cold environments; and 2) the thermal and metabolic responses of a dog in neutral and cold environments during and immediately after holding the hypothalamus at approximately 39.0°C by means of six thermodes surrounding the hypothalamus and perfused with water. The results indicate that 1) a resting animal shivers in a cold environment with the same or higher hypothalamic temperature as the same animal in a neutral environment; 2) a resting animal pants in a hot environment with the same or lower hypothalamic temperature as the same animal in a neutral environment; 3) the hypothalamus is nonetheless strongly responsive to an increase or decrease of 1°C; 4) the rate of heat loss increases at the onset of sleep while the hypothalamic temperature is falling; 5) the hypothalamic temperature is 1-2°C lower during sleep even though thermoregulatory responses are the same as when awake; 6) the rate of heat loss decreases upon awakening while the hypothalamic temperature is rising. The discussion of these results includes a suggestion that the set point for temperature regulation is 1) decreased by a rising or elevated skin and extrahypothalamic core temperature, 2) increased by a falling or lowered skin and extrahypothalamic core temperature, 3) decreased upon entering and during sleep and is increased upon awakening.

CONCEPTS OF THE CONTROLLER

Concepts of the controller of body temperature are evolving rapidly with increasing knowledge from neuropathophysiological studies and from thermal and calorimetric measurements. From the earliest observations that temperature changes in the brain stem result in thermoregulatory responses, there grew an awareness that brain temperature and skin temperature somehow combine somewhere in the brain stem to yield body temperature regulation.

Among the initial efforts to treat the temperature regulatory system as a controller operating against a set point were those of Hardy (14), who suggested that the thermal responses of the homeotherms could be considered as $T_{w} + 2T_{c}$, where $T_{w}$ represented tissue temperatures above the set point and $T_{c}$, tissue temperatures below the set point. However, no systematic relationship was offered between specific temperatures and the thermoregulatory responses other than to indicate involvement of the skin and "core" (rectal) temperatures. More recently, attempts at analyzing the available physiological data have been made incorporating controller equations (7, 8, 15, 28). As pointed out by Burton (6, 7), proportional control is one of the more likely control actions in which the responses are a linear function of the "load error" or deviations of the temperature from its "set point." This expression is:

$$R = \alpha_{R} (T_{h} - T_{h0}) + \beta_{R} (T_{s} - T_{s0})$$

where $\alpha_{R}$ and $\beta_{R}$ are the proportionality constants for heat-dissipating responses and for heat-conserving and heat-producing responses, $T_{h}$ is the hypothalamic temperature, $T_{h0}$ is a reference or set temperature for the hypothalamus, $T_{s}$ is the skin temperature, and $T_{s0}$ is the set point for the skin (for man $T_{h0} \approx 37$°C and $T_{s0} \approx 33$°C), and $R$ is the response magnitude. The addition of other terms for the effects of extrahypothalamic core receptors, etc., are not excluded.

Although these authors recognize that the $\alpha_{R}$s and $\beta_{R}$s are different and may be in different ratios for different responses, and that there are likely to be individual differences for the same response, they suggest that for each response there is a central component which sums with a peripheral component to yield the total response.

Steady-state measurements of evaporative heat loss, heat production, skin temperatures, and tympanic membrane temperature on human subjects in hot and cold environments at rest and in exercise have led
Benzinger to propose for heat-dissipating responses that

\[ S_w - S_{sw} = \alpha_w (T_h - T_h) \]  

where \( S_w \) is the evaporative heat loss, \( \alpha_w \) is the proportionality constant for sweating (\( \alpha_w = 13.5 \text{ kcal/hr kg per } ^\circ\text{C} \)), \( T_h \) is the “intracranial” temperature, and \( T_h \) is an invariant set point equal to 36.7 ± 0.1 C for the average individual (2). For skin temperatures above 33 C, Benzinger concluded that \( \beta_{sw} = 0 \), although he has more recently found that \( \beta_{sw} \) is not 0 for \( T_s < 33 \) C (3). Thus he has added a term, \( \beta_{sw} (T_s - 33 \) C), where \( \beta_{sw} = 1.6 \text{ kcal/hr kg per } ^\circ\text{C} \) for \( T_s < 33 \) C and 0 for \( T_s > 33 \) C.

