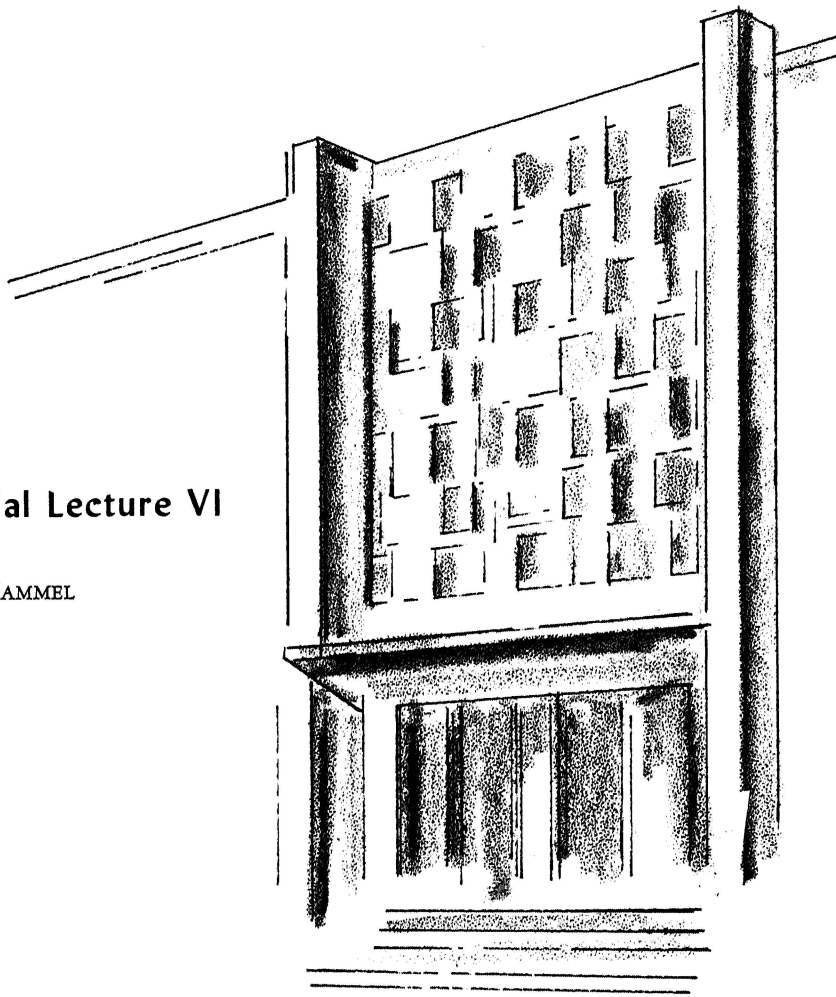
The Regulator of Body Temperature



Brody Memorial Lecture VI

H. T. Hammel

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University of Missouri

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DR. H. T. HAMMEL—BIOGRAPHY

H. T. Hammel was born in Indiana in 1921. He began his academic career at Purdue University where he was graduated in physics in 1943. He was invited to the Manhattan District's Los Alamos Laboratory where he worked in the Experimental Physics Division on nuclear reactors.

While obtaining an M.S. degree in Physics at Cornell University, he was attracted to Professor Donald R. Griffin from whom he subsequently obtained a Ph.D. in Zoology in 1953. Since graduating, his interests and development have ben strongly influenced by two other distinguished physiologists, Professor P.F. Scholander, Scripps Institution of Oceanography, and Professor James D. Hardy, University of Pennsylvania. He moved from Philadelphia to New Haven with Dr. Hardy and was appointed Fellow of the John B. Pierce Foundation Laboratory and head of the working group in physiology.

His major work has been in thermal physiology where his interests range from thermal regulation in dogs, rats, monkeys, and hibernators to responses to thermal stress in camel, reindeer, and jack rabbit; and on a cold adaptation in several ethnic groups of man including Australian Aborigines, Alacaluf Indians of Tierra del Fuego, Kalahari Bushmen, Eskimos, and Norwegian youth.

His interests have been broadened by frequent collaborations with Dr. Scholander. Most recently, with Dr. Scholander, he has developed a simple technique for measuring the negative hydrostatic pressure in the xylem sap of plants, providing direct evidence of tension in the sap of tall trees, mangrove trees, and desert plants.

Memberships: American Physical Society, American Society of Mammalogy; American Physiological Society, American Society of Zoologists.

Some recent publications are:

Jackson, D. C., and H. T. Hammel. Hypothalamic "Set" Temperature Decreased in Exercising Dog. *Life Sciences* No. 8, pp. 554-563, 1963.

Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk, J. D. Hardy, and S. B. Stromme. Temperature Regulation by Hypothalamic Proportional Control with an Adjustable Set Point. *J. Appl. Physiol.,* 18, No. 6:1146-54, Nov., 1963.

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Chowers, I., H. T. Hammel, S. B. Stromme, and S. M. McCann. Comparison of effect of environmental and preoptic cooling on plasma cortisol levels. *The American Journal of Physiology,* Vol. 207, No. 3. Sept., 1964. pp. 577-582.

Scholander, P. F., H. T. Hammel, Edda D. Bradstreet, and E. A. Hemmingsen. Sap Pressure in Vascular Plants. *Science,* April 16, 1965. Vol. 148, No. 3668, pp. 339-346.

Hammel, H. T. Neurons and Temperature Regulation. Physiological Controls and Regulations, Chapter 5. William S. Yamamoto and John R. Brobeck, Editors.

Hardy, J. D., J. A. J. Stolwijk, H. T. Hammel, and D. Murgatroyd. Skin Temperature and cutaneous pain during warm water immersion. *Journel of Applied Physiology,* Vol. 20, No. 5, September 1965.

Abrams, R. M., J. A. J. Stolwijk, H. T. Hammel and H. Graichen. Brain Temperature and Brain Blood Flow in Unanesthetized Rats. *Life Sciences,* Vol. 4, pp. 2399-2410, 1965.

Schmidt-Nielsen, K., T. J. Dawson, H. T. Hammel, D. Hinds and D. C. Jackson. The Jack Rabbit—a study in its desert survival. *Hvalradets Skrifter,* Nr. 48: pp. 125-142, 1965.

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The Regulator of Body Temperature

Presented February 17, 1966, University of Missouri

by

H. T. HAMMEL
John B. Pierce Foundation Laboratory
New Haven, Connecticut

There are many ways to begin a discussion of the regulation of an animal's body temperature, but on this occasion I think it is appropriate to begin with a quotation from Bioenergetics and Growth (p. 265), "Homeothermy has many aspects, theoretical, agricultural and engineering. The theoretical aspect is concerned with homeothermic mechanisms; the agricultural with the influence of environmental temperature and humidity on productivities and efficiencies of farm animals; the engineering with ventilation, heating and cooling." In a wry note, Professor Brody continues—"We shall discuss each of these. The theoretical and numerical discussions are presented in small type, the practical and general in large type." My discussion tonight will be presented in *very small* type because it is not only theoretical but also speculative.

I would like to orient you by reference to a generalized model of a regulating system as it pertains to body temperature, Figure 1. You will quickly recognize that Professor Brody and his colleagues have spent and his colleagues are spending an enormous amount of effort working the right side of this model.

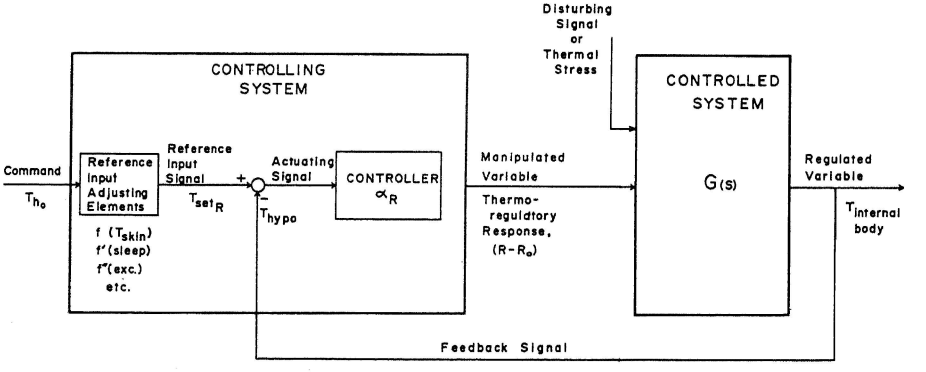

Fig. 1—Block diagram for regulation of hypothalamic temperature.

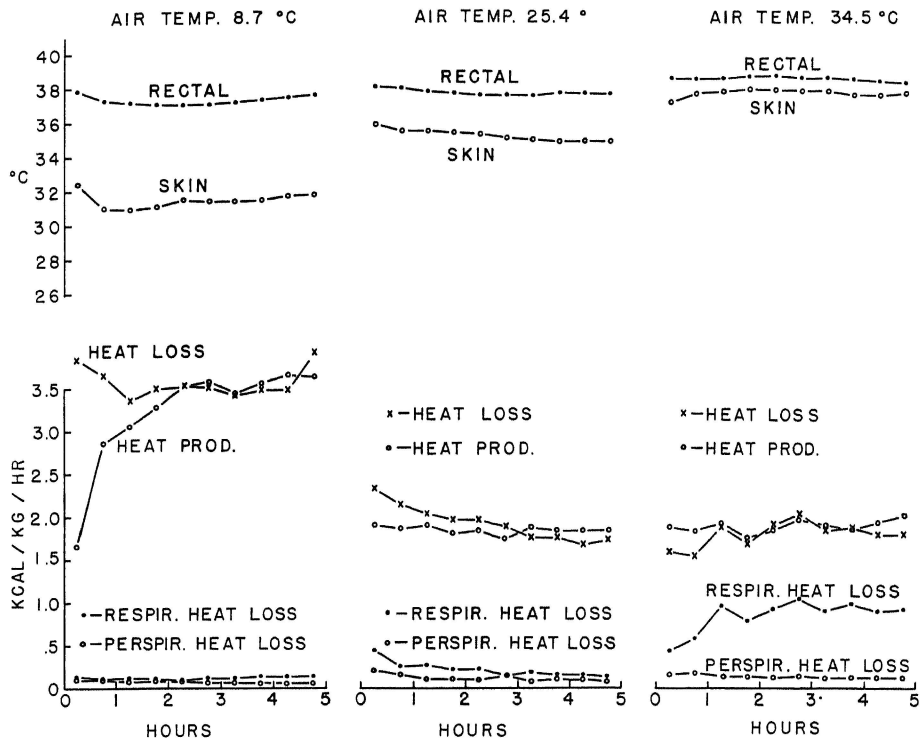

Fig. 2—Heat production, total heat loss, evaporative heat loss from mouth and from skin surfaces averaged over half hour periods, and rectal and average skin temperature for a resting dog in a cold, neutral, and warm environment. (Hammel, H. T., C. H. Wyndham and J. D. Hardy, 1958.)

