

# Introduction to PHYSIOLOGY

VOLUME 3

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## SUBJECT INDEX

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## CHAPTER 1

# The Control of the Body Temperature

### Chemical and Physical Thermoregulation

#### Heat Production and Dissipation

In Vol. 1 we have discussed the basic principles of energy consumption, and the dissipation of heat, by the organism, and we have seen that the body-temperatures of many homeotherms are maintained within fairly narrow limits as a result of the interplay of these two parameters. Thus the response to cold may involve an increased heat production—*chemical thermoregulation*—together with physiological reactions that reduce the loss of heat from the surface of the body—*physical thermoregulation*. The increased heat production is typically brought about by shivering, but “non-shivering thermogenesis” also contributes, and this is especially manifest in the consumption of “brown fat” during cold-stress. The reflex physical thermoregulation, in man, consists in a constriction of the blood vessels of the skin that reduces surface cooling of the blood; in hairy animals and birds, the erection of hairs, or fluffing of feathers, reduces heat losses by increasing the thickness of the layer of still air on the surface. More complex behavioural responses are the huddling of animals and the putting on of warm clothes by man.

#### Heat Dissipation

The response to an increased environmental temperature, or an increased heat-load through exercise, is a peripheral vasodilatation that increases the cooling of the blood, but the most significant response in man, so far as its effectiveness is concerned, is the secretion of sweat by the sweat glands; the evaporative heat loss may amount to some 800 kcal per hr in a nude human subject exposed to a high ambient temperature, i.e. it may be equivalent to some eight times the basal heat production. In many animals an increase in the respiratory rate

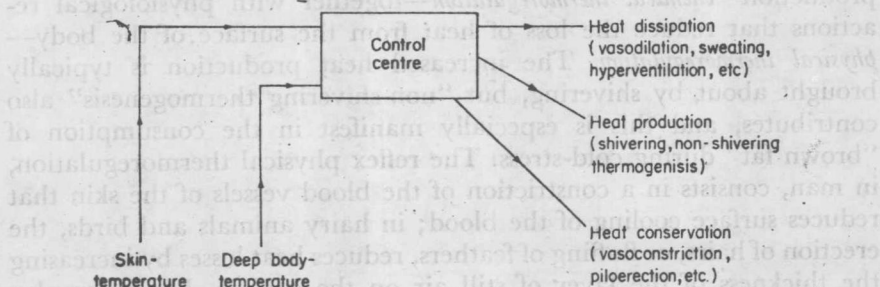
—typically seen in the panting dog—is an important mechanism for increasing evaporative heat-loss; and in experimental studies the respiratory rate of, say, a rabbit is a good index to its response to a heat-stimulus.

## Homeostasis

In the present chapter we shall consider the basic mechanisms through which this homeostasis of body temperature is brought about. Before describing some responses of man to changed thermal demands brought about experimentally, it will be convenient to suggest a sketch of the basic control mechanism, and to say a few words on the mechanism of chemical thermoregulation, which in man is manifest as shivering, and on the receptors in the skin that provide the signals for change in ambient temperature.

### Control System

Figure 1.1 illustrates a simple system through which temperature regulation could be maintained. Information regarding the body temperature is provided from two main sources, namely from the skin



**Fig. 1.1.** An illustration of a simple control mechanism by which temperature could be regulated.

and from the blood flowing in the deep parts of the body—the *skin-* and *core-temperatures* respectively. This information is passed to a central control zone, and after being sorted out, a thermoregulatory response is induced. This response can be brought about by exciting or inhibiting heat-dissipation, heat-producing, or heat-conserving centres.

## Core-Temperature

Of overriding importance will be the core-sensitive neurones, since the essence of the control mechanism is the maintenance of a steady

core-temperature; we may expect the thermoregulatory responses to a given change in core-temperature to be far stronger than those to the same change in skin-temperature, and, when these occur in opposite directions, we may expect the information from the core-temperature sensors to be dominant. The site of the neurones sensitive to deep body-temperature has been established by a variety of experiments to be in the anterior hypothalamus, a strategic location that permits a ready activation of the vasomotor and other reactions required to make the appropriate adaptation. The actual integrating centres, as opposed to the temperature-sensitive neurones, are also in the hypothalamus; in fact, it is not easy to distinguish the effects of stimulating a centre from those of stimulating heat- or cold-sensitive neurones.

### Set-Point

We may assume that there is a certain "set-point" on the temperature scale, and that any change in the core-temperature away from this "set-point" will result in thermoregulatory responses leading to a return to the set-point.