Benzinger’s basic ideas are reviewed in order that we may write a control equation describing his view of the metabolic response to cold. He postulates 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 and 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. We will attempt to formalize his view of the shivering response by the expression

\[ Sh = f \left( \frac{1}{T_h} \right) \beta_{ah} (33 \text{ C} - T_s) \]  

where \( f(1/T_h) \) is an inverse function of the anterior hypothalamic temperature and \( \beta_{ah} \) is 0 for \( T_s > 33 \) C and a positive proportionality constant for \( T_s \) below 33 C. Thus, the function of the cold receptors in 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” (4).

The role of the hypothalamic, core, and skin temperatures in controlling the thermal response of a resting dog and monkey was studied by two methods (13):

1. Measurements of hypothalamic, rectal, car skin, and trunk skin temperatures were made on the resting, fasting dog in its winter fur in hot, neutral, and cold environments while observations of respiration rate, shivering, and body position were made. Twenty-four-hour measurements were also made of the hypothalamic
FIG. 2. A: body temperatures of same dog as Fig. 1 resting and fasting exposed to neutral, cold, and hot environments. B: body temperatures of same dog as Fig. 1 resting and fasting exposed to neutral, cold, and hot environments.

dog is approximately 25 mm anterior to the ear bars. Several weeks after preparation, thermocouples were inserted into selected thermodes or the three anterior pairs were perfused with water from a two-chambered circulator mounted above the head (13), and a thermocouple was placed in one of the posterior pair of thermodes. When thermal stimulation of the hypothalamus was required, water from a constant-temperature bath was circulated through the upper chamber of the head circulator at a high rate. The bath temperature was held constant (±0.05°C), and the temperature could be quickly adjusted to any desired temperature between 30 and 45°C. The temperature of the water passing through the head circulator was continuously recorded with a thermocouple inserted in the upper chamber. Water from the upper chamber of the head circulator flowed to the tip of the thermode when the lower chamber was connected to a vacuum line.

The dog was trained to rest quietly on a platform in an air-conditioned box. Forced air entered the chamber through a 6-in. port in the top of the box above the dog. A baffle in front of the port prevented air from striking the dog directly. Air left the chamber through a 6-in. port low on one end of the chamber. The temperature of the ambient air in the box could be held constant at any desired level of temperature between 10 and 45°C, and rapid 8- to 12-min transitions could be made from one temperature to another.

Continuous recordings of oxygen consumption, rectal temperature, hypothalamic temperature, the average of eight to ten skin temperatures, the skin temperatures of the ear and trunk, air temperature, and temperature of stimulating water were made (13). The dog was

METHODS

Thermodes were implanted around the hypothalamus of mongrel dogs. The thermodes served both as re-entrant tubes for measurement of the hypothalamic temperature, by inserting a thermocouple to the bottom of the tube, and for thermal stimulation of the hypothalamus by perfusing the thermodes with water. Two rows of thermodes, each 4 mm from the midline, were placed stereotaxically at 19, 22, 25, and 28 mm anterior to the ear bars. The anterior commissure in the temperature of rhesus monkeys restrained in a primate chair in hot, neutral, and cold environments.

b) A “thermal clamp” was placed on the hypothalamus of a resting, fasting dog to hold the temperature of the hypothalamus at approximately 39°C while the thermal and metabolic responses were measured when exposed to a wide range of environmental temperatures. The response of such an animal may be attributed to the extrahypothalamic thermal receptors acting upon the hypothalamus. Subsequently, any increment of response that followed upon removal of the thermal clamp may be attributed to the hypothalamic receptors alone.

The objective for this study was to obtain a quantitative relationship between hypothalamic and skin temperature and the thermoregulatory responses of the animal. This objective was based on the assumption that there is a unique thermoregulatory response for each combination of skin and hypothalamic temperatures in the resting animal. The observations, however, did not seem to support this assumption.
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trained to wear a clear plastic hood over its head for metabolic measurements.