They have been particularly concerned with quantitative measurements of the thermoregulatory responses which the animal makes to various internal and external thermal stresses. This information is essential for the rational management of economically productive animals.

For other less practical reasons, we, too, have investigated by indirect and direct calorimetry the thermoregulatory responses of the resting dog to a range of environmental temperatures. Those responses of the dog which could be measured calorimetrically were plotted as a function of the time exposed to a hot, a neutral, and a cold environment (Figure 2).

In Figure 3, the steady state responses are plotted as a function of external environmental temperature. Here again these data are pertaining to the right side of the model in Figure 1. They may provide some information about the controlled system; about how its transfer functions relate the manipulated variables and the disturbing signals to the regulated variable, that is to say, the thermoregulatory responses and the thermal stresses to the internal body temperature.

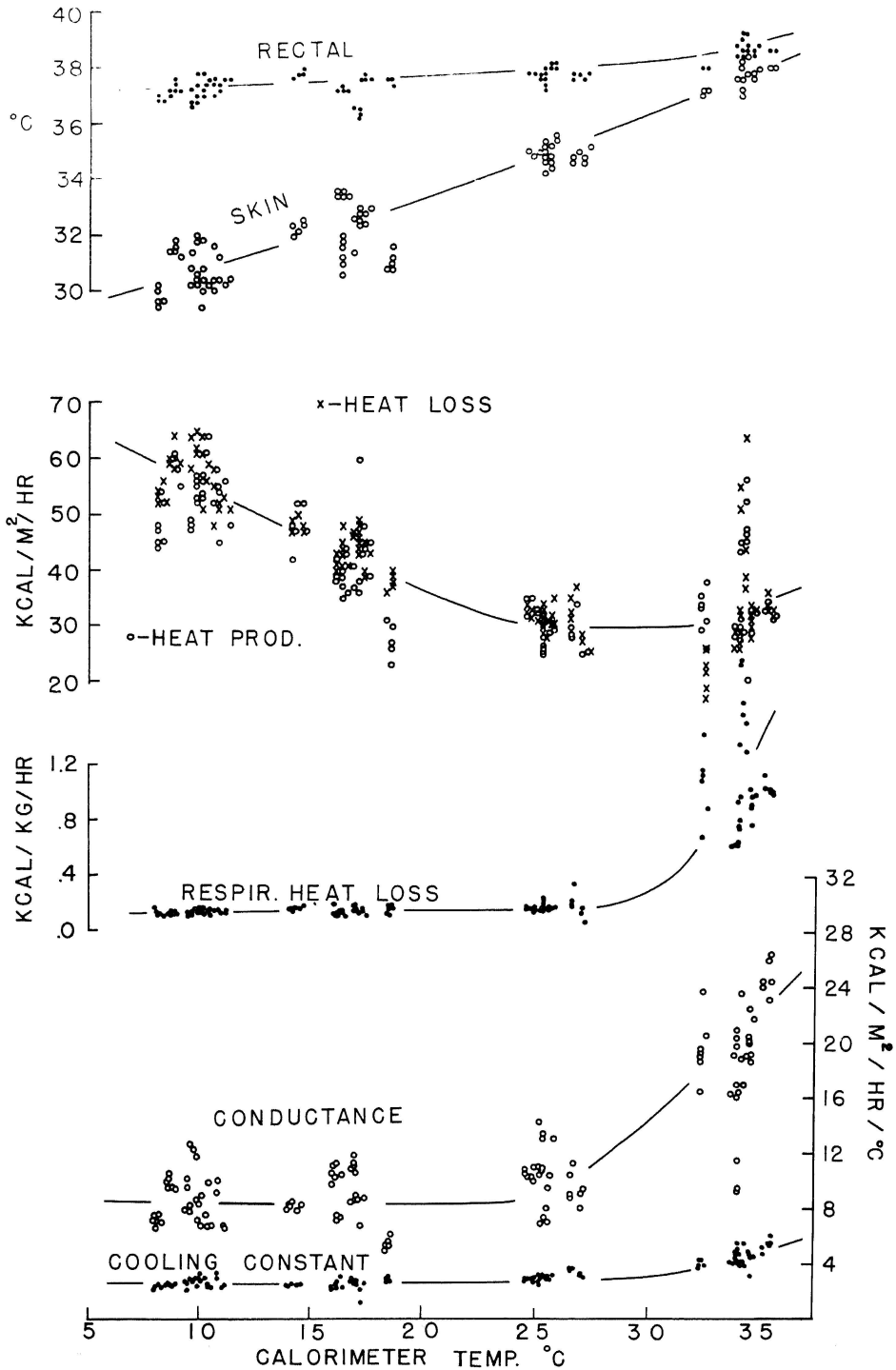

Fig. 3—Equilibrium values of heat loss, heat production, evaporative heat loss from mouth, rectal, and average skin temperatures, tissue conductance, and cooling coefficient of fur and overlying air over a range of environmental temperatures from 10° to 35° C. (Hammel, H. T., C. H. Wyndham and J. D. Hardy, 1958.)

At the very least, some of the thermoregulatory responses have been identified and quantified by these studies. Shivering is identified as oxygen consumption and equated to heat production. Panting is identified as respiratory evaporative heat loss. Variable peripheral blood flow is identified by its effect upon the thermal conductance of the tissue between the core and the skin surface. Heat transfer from the external body surface is identified as the difference between total heat loss and respiratory evaporative heat loss. The rate of change of heat content may be identified as the difference between heat loss and heat production. Air temperature is identified as one of the external thermal stresses and rectal temperature is indicated as one of the internal body temperatures and therefore a possible candidate for the regulated variable. The graphs provide some of the transfer functions that are involved within the controlled system.

This aspect of temperature regulation still demands further exploration to derive more sophisticated and detailed data and relationships describing (1) heat content of components of the body, (2) heat transfer characteristics from one component to another, (3) heat transfer characteristics from each part of the body surface to the environment, as well as (4) parameters of the physical environment.

I would like now to turn our attention to the other half of the model depicted in Figure 1, the controlling system.

Methods

Slowly we realized that little can be learned about the controlling system from the type of steady state data represented in Figure 3. Although we intuitively presumed that temperature sensing elements in the skin surface and in the core of the body somehow generate the regulatory responses, we could learn nothing about this process from the skin and rectal temperatures and the correlated steady state responses as we had plotted them. We realized that we had to use some technique for dissociating the several sensory inputs to the controlling system from one another so that one sensory input at a time could be varied and related to the regulatory responses while all other inputs remained unchanged.

Benzinger and his co-workers discovered one technique for achieving a partial dissociation of body temperatures in his extensive investigations on man (Benzinger, Kitzinger, and Pratt, 1963). By taking advantage of the natural or induced variations in three inter-related parameters, the evaporative heat loss by sweating, the tympanic membrane temperature, and the average skin temperature, and then extracting from these data a set of data (sweat rate vs. tympanic temperature) for one skin temperature and another set of data for another skin temperature, and so forth, over a range of skin temperatures, they were able to plot the sweating rate as a function of tympanic membrane temperature for each of several average skin temperatures even though the environmental temperature was in steady state. Unfortunately, for their results on sweating, they had to in-

duce variation in internal temperature by introducing exercise as a disturbing signal.

To relate the shivering response to tympanic membrane temperature, Benzinger *et al.,* immersed their subjects in stirred water, achieving thereby a constant skin-temperature, and again took advantage of natural and induced variations in the tympanic temperature.

Stolwijk and Hardy (1966) have used another dissociating technique. They monitor the metabolic rate and sweating rate continuously both before and after a step transition from one environmental temperature to another. Thus, in these investigations on man, it has been possible to dissociate skin temperature from internal temperature but, so far, it has not been possible in man to dissociate the effects of one internal sensory site from another. It would be especially desirable to dissociate the hypothalamic temperature from the other internal temperatures where sensory inputs are almost certainly generated and fed into the controlling system.

Concurrently, and over the past few years, we, too, have attempted to dissociate the sensory inputs by controllably manipulating the hypothalamic temperature by artificial means while recording the thermoregulatory responses in the conscious and wakeful dog. Figure 4 depicts the experimental system into

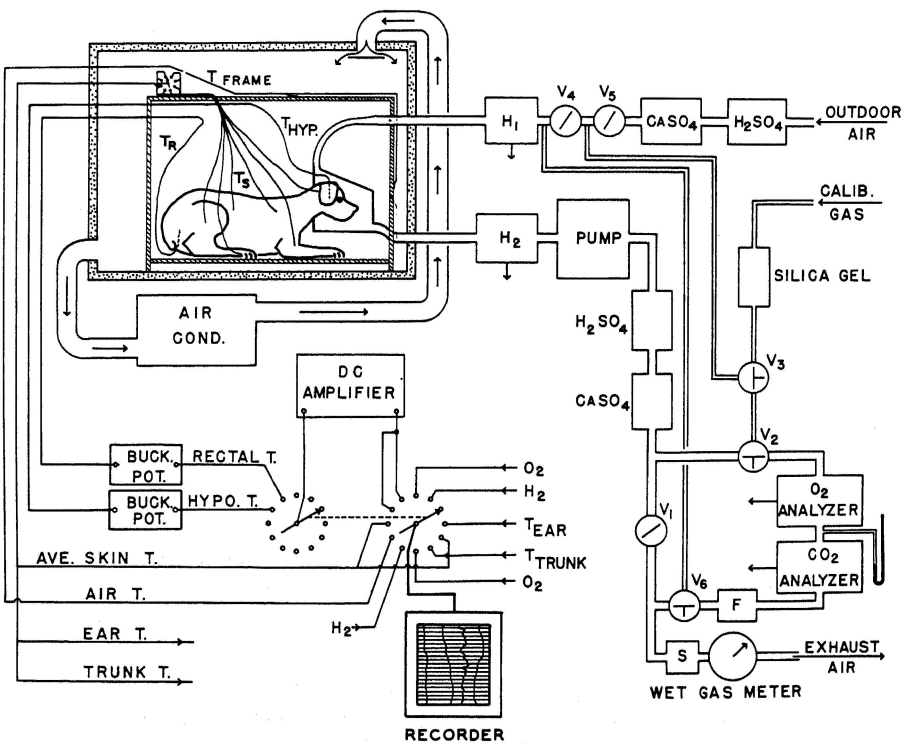

Fig. 4—System for recording oxygen consumption, evaporative heat loss from mouth, rectal, skin and hypothalamic temperatures, air temperature and temperature of stimulating water in head circular. (Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk and J. D. Hardy, 1963.)