At this set-point we may assume that neither heat-productive nor dissipatory processes are dominant; it must be appreciated, however, that the animal's heat regulating mechanisms are not exclusively determined by the core-temperature, so that the concept of a rigid point on the temperature scale, set once and for all, is too great a simplification. Under certain conditions the set-point may change, and this may be physiological, as in the hyperthermia during severe exercise, or pathological, as in the fever induced by bacterial pyrogens.

**Variable Set-Point.** Hammel *et al.* (1963) have introduced a *variable set-point theory* that allows of modifications in the core-temperature at which no thermoregulatory activities are manifest. Thus, we may use the engineer's concept of the "continuous proportional controller", which depends for its action on the difference between the actual temperature,  $T_h$ , and the set-point temperature,  $T_{ho}$ . The action depends on the "load error", i.e. the value of  $T_h - T_{ho}$ , so that the response,  $R - R_0$ , is given by:

$$R - R_0 = \alpha_R (T_h - T_{ho})$$

where the coefficient,  $\alpha_R$ , is constant for a given form of thermoregulatory activity, e.g. sweating. Thus, in dogs, the coefficient was 2.3 for panting and -1 to -1.5 for shivering. The essential point to the theory is that the set-point is variable; for example, it was 2°C greater for panting than for shivering in a cold environment, 2-3°C

greater than for shivering in a neutral environment, and  $4^{\circ}\text{C}$  greater than for shivering in a hot environment, the shivering being induced by artificially altering the hypothalamic temperature.

### Chemical Thermoregulation

#### The Shivering Mechanism

When an animal is placed in a cold environment we have seen (Vol. 1, Ch. 3) that the metabolic rate increases linearly with the degree of cooling, indicating that chemical thermoregulation is an important mechanism in maintaining homeothermy. This increased metabolic rate occurs in many animals without obvious shivering, a process called *non-shivering thermogenesis*; for example, rats exposed to cold and treated with curare to prevent muscular activity, still show an increased metabolic rate. Davis and Meyer divide the increased response to cold into a *physical thermogenesis*, due to muscular contraction, and a *chemical thermogenesis*, due to a generalized increase in cellular metabolism. Thus normal rats at neutral temperature had a basal  $\text{O}_2$ -consumption of  $1.7 \text{ ml/min/100 g}$ ; at  $5^{\circ}\text{C}$  this rose to  $3.8 \text{ ml/min}$ , and in curarized animals it only rose to  $2.54 \text{ ml/min}$ , so that the extra metabolism of the curarized animals was some 40 per cent of the normal extra metabolism. At first the muscular activity is of an unco-ordinated nature and only detectable by placing recording electrodes in the muscles; later it develops into the rhythmic involuntary co-ordinated act of shivering. This requires central coordination since Sherrington found that, when the spine is transected, the animal does not shiver below the level of transection.

**Shivering Centre.** Experiments on stimulation and ablation of various parts of the brain suggest that there is a region in the dorso-medial caudal hypothalamus, near the wall of the IIIrd ventricle, that may be described as a chemical regulation, or *shivering*, centre, corresponding with that marked P in Fig. 1.5 (p. 9); this part of the brain must remain intact if the animal is to be able to respond to lowered ambient temperature by an increased metabolic rate. This was first described by Isenschmid and Schnitzler in 1914 when they made rabbits poikilothermic by puncturing the brain in this region. As we shall see, however, this is not the main thermoregulatory centre, which is in the more rostral part of the hypothalamus, so that the shivering centre is under control from this rostral centre as well as from other parts of the brain (Hemingway, 1963).

**Energy Production.** Shivering is an effective manner of increasing heat production, the  $\text{O}_2$ -consumption being as much as 2–5 times the



resting value; this increase is small, however, by comparison with the 10–20-fold increase of exercise.

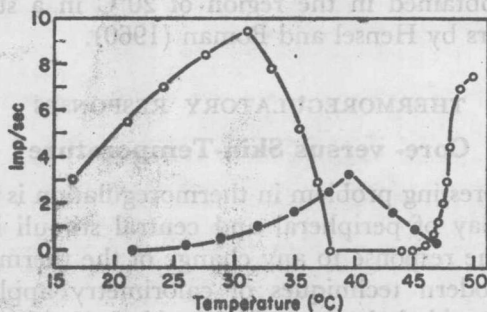
### The Peripheral Sensors

The detailed aspects of cutaneous sensation will be discussed later (Vol. 5); here we need only consider the responses of the cold- and warm-receptors of the skin. The skin is provided with numerous types of nerve ending, some of which are naked and come into relation with no organized receptor structure, whilst others end in relation to organized structures that have been given various names; thus the Meissner corpuscle is a receptor that mediates touch sensation, and it has been suggested that the Ruffini and Krause endings are concerned with thermal sensation, but this is by no means essential since thermal sensations can be evoked from areas of skin devoid of such nerve-endings, and it is likely that the naked ending, free in the tissue, subserves the function of temperature reception.