Rhesus monkeys were similarly prepared with thermodes in two rows 3 mm to the left and 3 mm to the right of midline at 12.5, 15.0 (level of the anterior commissure), and 17.5 mm anterior to the ear bars.

RESULTS

Hypothalamic, rectal, ear skin, and trunk skin temperatures on resting dog exposed to hot, neutral, and cold environments. Temperatures and notes on respiration rate and shivering are recorded in Figs. 1 and 2 for two runs on separate days on the same dog. The dog still had its winter underfur although living in heated animal quarters for 2 months. In the convective environment within the animal chamber, the neutral temperature for this dog was about 25°C. For the first 33 min of the record in Fig. 1, the dog rested quietly at 27°C. The high ear temperature indicates that the animal was vasodilated. The air temperature was raised to 35°C, which shortly thereafter initiated panting. With respiration rates in excess of 250 breaths/min, the dog was usually able to lower its hypothalamic and rectal temperatures. At an air temperature above 45°C the dog, by panting, dropped its hypothalamic temperature from 38.5°C down to 38.1°C. Both hypothalamic temperatures in Fig. 1 were recorded at the level of and below the anterior commissure.

In Fig. 2, the dog was again started in a warm environment of 27°C. Here is illustrated an event often seen in animals in neutral or warm environments (but not in cold). When the head was down, the hypothalamic temperature was lower than when the head was held up. The difference may be as much as 0.5°C and a decreasing temperature never elicits shivering nor does an increasing temperature elicit panting. The temperature of the hypothalamus is determined principally by its rates of heat production and heat gain or loss from the blood perfusing it. The time-dependent parameters affecting the temperature are heat production in, temperature of the blood entering, and rate of blood flow through the hypothalamus. The change in the hypothalamic temperature in Fig. 2 was probably not due to changes in the arterial blood temperature, since the hypothalamic temperature was changing so rapidly and there was no concomitant change in rectal temperature. The changes in temperature might be partly explained by changes in the blood flow rate of the brain stem. The falling hypothalamic temperature was, however, associated with drowsiness and sleep when the animal put its head down. Serota has suggested that the lowered brain temperature in the sleeping cat is due to a lower cell metabolism rather than to any marked change in blood flow, indicating that sleep may be associated with a decreased rather than an increased heat production of the hypothalamus.

At 58 min (Fig. 2A) the air temperature was dropped
from 27 to 10°C. Within 30 min, traces of shivering occurred at a hypothalamic temperature of 38.5°C. The shivering was not vigorous enough to prevent a decline to 38.1°C. Note that, in Fig. 1, the animal exposed to heat was panting at the same and even lower hypothalamic temperatures. The animal can shiver enough to regain hypothalamic temperature, as seen at 120-150 min in Fig. 2A.

Figure 2B is a continuation of Fig. 2A. Starting at 167 min, the air temperature was increased to 45°C. The hypothalamic temperature passively increased to 38.6°C with no panting; 45 min later the dog was panting vigorously, although the hypothalamic temperature was down 0.1°C, to 38.5°C. Note, this is no higher than it was when the animal was shivering vigorously; also, it is 0.4-0.5°C higher than it was in Fig. 1 when the same dog was panting no less vigorously and had no higher skin temperature.

Hypothalamic temperature of monkey exposed 24 hr to hot, neutral, and cold environments. The hypothalamic temperature of a rhesus monkey exposed for 24 hr to a hot environment (35°C), neutral environment (30°C), and a cold environment (20°C) is seen in Fig. 3. The relative humidity was held to 50% at each temperature. On each of these 3 days, the light in the climatic chamber was turned off at 1800 and turned on again at 0900. After 0615, 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 8 months, since the time 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 ± 0.3°C for all environmental temperatures. In each instance, soon after the light was turned on, 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 2 hr 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, and the daytime temperature was achieved by about 1000.

Hypothalamic and ear pinna temperature of monkey alternately sleeping and waking. 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 (Fig. 4). 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 tem-
temperature increased each time its eyes opened during 7 hr 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 (17). Clearly the temperature regulator is modified by going to sleep or waking up again.