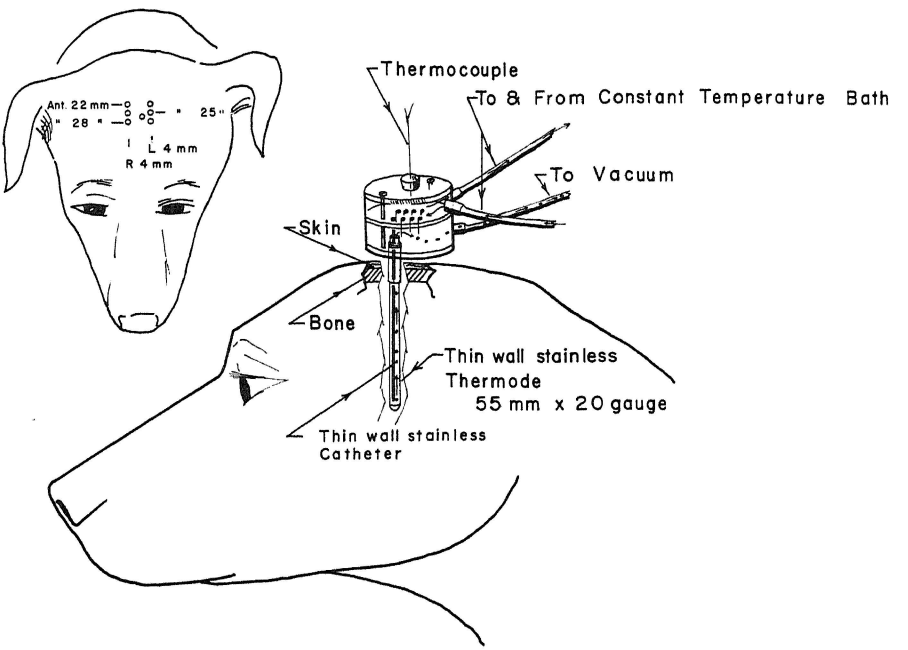

Fig. 5—Details of thermode (or re-entrant tube) and circulator construction. The circulator is shown in place for thermal stimulation of the hypothalamus. Only the lower acrylic plate or bottom of the circulator is left permanently attached to the thermodes and guides by epoxy resin. (Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk and J. D. Hardy, 1963.)

which the dog is introduced for monitoring its regulatory responses. Long and arduous training is required to train the dog to accept the experimental procedure without discernible emotional reaction even though there is never any pain or even discomfort associated with the experience. Up to two years prior to experimentation, the dogs were implanted with seven thermodes surrounding the pre-optic area and anterior hypothalamus as depicted in Figure 5. About 150 ml/min of water at any selected temperature perfuse the thermodes during an experimental period. The small plastic circulator with its thin wall stainless catheters (0.015 "ID and 0.019" OD) projecting into the thermodes is shown mounted above the thermodes and on the head. In addition, a re-entrant tube passes through the brain to the anterior commissure and 1 mm from the midline. A thermocouple is introduced into this tube to monitor the temperature of the hypothalamus. A cross section through the brain stem at a level of 25.5 mm anterior to the stereotaxic ear bars, Figure 6, clearly shows how the pre-optic tissue between the optic chiasm and anterior commissure is straddled and surrounded by thermodes. Although the damage to the hypothalamic tissue is minimal and negligible after a recovery period of one week, there is an obvious

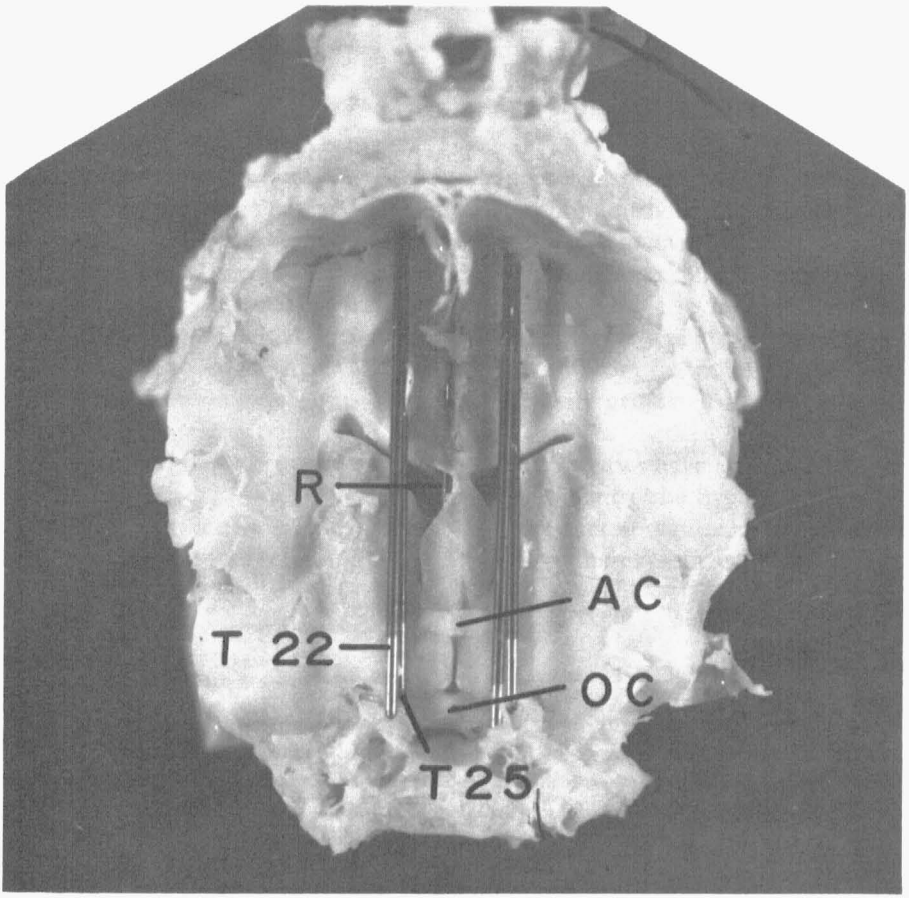

Fig. 6—Section through the brain of dog at 25.5 mm anterior to stereotaxic ear bars showing AC, anterior commissure; OC, optic chiasm; T25, thermode at 25.0 mm; T22, thermode at 22.0 mm; and R, re-entrant tube at 26.5 mm, left 1.0 mm from midline.

limitation to this method of thermal stimulation of the hypothalamic tissue. Heat is transferred to (and from) the tissue from (and to) the thermodes by conduction through the tissue and by the blood perfusing this highly vascular area. There are, therefore, unavoidable temperature gradients throughout the tissue whose response is investigated. Furthermore, since we are unable to control the position of the thermodes with respect to the major vessels subserving the pre-optic region, we cannot predict the pattern of the isotherms through the tissue, nor can we say how the one temperature measured in the re-entrant tube relates to the average pre-optic temperature. I have dwelt briefly on this technical limitation, since I shall have to refer to it again in order to explain some bizarre re-

sponses observed when the pre-optic temperature is greatly displaced (as much as 5° C) from the internal blood temperature.

The Regulated Temperature

In an inconspicuous way, I have introduced one major assumption which requires further comment. I have inferred that the temperature of the hypothalamus is the regulated internal body temperature. Actually, I can only expect to convince you by direct evidence that it is an important temperature input to the controlling system. That the hypothalamic temperature is the regulated temperature of the body can only be inferred from its relationships to other body temperatures and the thermoregulatory responses.

Any recent review of temperature regulation (Hardy, 1961; von Euler, 1961) is replete with evidence that sizeable displacements of the hypothalamic temperature (3° to 5° C) will activate panting or shivering in many species (unanesthetized); and if the displacement is great enough (5° to 20° C), Andersson's group have shown that neuro-humoral responses are activated with obvious thermal consequences (Andersson, Gale, and Hokfelt, 1964). In a way, Figure 7 may serve to summarize the evidence that the rostral hypothalamus is sensitive and responsive to small displacements of its own temperature. The widely swinging

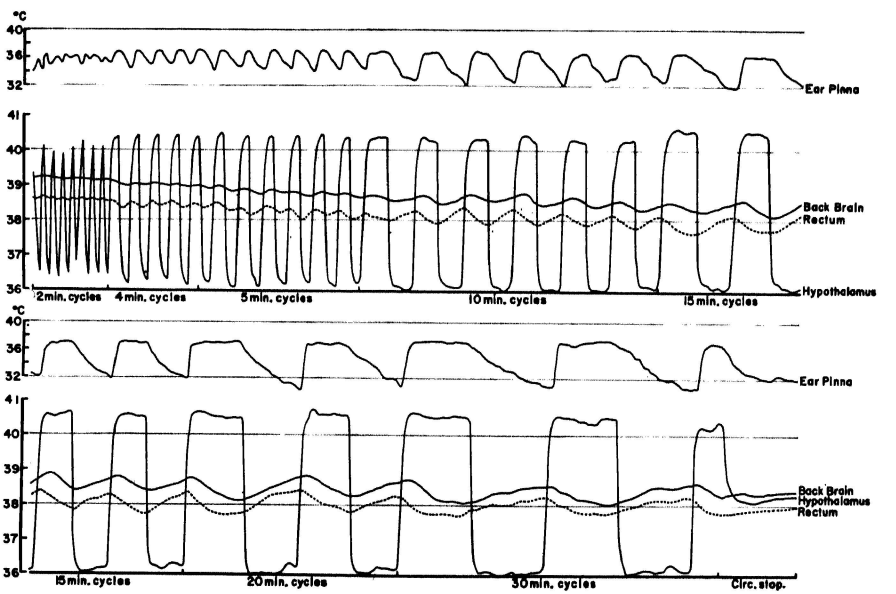

Fig. 7—Cyclic heating and cooling of hypothalamus with water perfusing thermodes alternately at 41.0° C and 35.0° C. Ambient temperature was 25° C. The 30 minute cycle equals 15 minutes heating and 15 minutes cooling. (Hammel, H. T., S. B. Stromme, and R. W. Cornew, 1963.)