#### Cold- and Warm-Fibres

Electrophysiological studies have shown that there are sensory nerve fibres from the skin that respond in a characteristic fashion to cooling and others, the “warm-fibres”, to warming. Fig. 1.2 shows the steady discharges of a cold- and warm-fibre innervating the tongue when subjected to steady temperatures.

The cold-fibre, whose responses are shown in open circles, is silent at temperatures of 37–45°; on cooling below 37°C (about the normal tongue-temperature) the discharge increases, to give a maximum at



**Fig. 1.2.** The rate of discharge of three single fibres from the tongue as a function of temperature. Left open circles, cold-fibre; filled circles, warm fibre; right open circles, “paradoxical cold-fibre” which discharges at high temperatures as well as in the usual cold-fibre range. (Dodt and Zotterman, *Acta physiol. scand.*)

about 30°C; at lower temperatures the discharge-rate falls. The warm-fibres are characteristically different, being differentiated from cold-fibres by the fact that their steady discharge increases on warming the tongue from 30° to 40°C whilst on cooling from 40° to about 30°C the firing ceases. Thus, when the tongue is cooled to, say, 22°C only the cold-fibres are responding; as the tongue is warmed, the responses of cold- and warm-fibres increase, and it is only when the temperature is above 32.5°C that the cold-fibres show diminished discharges with further rises in temperature, whilst the warm-fibres continue to increase their discharges.

### **The Composite Message**

The temperature of the skin is indicated to the central nervous system by the combined messages in warm- and cold-fibres; if we look at Fig. 1.2 we see that at 20° and 37°C the cold-fibre is giving the same response of about 4 impulses/sec and so the message sent by this fibre is by itself equivocal, it could indicate either a cool temperature of 20°C or a warm one of 37°C. However, at the cool temperature the warm-fibre is not discharging, whilst at the warm temperature it is discharging strongly; and it is the combined message in the two types of fibre that informs the central nervous system of the skin-temperature.

### **Human Thermal Receptors**

The temperature-sensitive units studied by Dodt and Zotterman, and illustrated in Fig. 1.2, were in the tongue, which has normally a temperature of about 37°C; the skin-temperature of man, for example, is considerably lower than this, so that we may expect the cold-sensitive units to operate over a different range, and in fact a maximal discharge was obtained in the region of 20°C in a study of human thermal receptors by Hensel and Boman (1960).

## **THERMOREGULATORY RESPONSES**

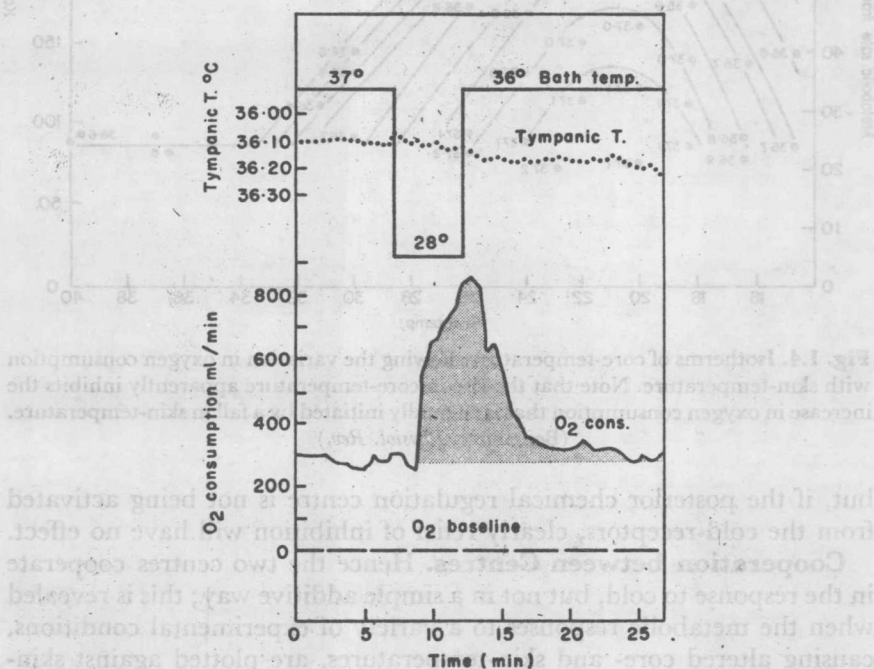
### **Core- versus Skin-Temperature**

The most interesting problem in thermoregulation is that concerned with the interplay of peripheral and central stimuli in determining quantitatively the response to any change of the thermal demands on the animal. Modern techniques of calorimetry applied to human subjects have provided the basis for elucidating some of these interactions. The temperature of the blood flowing in the hypothalamic region is best indicated, as we have seen (Vol. 1), by the temperature recorded by a thermocouple placed close to the tympanic membrane

of the ear, rather than the rectal temperature so often used in the classical studies. By ingestion of large amounts of ice-cream, the tympanic temperature may be reduced quite considerably and in this way the interaction between reduced core-temperature (or rather hypothalamus temperature) and skin-temperature may be studied. Alternatively, the human subject may be cooled in a bath to the point where his core-temperature is reduced by a given amount, and then his skin temperature may be changed by placing him in a bath at a different temperature.