Thermal and metabolic responses of a resting dog exposed to neutral and cold environments with thermal clamp on hypothalamus. For a full hour, the dog studied in Fig. 5 rested quietly in a warm 30 °C environment and its metabolism was basal at 1.6 kcal/kg hr. At time 5 min, the thermodes were perfused with 44 °C water which elevated the hypothalamic temperature to 39.3 °C at the point measured. This did not affect the skin temperatures, since they were already high. The metabolism was only slightly diminished and respiration rate was doubled so that the rectal temperature started to fall. Fifteen minutes later, the air temperature was dropped from 30 to 14 °C. Although the animal did not appear to vasoconstrict (the ear temperature was held at 30 °C), the skin temperatures fell 5–5 °C and there followed a good 50% increase in heat production by shivering. This shivering must have resulted from extrahypothalamic receptors, from skin receptors, or core receptors stimulated by a core temperature of 37.5 °C (or lower) acting upon the regulator, despite an extraordinarily warm hypothalamus. At 45 min the thermal clamp was shut off. The hypothalamic temperature quickly fell to 37.2 °C, which is about 1 °C below normal for the dog, and the heat production increased to four times basal.

At the same time the ear vessels vasoconstricted, since the skin temperature curve turned sharply downward. As the hypothalamic temperature increased rapidly to above 38 °C, the heat production markedly diminished to 25–50% above the resting level.

DISCUSSION

Any current description of the mechanism of temperature regulation in homeotherms should account for the following observations:

1) Whenever an animal is placed in a hot or a cold environment, its hypothalamic temperature changes very little and may, in fact, be higher in a cold environment when it is shivering than in a hot environment when it is panting.

2) The steady-state hypothalamic temperature may be lower when asleep at night than during the day in all environments by an amount depending on whether it is hot, neutral, or cold.

3) At the onset of sleep there is an immediate increase in the rate of heat loss even though the hypothalamic temperature is falling as a result of the increased heat loss and, possibly, reduced heat production. Conversely, upon awakening from sleep, there is an immediate reduction in the rate of heat loss in spite of and resulting in a rising hypothalamic temperature.

4) The thermoregulatory mechanism is responsive to physiological changes in its own temperature. Few will doubt that an elevated hypothalamic temperature will increase heat loss. Figure 5 clearly demonstrates that a fall in hypothalamic temperature to no more than 1 °C below the daytime normal will elicit a fourfold increase in the rate of heat production in a cool environment.

Thus, an adequate description of the central temperature controller must account for its sensitivity and responsiveness to physiological or experimental displacements in its own temperature. At the same time such a description must account for a response of the central controller to external thermal stress when there is no change in its own temperature and, finally, the description must allow for a response which is the reverse of the normal response during the transition from wakefulness to sleep or vice versa, and for normal responses during wakefulness and sleep even though the temperature of the central controller during sleep may be as much as 2 °C lower than in wakefulness.

We would now like to propose another control equation as an alternative to equation 1 which was suggested to us by the above observations.

The proposal is that temperature regulation is achieved, by and large, by proportional control and that all thermal responses regulated through the hypothalamus are described by essentially the same expression, which is

\[ R - R_e = \alpha_R (T_h - T_{wd}) \]

where \( R - R_e \) is the response (shivering, panting or sweating, skin blood flow, etc.), \( T_h \) is the hypothalamic temperature, \( \alpha_R \) differs only in magnitude for each response and is positive for heat-dissipating responses and negative for heat-conserving and heat-producing responses, and is never 0 for the living, unanesthetized, nonhibernating homeotherm. Since the form of the equation is the same for all responses, we propose that the same controller is involved in all responses and that
it is located in the anterior hypothalamus where it drives heat loss and heat production centers located in the anterior and posterior hypothalamus, respectively. Finally, we propose that all known factors which influence temperature regulation have their effect either by adjusting the set point, \( T_{\text{set}} \), or by adjusting \( \alpha_n \). Thus the functional set temperature, \( T_{\text{set}} \), is conceived as an intrinsic hypothalamic set temperature, plus a temperature-dependent term derived from the cold receptors in the skin, minus a term derived from the warm receptors in the skin, minus a term dependent upon the core temperature, and plus a term which is not zero when awake.