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 7) 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 rising 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 by equal amounts below or above its unperturbed level.

We conclude from this that the anterior hypothalamus is responsive to both heating and cooling and with equal sensitivity to moderate heating and cooling. We may also note that the response time of the controlling system is less than one minute, i.e., within a minute after the hypothalamic temperature decreased, the ear pinna temperature begins to decrease and begins to increase after the hypothalamic temperature is increased. This example illustrates that the controlling system, as well as the system which is controlled, namely the vasomotor response, possess a rapid response time. The example also illustrates that the rate of change of internal temperature following a step change in hypothalamic temperature is greatest initially and gradually diminishes 10 to 15 minutes after the hypothalamic temperature change.

If we are convinced that induced deviations of the hypothalamic temperature by a few degrees above and below some normal value do activate appropriate thermoregulatory responses, we should then wonder how much the hypothalamic temperature departs from the norm during a natural thermal stress when these same regulatory responses are activated. In a neutral environment, the hypothalamic temperature is variable in a resting dog; in an average dog, it may range from 38.1° to 38.6° C during a period of a few hours. It is also variable in a hot environment and in a cold environment and in a way which is not distinguishable from the variability in the neutral environment. My colleague, Dr. B. Hellstrom, has found that the range of the hypothalamic temperature, the mean hypothalamic temperature and its standard deviation are not different in the same dog when in a hot, a neutral, or a cold environment, even though panting is vigorous in the hot environment (40° C) or shivering is vigorous in the cold environment (10° C) and there is neither panting nor shivering in the neutral environment (25° C). Of course, the hypothalamic temperature can be forced to deviate from its normal range by a stress so severe as to produce a near maximum response.

To summarize our findings so far, we believe we have established the preoptic region rostral to the hypothalamus to be a temperature-sensitive part of

the brain stem responding to moderate heating by activating heat dissipation and to moderate cooling by activating both heat conservation and increased heat production. Moderate heating and cooling may mean only 1 or 2 or 3° C above or below 38.5° C, yet we never saw deviations in the hypothalamic temperature of this magnitude when the resting animal was exposed to a range of external thermal stresses. In fact, no differences in hypothalamic temperature were produced by the environmental temperature.

Properties of the Controlling System

We now must recognize two essential features of any regulated system; these are depicted in Figure 1. First, the output of the controlled system must somehow be fed back as a signal to the controlling system. In temperature regulation, the consequence of the thermoregulatory responses and the thermal stresses acting upon the controlled system yield, after appropriate transformations, an output which is the internal body temperature. The output, or some part of it, the hypothalamic temperature, is fed back to the controlling system. Second, within the controlling system there is always some provision for generating a reference signal with which the feedback signal is compared and from which an activating signal is derived. The final consequence of the activating signal is such as to reduce the difference between the feedback and reference signals.

Recognizing that the hypothalamic temperature has no significance by itself and meaning is given to it only when there exists some mechanism for comparing it with a reference signal and from which a difference or an error signal can be generated which can activate a corrective response, we are now led to wonder about the nature of the reference signal. Is the reference signal, often called the set temperature, generated within the hypothalamus (or its associated preoptic area) so that this area by itself could regulate body temperature without additional inputs? Is the reference signal or set temperature invariant and uneffected by other known inputs to the hypothalamus or is it modified, modulated, adjusted by some or all of the inputs to the hypothalamus? What are the relationships between the activating signal and the thermoregulatory responses; are they linear? Are the relationships modified by other inputs to the hypothalamus?

Of course, these questions would be answered if we knew how the neurons in the hypothalamus and the preoptic area are interconnected and function. However, we do not know the neuron circuitry for the controlling system for temperature regulation; therefore, we are compelled to seek experimental evidence relevant to the questions and then perhaps make some reasonable guesses about the neuron circuitry.

We have undertaken to explore these questions in a systematic way in the dog and other experimental animals. We are using two approaches which yield complementary information. Our first approach is illustrated in Figure 8. For this record, the dog was awake and resting in a neutral environment and was

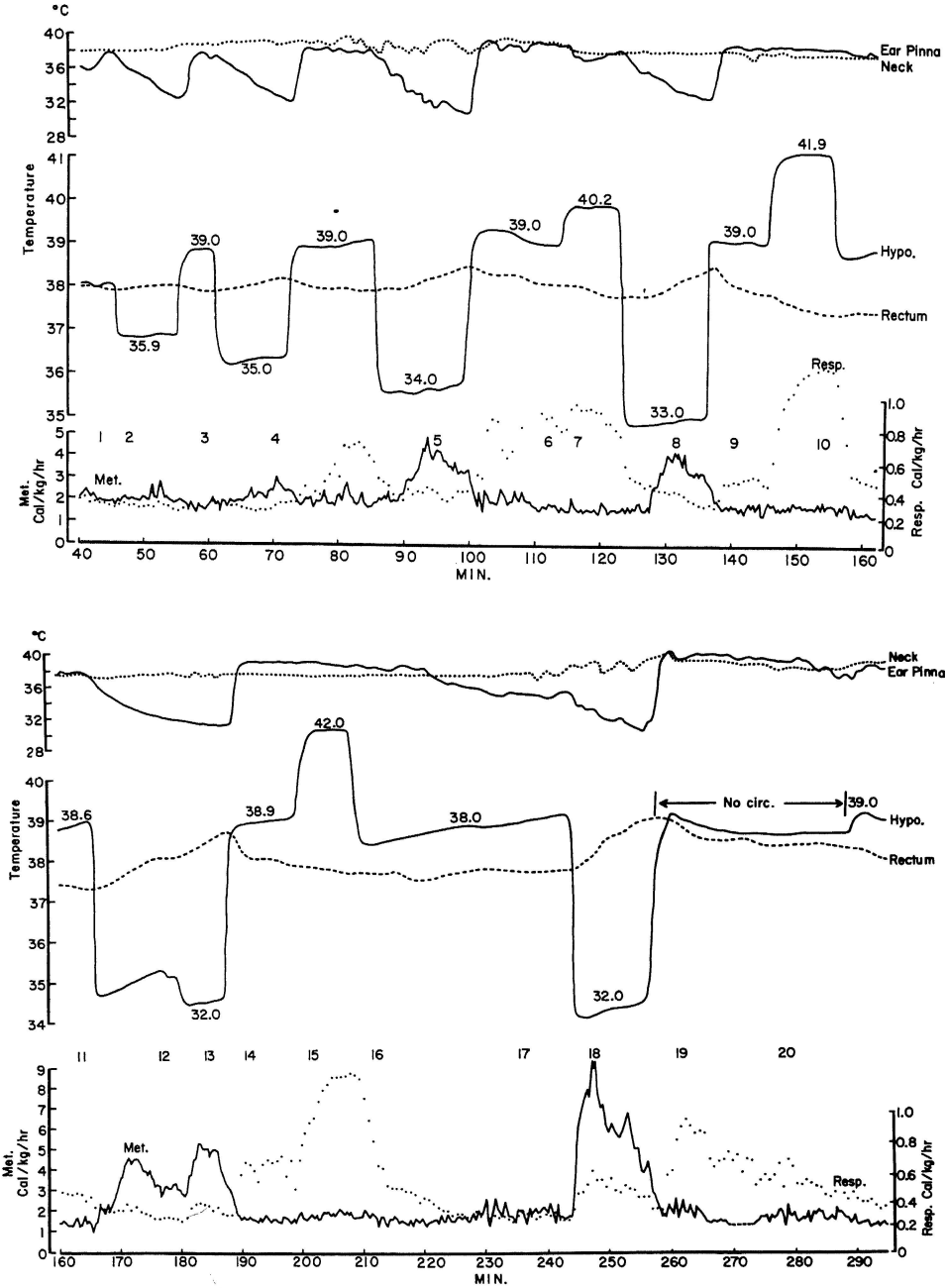

Fig. 8—Heat production, respiratory heat loss, and skin and rectal temperatures in response to heating and cooling hypothalamus. Air temperature = 23.0 ± 0.5° C from 0 to 273 min. Numbers over level segments of hypothalamic temperature indicate temperature of water circulating in thermodes. (Hammel, H. T., S. B. Stromme and R. W. Cornew, 1963.)

isolated in an environmental chamber. Its hypothalamic temperature was manipulated to several levels above and below normal for approximately 10 minutes each by perfusing the thermodes with water at the appropriate temperature (noted in Figure 8 by the number above the level segment of the record of hypothalamic temperature). The oxygen consumption and the evaporative water loss of the dog were recorded as heat production and respiratory heat loss in Kcal kg^{-1} hr^{-1}. Ear pinna, neck skin and rectal temperatures were also recorded. Since we believe that internal body temperatures (other than hypothalamic) are also sensed and provide input signals to the controlling system, each displacement of hypothalamic temperature from normal was initiated only after the rectal temperature returned to 38.1° C. For the same reason, each period of hypothalamic temperature displacement was kept short; any strongly activated regulatory response would markedly alter the internal body temperature when applied for even 10 minutes and this altered internal body temperature would, in turn, effect the activating signal.

The results shown in Figure 8 are utilized in Figure 9 where, for example, in the neutral (23° C) environment the heat production for a 3-minute interval (including the peak response) was plotted as a function of hypothalamic temperature. From this curve, two important characteristics of the regulating system may be determined for the metabolic response: (1) The threshold hypothalamic temperature above which only basal or resting metabolism was obtained and

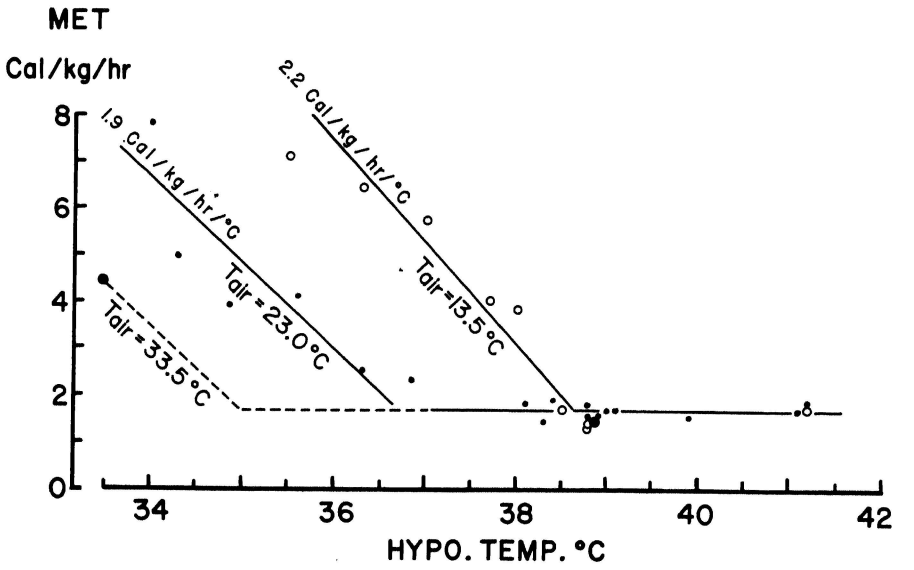

Fig. 9—Heat production as a function of hypothalamic temperatures for a quiet, resting, wakeful dog at three air temperatures, 13.5° C, 23° C, and 33.5° C. (Hammel, H. T., S. B. Stromme and R. W. Cornew, 1963.)

below which the metabolism of shivering was added and, (2) the shape of the shivering response curve for hypothalamic temperatures below threshold. For this wakeful, resting dog in a neutral environment, the threshold temperature was approximately 37° C or about 1.5° C below the unperturbed hypothalamic temperature. The shape of the response curve below threshold may be roughly approximated by a straight line with a slope of about 2 Kcal kg^{-1} hr^{-1} C^{-1}.