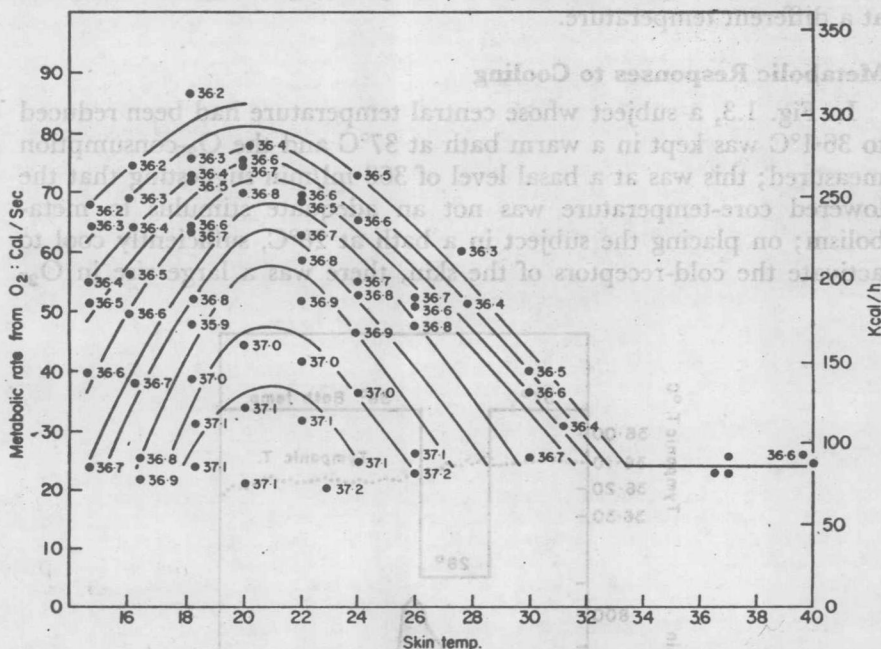
### Metabolic Responses to Cooling

In Fig. 1.3, a subject whose central temperature had been reduced to  $36.1^{\circ}\text{C}$  was kept in a warm bath at  $37^{\circ}\text{C}$  and the  $\text{O}_2$ -consumption measured; this was at a basal level of 360 ml/min suggesting that the lowered core-temperature was not an adequate stimulus to metabolism; on placing the subject in a bath at  $28^{\circ}\text{C}$ , sufficiently cool to activate the cold-receptors of the skin, there was a large rise in  $\text{O}_2$ -



**Fig. 1.3.** Metabolic response to cooling of the skin. At a constant low central temperature of  $36.15^{\circ}\text{C}$ , transient cooling of the skin to  $28^{\circ}\text{C}$  in a water-bath caused a large increase in oxygen consumption. (Benzinger, *Physiol. Rev.*).

consumption. Thus the lowered core-temperature apparently requires a lowered skin-temperature to exert any effect, and Benzinger suggested that the lowered core-temperature acted on the chemical-regulation (or heat-production) centre by release of inhibition. On this basis, at normal core-temperature or above, the cold-response is held in check by the anterior hypothalamic (or heat-dissipation) centre; cooling the anterior hypothalamic centre removes this inhibition



**Fig. 1.4.** Isotherms of core-temperature showing the variation in oxygen consumption with skin-temperature. Note that the rise in core-temperature apparently inhibits the increase in oxygen consumption that is normally initiated by a fall in skin-temperature. (Benzinger, *Physiol. Rev.*)

but, if the posterior chemical regulation centre is not being activated from the cold-receptors, clearly relief of inhibition will have no effect.

**Cooperation between Centres.** Hence the two centres cooperate in the response to cold, but not in a simple additive way; this is revealed when the metabolic responses to a variety of experimental conditions, causing altered core- and skin-temperatures, are plotted against skin-temperature. Merely plotting the results gives a confusing array of dots, but if results for the *same* core-temperature are plotted, to give a curve of  $O_2$ -consumption against skin-temperature, as in Fig. 1.4, a