At present, there appears to be no need to have \( \alpha_n \) adjustable, although additional observations may also require this.

All of the above observations are readily described by a proportional controller which has evolved in such a way to permit its set point to be modified by skin temperature, core temperature, state of consciousness, etc. Indeed, it is a device by which the load error for driving a thermoregulatory response is achieved not by requiring the regulated hypothalamic temperature to deviate greatly from an invariant set point, but rather by offsetting the set point according to needs of the organism. Thus, by this thesis, when the skin temperature falls in a cold environment, the steady-state and phasic firing rate of cold receptors in the skin increases (16) and elevates the set point so that the hypothalamic temperature, without changing, would be below the set point and would drive heat conservation or increase 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 (16) and would, thereby, lower the set-point temperature below the hypothalamic temperature and drive increased 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. We have already shown that alternate heating or cooling of the hypothalamus alone alternately increases heat loss or heat production, having the effect of alternately increasing or decreasing heat storage at about equal rates (11).

The carefully executed steady-state data from Beuzinger's laboratory clearly indicate that the set point is adjusted by the skin temperature (4) so that the lower the skin temperature the higher is the set temperature for increased heat production by shivering and, likewise, the higher the skin temperature the lower the set temperature for sweating in man. There is some difficulty in interpreting his results, which were obtained by relating sweat rate to tympanic membrane temperature, since the data were compiled from resting and exercising man. At present, it is not known to what extent increasing exercise decreases the set point or perhaps also increases the proportionality constant, \( \alpha_m \).

There is an increasing amount of evidence that thermal receptors in the core (5, 11, 26) or in veins draining active muscle (19) may also be effecting temperature regulation. Again, we are proposing that this effect be achieved by adjusting the set point; that is to say, a lowered core temperature would increase the set point and a raised core temperature would lower the set point.

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 some dramatic change has occurred in the regulation of body temperature. The only question is whether the set-point temperature has decreased (9), or whether the responsiveness of the controller, $\alpha_k$, has decreased.

The hypothalamic temperature of the dog during the night was found to be below 37.0°C when the animal was presumably asleep. Similarly for a monkey, when the light was turned off at 1800, the hypothalamic temperature fell in 2 hr from the daytime temperature of about 39.0°C to below 37.0°C, and remained so throughout the night in a neutral environment. A similar observation has also been described by Hamilton (10).

The regulation of the hypothalamic temperature of the monkey in the daytime in hot, neutral, and cold environments is diagrammed in Fig. 6. In the day neutral environment the set temperature is shown to be 39.0°C and the actual temperature is about the same; that is, zero load error and no regulating responses. In the hot environment, the set point would be lowered according to our hypothesis. Only a slight (or no) increase in hypothalamic temperature would suffice to drive heat loss mechanisms to maintain the hypothalamic temperature constant throughout the day. In the cold environment, the set point would be increased so that if the hypothalamic temperature remains the same or even increases a little there is sufficient load error to drive shivering and prevent a fall in hypothalamic temperature.

For comparison, the actual and set point temperatures during the night are also shown. In the neutral environment the set point has dropped 2°C from what it was during the day, but it also has the actual hypothalamic temperature and there is zero load error. It is suggested that, in the hot environment, the decrease in the set point during the night was not so great as in the neutral environment, due to a greater difficulty in sleeping in the heat. Nevertheless, the set point was about the same as in neutral environment because it was also lowered by an increased skin temperature. The actual temperature was above the normal set point by a load error sufficient to produce an amount of heat loss to maintain a constant temperature of about 38.0°C. Note that the day and night load errors in the hot environment were chosen to be about the same. In the cold environment, sleep was again more difficult. Also, the cold skin had the effect of raising the set point so that it was high. The actual hypothalamic temperature was 37.5°C during the cold night or enough below the set point so that the load error would drive enough shivering to maintain a constant hypothalamic temperature. The load error in the cold at night was chosen to be about the same as the load error in the cold during the day.