Repeating the same procedure that was used for Figure 8 and in the same wakeful, resting dog but in a cool environment (13° C), another set of results were obtained which are shown in Figure 9. In the cool environment, the threshold hypothalamic temperature for shivering has now increased to about 39° C. The normal range of hypothalamic temperatures is below the threshold level so that the dog shivers a little even without any artificial displacement of temperature below normal. The shape of the response curve was roughly the same as was found in the neutral environment and the slope was about 2 Kcal kg^{-1} hr^{-1} C^{-1}.

The threshold for panting was approximately 39° C in the neutral environment and about 41° C in the cold environment. The slope of the curve for the panting response was estimated to be between 1 and 5 Kcal kg^{-1} hr^{-1} C^{-1}. My colleague, Dr. Hellstrom, has thoroughly investigated the thresholds and slopes of the response curves for both shivering and panting in hot, neutral, and cold environments for dogs in the resting and wakeful state. Although his results (still unpublished) are much more extensive, they are similar in magnitude and shape to those reported here. Even though he has many more data, the variability in the activated regulatory response for a given hypothalamic temperature is no less than is evident in Figure 9, suggesting that we were either unable to control all other inputs to the controlling system or that the controlling system is inherently noisy.

Our second experimental approach for obtaining the characteristics of the controlling system is illustrated in Figure 10. In these experiments, the normal combination of hypothalamic, internal body, and skin temperatures is dissociated by prolonged displacement of the hypothalamic temperature. This leads to hypothermia or hyperthermia in the other internal body temperatures, the magnitude depending upon the environmental temperature.

In the experiment of Figure 10, the hypothalamus was heated, during which time the dog was in a neutral and then in a cold environment. The heat content of the body was markedly reduced as indicated by a decrease in rectal temperature, a decrease greater than 1° C. Upon release of the thermal clamp on the hypothalamus, the hypothalamic temperature fell approximately 2° C to assume a value slightly above the hypothermic rectal temperature. The shivering present just prior to clamp release (and which could only be attributed to some non-hypothalamic, internal body temperatures providing inputs which react in some way with the hypothalamus) was followed by a large increase in metabolism (nearly four times the resting level) just after the clamp release. Assuming that

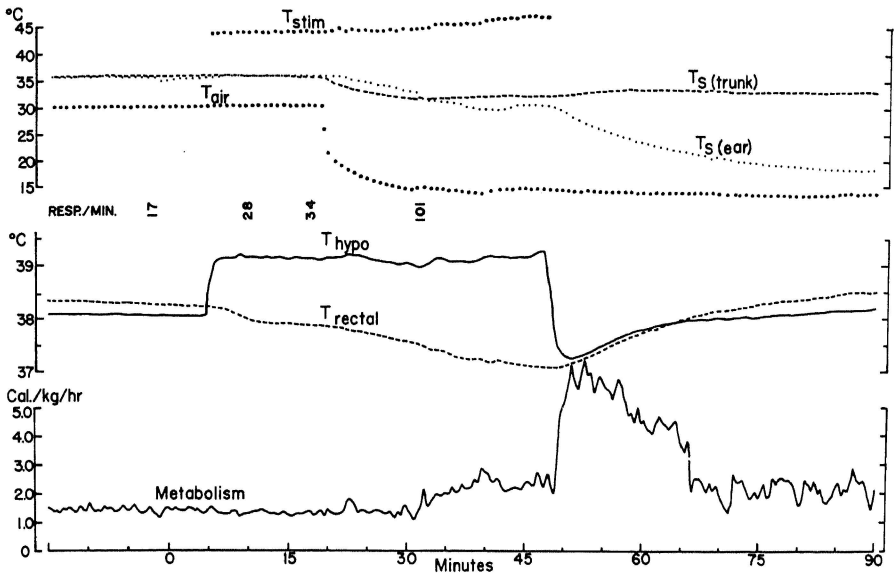

Fig. 10—Body temperatures and heat production of resting, fasting dog exposed to neutral and cold environments during manipulation of its hypothalamic temperature. (Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk, J. D. Hardy, and S. B. Stromme, 1963.)

no changes in the internal body temperature or skin temperatures occurred during the brief interval that the metabolism and hypothalamic temperature were changing from one level to the other and assuming that no other inputs to the hypothalamus changed so that the threshold for shivering was the same before and after clamp release, we can then calculate from the shivering metabolism and its associated hypothalamic temperature both before and after clamp release what the slope of a linear response curve would be. In this test, the slope was found to be 2.0 Kcal kg^{-1} hr^{-1} C^{-1}. After the slope is known, the threshold during the interval when we are assuming that it is not changing may also be calculated. It was 39.6° C in this test.

I have described two procedures whereby we can dissociate the hypothalamic temperature from the other thermal inputs to the controlling system in experimental animals and from these results determine at least roughly the threshold values and the shapes of the response curves for any thermoregulatory response under any set of experimental conditions. Eventually, we expect to obtain this information for suitable experimental animals under the following conditions: at rest and in exercise; awake and asleep; exposed to hot, neutral, and cold environments; in the normal and the fevered state; during hibernation and out; during emotional stress; during pharmacological stress; cold and heat acclimated, etc.

Adjustment of the Set Point

I would next like to anticipate some of the results to be obtained from the systematic investigation of the multifarious aspects of body temperature regulation I have just outlined. To do so, I will describe briefly some preliminary experiments which served to give direction to our experimental program.

The effects of sleep upon body temperature regulation may be anticipated by the results shown in Figure 11. The hypothalamic temperature of a rhesus monkey restrained in a primate chair was recorded during a 24-hour period of exposure to a hot (35° C), a neutral (30° C), and a cool (20° C) environment. At 1800 each day, the lights in the environmental chamber were turned off and at 0900 the next day they were on again, although daylight entered through the chamber window after 0600.

At each environmental temperature, it appears as if the thresholds for thermoregulatory responses were reduced by one or more degrees C during the dark period when, presumably, the monkey was less active and asleep. At first, we might suppose that the fall in brain temperature at the onset of sleep in the neutral and cool environments could be due to a reduced level of heat production combined with a decrease in the slope of the thermoregulatory response curves. However, if the slope of the response curves had diminished at the onset of sleep, then in the hot environment the brain temperature would have increased to a higher

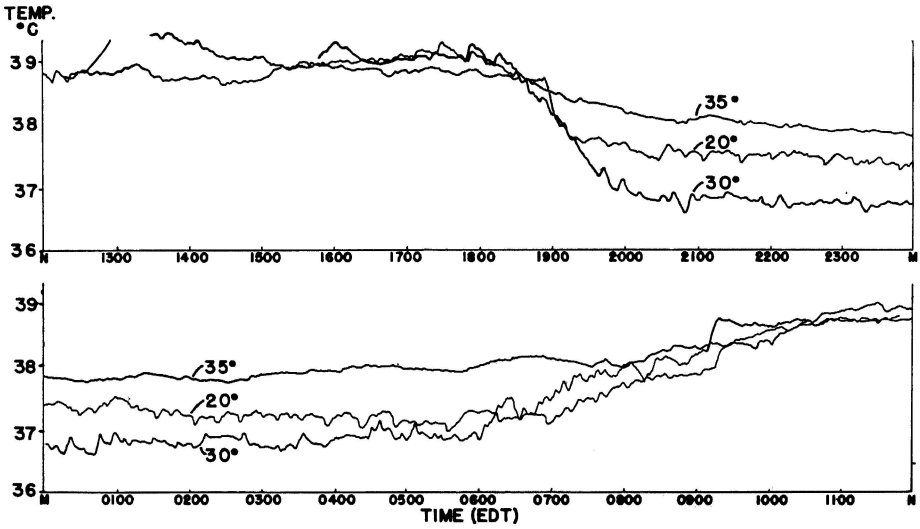

Fig. 11—Hypothalamic temperatures of a rhesus monkey restrained in a primate chair in hot (35° C), neutral (30° C), and cold (20° C) environments (50 percent relative humidity) for 24 hour periods with normal day-night lighting. (Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk, J. D. Hardy and S. B. Stromme, 1963.)

level during sleep in order to activate an increased heat loss to balance the heat production. In fact, the brain temperature decreased even in the hot environment. Figure 12 may be interpreted in the same way.

For this record, the ear pinna and hypothalamic temperatures were related to the eyelids in a rhesus monkey in a cool environment for 7 hours. On every occasion when the monkey closed its eyes, its ear pinna temperature increased even though its hypothalamic temperature was decreasing at the same time. Conversely, when the animal opened its eyes, its ear pinna temperature fell while its hypothalamic temperature was increasing. Increase or decrease in activity, when the eyes were open, did not affect hypothalamic or ear pinna temperatures. These results suggest that the thresholds for thermoregulatory responses are decreased at the onset of sleep and increased upon awakening. They do not suggest that the slopes of the response curves are effected by sleep.

Even more convincing are observations of the increase in sweat rate in man at the onset of sleep obtained by Kosuge in 1936 and discussed by Kuno (1956). In one series of experiments at 19° to 20° C in the winter, subjects did not sweat on the chest before or during sleep. At 29° C, a subject did not sweat before sleeping but within 30 minutes of the onset of sleep the subject began to sweat moderately on the chest and stopped as soon as he was awakened. In

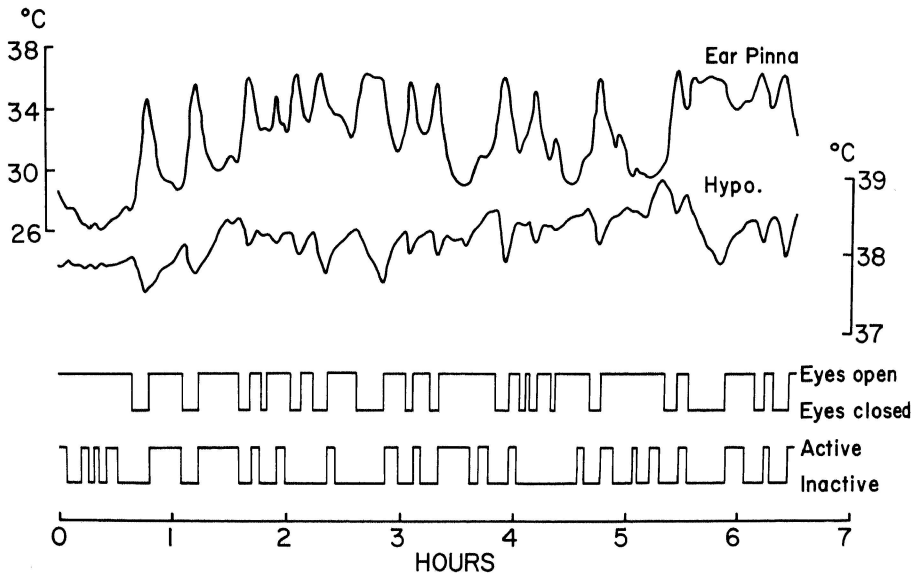

Fig. 12—Hypothalamic and ear pinna temperatures of a rhesus monkey in a primate chair in cool environment (22°-24° C). Open or closed eyes and activity are noted. (Hammel, H. T., D. C. Jackson, J. A. J. Stolwijk, J. D. Hardy and S. B. Stromme, 1963.)

other experiments at 29° to 32° C in the summer, the waking subjects sweated more or less (77 to 140 gm per hour). Sweating increased at once, after they fell asleep, and varied from 95 to 180 gm per hour. It subsided immediately when the subject was awakened. Kuno assumed that the increase in sweating was due to an increase in excitability of the thermal sweat center resulting from a reduced tonic inhibitory action from an inhibitory center in the cerebral cortex. He supposed that the increased excitability of the sweat center was due to an increased sensitivity; i.e., a greater response was obtained from the same stimulus. I would reinterpret these observations by suggesting that the sensitivity (slope of the response curve) does not increase at the onset of sleep, but that the set temperature (threshold) decreases at the onset of sleep and increases again upon awakening.

In a preliminary investigation of the regulation of body temperature during exercise in the dog, we concluded that the set temperature was decreased at the onset of exercise, other conditions remaining the same. This conclusion is contrary to the interpretation which Nielsen placed upon his data in man (Nielsen, 1938), from which he decided that the set temperature increased during exercise. He observed that the rectal temperature always increased to the same level for a given work load regardless of the environmental temperature. Although Nielsen's observations have been confirmed many times, and his interpretation has been repeatedly subscribed to by subsequent investigators, it seems unreasonable to us to suppose that the set temperature should increase. An elevated set temperature would deprive the regulator of a fraction of its activating signal and would require the regulated temperature to climb to still higher levels in order to generate a signal which could activate the required and greatly elevated heat loss during exercise. At least, the set temperature should not increase and at best it should decrease at the onset of exercise, thereby generating an immediate signal to activate increased heat loss in anticipation of the need to dissipate the increased heat production. In Figure 13 is a summary of the evaporative heat loss by panting in three exercising dogs (running at 4 mph) plotted as a function of the hypothalamic temperature. The evaporative heat loss for the same dogs while resting just prior to running is also shown. In order to obtain a range of hypothalamic temperatures, dogs were run in hot, neutral, and cold environments. The slope of the response curve during exercise was about 6 Kcal kg^{-1} hr^{-1} C^{-1}. However, this slope is probably greater than would be obtained if the environmental temperature had been the same throughout. For the higher hypothalamic temperatures in Figure 13, the air temperature was 30° C so that the rectal temperature was a few tenths of a degree higher than was found in the neutral environment and the skin temperature was 1° to 2° C higher. Therefore the evaporative heat loss for the highest hypothalamic temperatures was higher than it would have been in a neutral environment. For the same reasons, the evaporative heat loss for the lowest hypothalamic temperatures (obtained at an air temperature of 15° C) was lower than it would have been in a neutral en-

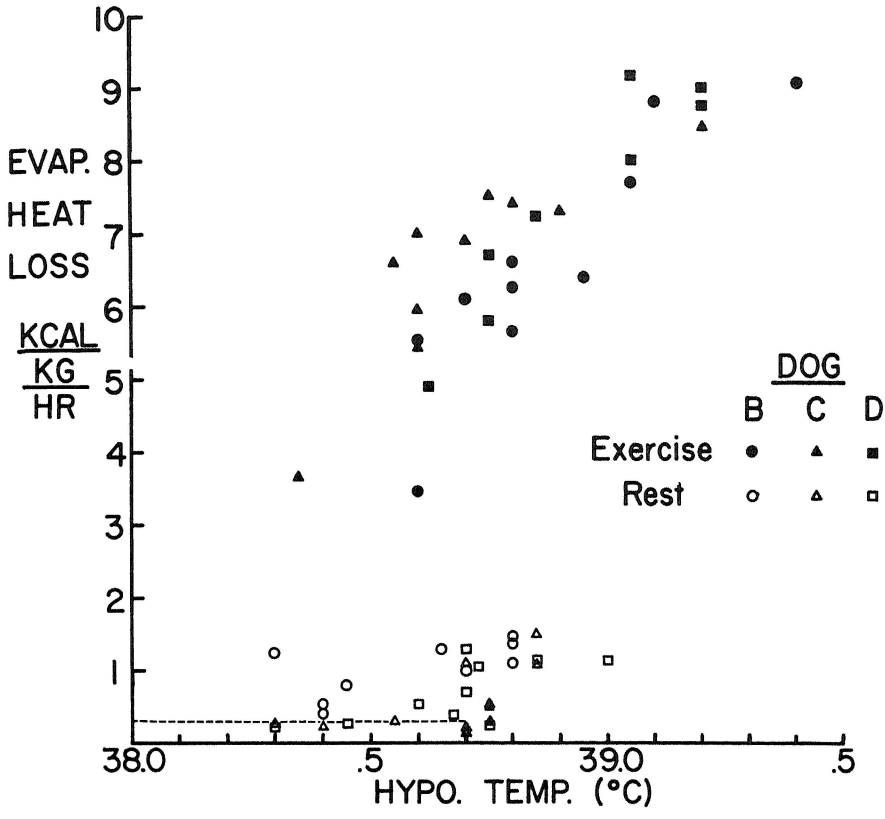

Fig. 13—Evaporative heat loss as a function of hypothalamic temperature at rest and in exercise. (Jackson, D. C. and H. T. Hammel, 1963.)

vironment. Although we cannot ascertain precisely what the slope would be during exercise in a neutral environment, we may readily see that the response curve would extrapolate to a threshold level of panting at a hypothalamic temperature below 38° C, possibly 37° C or even lower. Since the threshold hypothalamic temperature for panting in the resting dog in a neutral environment is about 39° C, the set temperature while running at 4 mph was approximately 2° C below the resting set temperature. It is certain that the threshold temperature for panting did not increase during exercise even though the hypothalamic temperature did increase.

The set temperature appears to shift downward immediately with the onset of exercise and to shift upward again when exercise stops. This deduction may be made from Figure 14. The measured evaporative heat loss by panting increased immediately (limited only by the response time of the measuring system) with

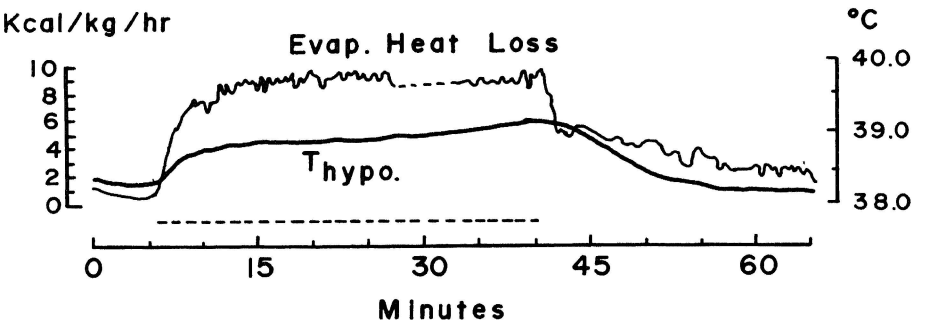

Fig. 14—Continuous evaporative heat loss recording on Dog D at 30° C. Exercise at 4 miles per hour is indicated by dotted line. Note sudden changes in evaporative heat loss associated with the beginning and end of the exercise period. (D. C. Jackson, 1963.)

the onset of exercise and before any significant change in hypothalamic temperature occurred. The panting, of course, continues to increase as the hypothalamic gradually increases. When exercise stopped, there was an immediate decrease in evaporative heat loss, although it did not decrease to its normal resting level in a 30° C environment since the hypothalamic was still elevated well above its normal range. Only gradually did panting diminish as did the hypothalamic temperature.

In 1936, Iwatake made parallel observations in man which are discussed by Kuno (1956). Sweating increased greatly above a low pre-running sweat rate and within minutes of the onset of running, before any significant increase in rectal temperature was observed. The rate of increase and the profuseness of the sweating was dependent upon the speed of running. At the end of running, there was an immediate decrease in sweat rate with no change in rectal temperature followed by a gradual decline in sweat rate. Again, a decrease in the set temperature at the onset of exercise and an increase in the set temperature at the end of exercise seems to describe the changes in the regulatory system controlling sweating in exercising man.