An alternate suggestion might be that the onset of sleep does not lower the set point, but that by some means the gain of the regulatory mechanism is reduced. However, 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 whereas, in fact, 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 better 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.

A drop in the set-point temperature in sleep would account for a number of interesting thermoregulatory phenomena associated with going to sleep. A rapid fall in the rectal temperature of 1°C or more during the first hour or two of sleep in both Europeans and primitive men has often been observed in studies on cold acclimation while exposing them to moderate cold at night (12, 17, 23). The falling rectal temperature is often accompanied by a rapidly rising foot temperature, followed by vasoconstriction and a falling foot temperature. In warm environments, the rectal temperature of both European and primitive men also fell rapidly during the first hour of the night and was always accompanied by a very fast rising foot temperature and average skin temperature. In studies on sweat rate of resting men in hot environments, sweating was often noticed to increase when the subject became drowsy and fell asleep (25).

By a simple assumption, the elevation of body temperature in fever may be accounted for (18). The endogenous pyrogen may act by raising the set point. Regulation would now be in all ways normal except in one; namely, the hypothalamic temperature would be elevated by the amount of the fever in all instances. Heating the hypothalamus will produce panting and cooling will produce shivering or, if during the chill phase the hypothalamus is heated, no fever develops until the local heating is terminated. Similarly, if the hypothalamus is locally cooled during the chill phase, a hyperfever is produced so that when cooling stops the dog pants to restore the hypothalamic temperature to the fever level (1).

A formal statement offering a description of a function of the central nervous system should be accompanied by at least one plausible scheme showing how neurons may be connected to achieve the relationships stated in the formal equations. Therefore, we have proposed and described in some detail (19) a scheme based on the assumption that there are in the anterior hypothalamus two sets of temperature-sensitive neurons both of which increase their activities (firing rate) with increasing temperature, as described by Nakayama et al. (20, 21).

The only difference between the two sets of neurons is that they have widely different $Q_{10}$ relating firing rate to temperature, and the set of sensors having the higher $Q_{10}$ provides facilitation to effector neurons subserving shivering and inhibition to effector neurons subserving thermoregulation and heat conservation. Conversely, the set having the lower $Q_{10}$ provides facilitation to neurons subserving shivering and inhibition to neurons subserving heat dissipation. When the temperature of the sensors is at the set-point temperature, that is, the temperature at
which the activity curves of the two sets of neurons intersects, then the firing rates of both sets of neurons are equal so that the facilitation of one set equals the inhibition of the other set and the activity of the common effector neuron is zero. These then are the necessary conditions for establishing an intrinsic reference temperature for the regulation of body temperature.

Adjustment of the set point was achieved in our scheme by proposing facilitation of the sensor neurons. Afferents from skin receptors which have a low, steady-state discharge at neutral skin temperatures, when cooled (16), were suggested to facilitate the set of sensor neurons of low $Q_{10}$. Likewise, afferents from the reticular activating system of the brain stem, which has its upper end in the posterior hypothalamus and lower thalamus, were proposed to facilitate the low-$Q_{10}$ sensors (27). Afferents from skin receptors which give a phasic discharge with rising skin temperature and a steady-state discharge at very high skin temperatures (above 37 C) (16) were proposed to facilitate the high-$Q_{10}$ sensors. Thus, by increasing or decreasing facilitation of the low-$Q_{10}$ sensors, the set-point temperature would be raised or lowered. Likewise, increasing or decreasing facilitation of the high-$Q_{10}$ sensors would, in this scheme, lower or raise the set point. By this scheme, or others, temperature regulation by proportional control with a set point adjustable by skin temperature, sleep, etc., is plausible. If temperature regulation in homeotherms could be demonstrated to occur by means of the equivalent of a proportional controller with an adjustable set point, then there would be some encouragement for investigating the applicability of this type of system to other physiological control systems, e.g., respiration.

REFERENCES