Next, I would like to consider the cortical input into the system which regulates body temperature. We all are familiar with our own ability to suppress voluntarily the shivering response at least for a short time even in a very cold environment. We also can simulate shivering in a neutral or hot environment. Presumably, the dog can do the same thing, as indicated in Figure 15. Heat produced by shivering in a cold environment was interrupted for about 10 minutes in these three examples, so that the metabolic rate dropped to the resting level (broken line). Because of the reduced heat production, the internal body temperature fell 0.1° to 0.2° C. We could not argue the converse; the heat production did not drop to the resting level because the internal body temperature

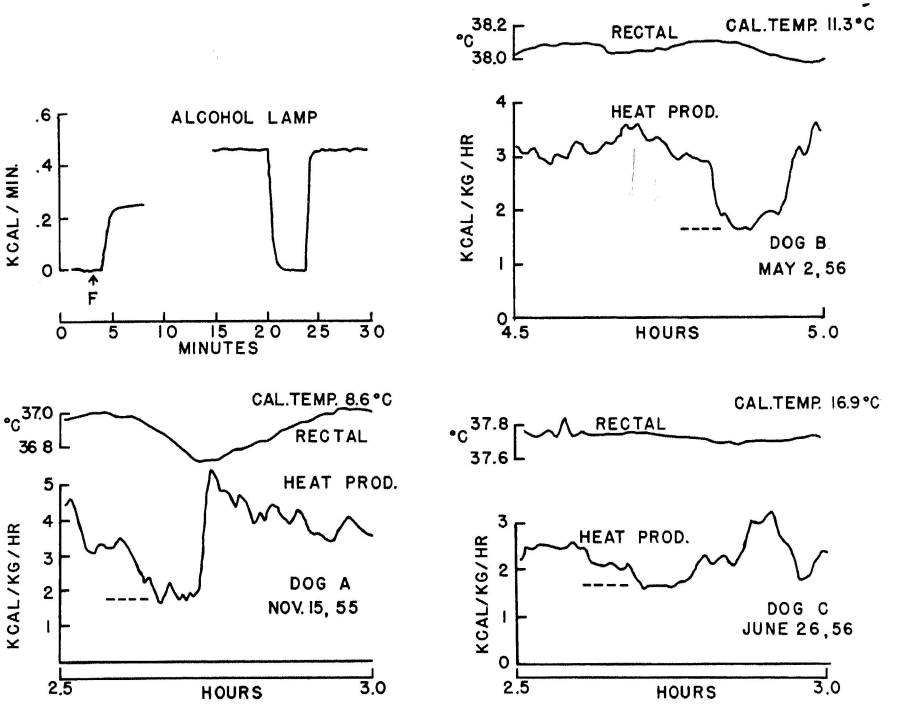

Fig. 15—Records of oxygen consumption and rectal temperature in three dogs exposed to cold environment. The records were selected to cover the brief period when the shivering metabolism was voluntarily suppressed so that heat production dropped to the resting level indicated by the broken line. A record of firing of one alcohol lamp and a record of two burning alcohol lamps with a brief switch to outdoor air indicate the response time of the O_2 meter.

overshot the threshold temperature and turned off the shivering. Shivering did not start again because the internal temperature dropped well below the threshold. Part of the overshoot in heat production in Dog A may have been due to the marked drop in rectal temperature during the period of suppressed shivering. In a similar way we may presume that the dog can voluntarily interrupt panting for short periods in a hot environment.

Of course, we cannot say how the cortical input enters the controlling system, but it acts as if the threshold is lowered to suppress shivering voluntarily in a cold environment or is raised to suppress panting in a hot environment. Similarly, shivering may be voluntarily activated in a hot environment by raising the threshold to a level above the actual hypothalamic temperature. Whether the threshold for panting (or sweating in man) is also raised by the same amount by the cortical input is not known. If it were to increase, then panting (or sweat-

ing) should be suppressed while shivering is activated. Alternatively, the cortical input may enter the final pathway for the activated regulatory response after the activating signal has been generated in the hypothalamus. Then only a single response would be affected voluntarily.

If I were a cautious experimentalist, I would wisely terminate this discussion of temperature regulation with a summary of our experimental evidence. The evidence suggests to us: (A) The pre-optic region associated with the hypothalamus is responsive to its own temperature and when its temperature is displaced, thermoregulatory responses are activated. (B) The hypothalamic temperature by itself cannot activate a regulatory response. An activating signal is generated only when the hypothalamic temperature is compared with a reference signal (which may be identified as the threshold temperature for a given regulatory response). (C) The magnitude of the regulatory response is a function of the activating signal; the latter is taken to be the difference between the hypothalamic temperature and the reference (or threshold) temperature and the function are defined by the shape of the response curve. (D) The response curve may be linear with a slope which is characteristic for the response. (E) The sign of the activating signal determines which response is activated. The appropriate responses are those which tend to reduce the magnitude of the activating signal. (F) Environmental thermal stress, internal heat stress, and other known inputs to the controlling system act as if to adjust the reference input signal. A cold stress acts to raise the thresholds for all regulatory responses, a heat stress acts to lower the thresholds; exercise acts to lower the thresholds; so also does sleep lower the thresholds, etc.

I should stop at this point. However, I wish to continue in order to (1) formalize these summary statements, and (2) suggest a model of interconnected neurons which could conceivably perform the function of the controlling system for temperature regulation.

The Law of the Controlling System

An important step in elucidating the nature of a controlling system is to obtain the so-called "law of the controlling system," that is, the relationship between inputs and outputs. All of the above summary statements are described by an equation of the form

$$R - R_o = \alpha_R (T_{hypo} - T_{set_R}) , R - R_o \geq O$$

where $R - R_o$ is the thermoregulatory response (metabolism, vasomotor activity, sweating, panting, behavior, and so forth); 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 point (or threshold) temperature for response R, is the reference input signal; $(T_{hypo} - T_{set_R})$ is the actuating signal; and α_R is the propor-

tionality constant for the response ($R - R_o$).

This equation states that a given thermoregulatory response is proportional to an actuating signal which is the difference between the actual hypothalamic temperature and some threshold temperature for that response. The equation formalizes summary statements (a) through (e). Summary statement (f) may be formalized by stating that the set (or threshold) temperature for response R is a function of all the inputs into the controlling system. Perhaps the simplest function would be a sum of constant and variable terms, each term representing the effect of each of the inputs. Thus,

T_{set}_R = an intrinsic (and constant) hypothalamic set point

$\pm$ a constant offset term ($+$ for panting and $-$ for shivering)
$+$ f (skin cold receptors)
$-$ g (skin warm receptors)
$-$ h (non-hypothalamic core receptors)
$-$ a sleep term (possibly graded)
$+$ a fever term
$-$ an exercise term (possibly graded)
$\pm$ a cortical term

The second or "offset" term was introduced to account for the fact that the threshold or set point temperature for panting is higher than that for shivering. The first two terms, the "intrinsic" and the "offset" terms, are presumably generated within the pre-optic area so the hypothalamus could function as an autonomous controlling system requiring no additional inputs and generating a regulatory response simply by the deviations of the hypothalamic temperature from the fixed set temperature.

To characterize the other functional terms in any quantitative way is impossible at present. It may be instructive, however, to utilize what is known about thermal receptors within the body in order to discern how these terms may vary. We may reasonably assume that the functional term for the skin cold receptors is proportional to the firing rate of the cold receptors. Limiting our attention to the initial and near linear portion of the steady state discharge rate of the "cold" receptors as obtained by Hensel *et al.,* in the cat tongue (1951), cat furred surface (1960), and human skin (1960), we may say that the firing rate is proportional to ($40 - T_{skin}$), i.e., as the skin temperature decreases below 40° C the discharge rate increases about linearly down to about 20° C. If the skin temperature is changing in time, then of course there is also a phasic discharge rate. We may guess, therefore, that

$$f \text{ (skin cold receptors)} = \beta\ (40 - T_s) + \beta\ T_s.$$

In a similar way we may guess that

$$g \text{ (skin warm receptors)} = \gamma(T_s - 37) + \gamma\ T_s$$

where β, β, γ and γ are unknown proportionality constants. Although we have ample evidence to presume that there are thermal receptors within the core of the body in addition to those within the hypothalamus, these have not been investigated in a way to relate discharge rate to temperature; therefore we shall guess only that

$$h \text{ (non-hypothalamic core receptors)} = \delta T_{i.b.}$$

where $T_{i.b.}$ is the internal body temperature.

Ignoring the other inputs, such as exercise, sleep, etc. and considering only the interactions due to external thermal stress as this stress affects skin and internal body temperatures, we can combine the above terms into the controlling equation and obtain,

$$R - R_o = \alpha_R \quad T_{hypo} - T_{h_o} \mp \Delta T_R - \beta\,(40 - T_s) - \beta\, T_s. \\ + \gamma\,(T_s - 37) + \gamma\, T_s + \delta\, T_{i.b.}$$

Ignoring the possibility that our several simplifying assumptions may need correction, and ignoring the possibility that a measurement of the average skin temperature is not properly weighted for its effect upon the controlling system, the above equation is still of little value in obtaining a quantitative estimate of the thermoregulatory response since there are at least five unknown constants. The equations indicate what we already know which is that, at least, the hypothalamic temperature, internal body temperature, skin temperature, and time rate of change of skin temperature are involved in generating the response. At the present time we are satisfied to express the effect of environmental temperature as a measurable shift in the functional set temperature.*

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* - Footnote added when editing the lecture

In considering the simplest function to be used for expressing the functional set temperature, we chose to use a sum of terms. Equally simple would have been a product of terms, but this can be easily ruled out. If any one of the terms is zero, then there would be no reference input signal and, consequently, no regulation. The experimental evidence is strongly against this possibility.

We may wish to guess as suggested by Hardy and Stolwijk that the regulatory response is also derived from a product of terms, from the hypothalamus, the skin, the internal body temperature, etc. Thus, for example,

$$R - R_o = \alpha_R\,(T_{hypo} - T_{h_o})\,(T_s - T_{s_o}) \qquad R - R_o \geq O.$$

This expression is also clearly forbidden. It states that if any of the terms including the hypothalamic term is zero or negative, there will be no regulatory response no matter what the magnitudes of the other terms are. Gentle prolonged heating of the hypothalamus of a dog, which is shivering in a cold environment, will suppress shivering initially; but as the internal body temperature falls, shivering is restored to almost the same level, and the internal body temperature levels off to a slightly lower level. Shivering is not indefinitely suppressed and profound hypothermia is not produced by gentle warming of the hypothalamus. Similarly, gentle prolonged cooling of the hypothalamus of a dog which is panting in a hot environment does not indefinitely suppress panting and does not lead to fatal hyperthermia. The panting is initially suppressed but is restored within a few minutes as the internal body temperature rises to a new and slightly higher level. The effect is as if the increased internal body temperature dropped the set temperature for panting to below the level to which the hypothalamus is being cooled so that panting is restored.

Ultimately, we would hope to be able to understand the relationships between the inputs and outputs, the law of the controlling system, in terms of the circuitry and activity of those neurons which are presumed to constitute the controlling system. At present, any treatment of the controlling system in terms of its neurons will be clearly recognized as guessing. Nevertheless, I shall attempt to make a guess (Hammel, 1965).

Neuron Model of Temperature Regulator

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 neurons.

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

3. The primary motor neurons 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 neurons.

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

5. Although studies employing experimentally induced lesions and electrical and thermal stimulation may indicate that primary sensory and motor neurons are found in high concentrations in certain hypothalamic sites, these results cannot be interpreted to mean that neurons 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. 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 neurons designated as lo-Q_{10} sensory neurons is located in the rostral hypothalamus in the same region as the hi-Q_{10} sensory neurons. The lo-Q_{10} sensory neurons are assumed to have spontaneous firing rates over the range of deep body temperature. Further, suppose that the cells are either not strongly temperature dependent, i.e., $Q_{10} \simeq 1$, or they increase their firing rate with decreasing temperature, i.e., $Q_{10} << 1$. Like the hi-Q_{10} sensory neurons, the lo-Q_{10} sensory neurons are assumed to synapse with and facilitate or inhibit the action of the primary motor neurons which activate regulatory responses.

In Figure 16, we are suggesting one way in which the hi-Q_{10} and lo-Q_{10} sensory neurons are connected with three classes of primary motor neurons which

respectively activate panting, vasoconstriction, and shivering. In this figure we have included two more assumptions, one essential and the other trivial. It is essential to assume that the hi-Q_{10} sensory neurons facilitate primary motor neurons increasing heat loss, e.g., panting, and at the same time inhibit primary motor neurons which lead to vasoconstriction and shivering. Conversely, the lo-Q_{10} sensory neurons must inhibit panting and at the same time facilitate vasoconstriction and shivering. The other assumption is that the primary motor neurons for panting and shivering in Figure 16 have no spontaneous firing rates. To obtain different set-point temperatures for panting and shivering, we have shown more inhibition than facilitation from the sensory neurons synapsing with the neurons for panting and shivering. This provision generates the "offset" term in our formal equation describing the functional set temperature. The same condition could also be achieved by assuming the motor neurons to have a negative bias so that more facilitation than inhibition would be required to activate panting and shivering.

The activity curves of the sensory and motor neurons below the diagram in Figure 16 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 neurons are equal, i.e., intersect, the facilitation and inhibition from these sensory neurons upon the vasoconstriction (v.c.) motor neurons nullify each other so that the v.c. motor neuron 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} neurons 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 neuron 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-point 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 neurons are more inhibited than facilitated, so there is no panting or shivering. As the hypothalamic temperature increases, the facilitation of panting increases faster than the 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 motor neuron mediating

** - T_{h_n} may differ from the intrinsic hypothalamic set-point 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.

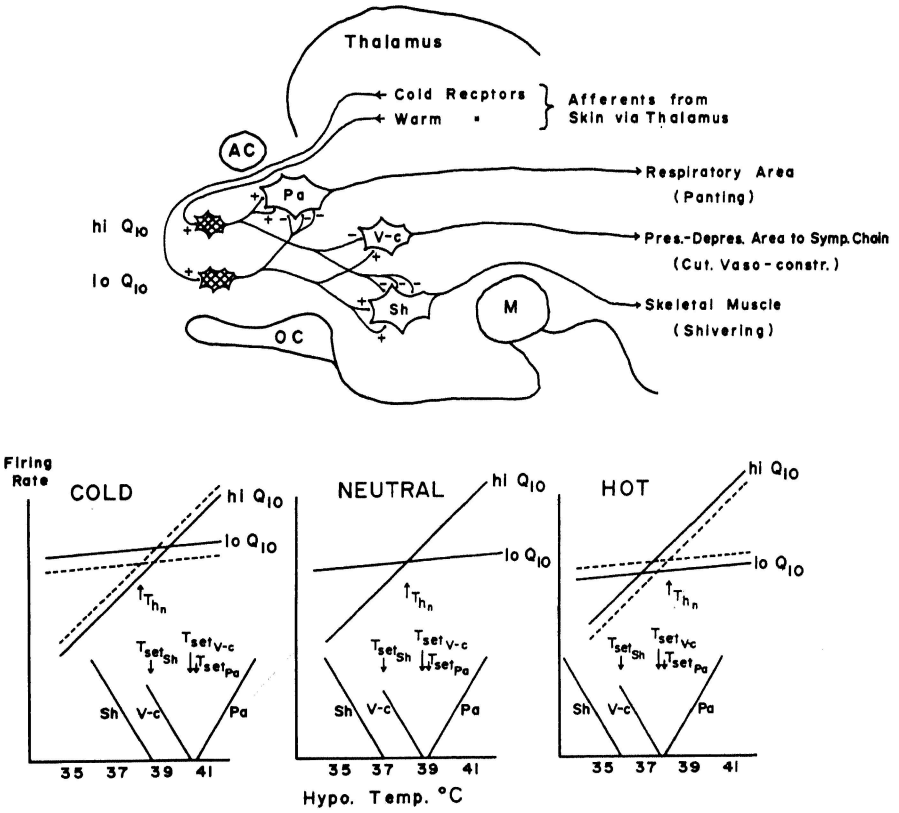

Fig. 16—A physiological model for establishing a set-point temperature and illustrating possibilities for adjusting the set point. AC, anterior commissure; OC, optic chiasm; M, mammillary body; Pa, primary neuron for panting; Sh, primary neuron for shivering; v-c, primary neuron for vasoconstriction; crosshatched cell bodies, low-Q_{10} and high-Q_{10} primary sensory neurons. (Hammel, H. T., 1965.)

shivering 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 input from outside itself, i.e., no input from peripheral receptors in the skin, from extra hypothalamic core receptors, from the reticular activating system, or from any other source. The model postulates that the primary sensory and pri-

mary neurons alone can activate thermoregulatory responses and, to do so, require only an appropriate displacement of the hypothalamic temperature from the functional set-point 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-point 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 needlessly sensitive to changes in its own temperature, but rather that an afferent input into the hypothalamus from thermal receptors in the skin somehow shifts the functional set-point temperature for each regulatory response. Our results obtained by displacing the hypothalamic temperature with the dog in neutral, cold, and hot environments (Fig. 9), support this interpretation. They also suggest that the environmental temperature shifts only the functional set-point temperatures and not the proportionality constants.

The effects of afferent input into the hypothalamus consistent with our experimental results may be readily and simply achieved by running afferent fibers to the primary sensory neurons where they either facilitate or inhibit the spontaneous and temperature-dependent activities of these sensory neurons. In Figure 16, afferents from the cold receptors in the skin are shown to facilitate the lo-Q_{10} sensory neurons and afferents from the warm receptors in the skin are shown to facilitate the hi-Q_{10} sensory neurons. In the cold environment, the activities of the primary sensory and motor neurons are presumed to be as shown in the lower left graph of Figure 16. The increased firing rate from the cold receptors in the skin is shown to facilitate the activity of the lo-Q_{10} sensory neurons, and the decreased firing rate from the warm receptors in the skin is shown to reduce the activity of the hi-Q_{10} sensory neurons with the combined effect of raising all functional set-point 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-point 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 neurons in the hot environment are presumed to be as shown in the lower right graph of Figure 16. Reduced firing rates from cold receptors in the skin are shown to reduce the activity of the lo-Q_{10} neurons, and increased firing rates from warm receptors in the skin are shown to increase facilitation of the hi-Q_{10} neurons, with the combined effect of lowering all functional set-point 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 neurons, it is possible to account for the apparent shifts in the functional set-point 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 neurons 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-point temperatures—without changing any of the α_R's.

We recognize that terminating all inputs to the hypothalamus upon the sensory neurons is not the only way to affect temperature regulation. It is possible that some or all of the peripheral inputs feed into the motor neurons directly and facilitate or inhibit these neurons. But to do so would require that the peripheral inputs would also have to exercise antagonistic control over the classes of primary motor neurons. For example, in order to shift all functional set-point 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 neurons for shivering but at the same time inhibit the primary neurons mediating panting. Similarly, the warm receptors in the skin must not only facilitate the primary neurons for panting but also inhibit the neurons for shivering. If the peripheral inputs do go directly to the primary motor neurons rather than to the primary sensory neurons, 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 neurons or go directly to the primary sensory neurons, we have favored the latter view because it is a simpler arrangement and because it does not render the hypothalamus so needlessly sensitive to changes in its own temperature.

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

sponse and therefore increasing α_R. At present, the evidence is too meager to speculate further on this possibility.

I have discussed my opinion about the regulator of body temperature, and formalized and expressed it again in terms of a speculative model of interconnected neurons. I would like to close with a discordant note. While heating the hypothalamus of the dog in a cool environment, we always found, as noted in Figure 10, that the falling rectal temperature was followed by an increase in metabolism due to the onset of shivering. We interpreted this response to mean that the lowered internal body temperature increased the threshold temperature for shivering to a level above the temperature of the heated hypothalamus. We should also note that the ear pinna vessels remain dilated even after shivering is activated. Only after the thermal clamp was released did vasoconstriction occur in the ear pinna. It is even possible to activate a more bizarre response. Extreme cooling of the hypothalamus to 34° C in a cold environment will activate intense shivering and drive the internal body temperature rapidly up to 39.5° C. If the environmental temperature is rapidly increased to 40° C while hypothalamic cooling continues, some dogs will repeatedly pant with interspersed bouts of shivering at the same time. These unexpected results are lacking a satisfactory explanation, but perhaps they are indicating a consequence of the technique we have used for temperature displacement of the hypothalamus to which I have already referred. When water of extreme temperatures are perfusing the thermode surrounding the hypothalamus and when this acts to produce extreme internal body (and blood) temperatures in the opposite direction, marked thermal gradients throughout the stimulated region may be expected. Because the pattern of blood flow with respect to the thermodes may be highly irregular, we may expect irregular gradients through the pre-optic tissue. Therefore it may not be so surprising to find that contradictory regulatory responses are activated simultaneously under such extreme thermal conditions. Obviously we should heat or cool one side of the hypothalamus only or heat one side while cooling the other in order to explore the consequences of temperature asymmetries within the hypothalamus and its associated pre-optic region.

I am ending on this reference to an inherent fault in our technique, to indicate that I, too, am uncertain about our own effort to understand the regulator of body temperature.

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