PHYSIOLOGY AND PHARMACOLOGY OF TEMPERATURE REGULATION

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Since the end of the 18th century it has been recognized that the remarkable temperature constancy of homeothermic organisms is maintained by self-actuated reactions keeping heat production and heat loss in balance. At that time the emphasis was laid mainly on the regulation of heat production to compensate for variations in heat loss. Crawford in 1788 (66), for instance, found that the heat production in guinea pigs was considerably greater in cold than in warm ambient temperature and that wetting the fur increased the heat production because the animal lost heat at a greater rate by evaporation from the surface. The importance of precise regulation of heat dissipation to meet the variations in heat production was pointed out by Bergmann in 1845 (37).

On speculating about the possible mechanisms governing the thermal vasomotor reactions that he had been studying, Bergmann discussed two alternative explanations: An increase in blood temperature, he argued, may have a direct effect on the skin and the cutaneous blood vessels causing vasodilatation, which permits more heat to be dissipated and the blood temperature to be restored; or alternatively, the raised temperature may act on some temperature sensitive structures in the brain from which the relaxation of the skin vessels is determined. It was known that the blood vessels are under the influence of brain structures. On the supposition that the latter hypothesis was true, *i.e.*, that there are temperature sensitive brain structures responsible for the thermal vasodilatation, Bergmann concluded from his own observations that these parts of the

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central nervous system would have to change their sensitivity to heat in the morning and in the evening to permit diurnal temperature variations.

At the time there was, however, no experimental evidence in favour of Bergmann's remarkably prescient concept on heat sensitive brain structures initiating thermoregulatory events and on the control of the threshold temperatures for the latter. With the work of Kahn (185), Barbour (21), Hashimoto (143, 144), and Prince and Hahn (230), the existence of thermoceptive structures in the brain was shown. The accomplishments of Magoun *et al.* (207) in precisely localizing these structures to the pre- and supra-optic regions of the hypothalamus, as well as their technique of diathermy heating introduced a new era of animal experimentation in this field. The recent work of Benzinger and Kitzinger (32, 35) seems now to have established that the hypothalamic thermodetectors are of greatest physiological significance even for man.

Much interest has been focused on the peripheral temperature sense and its role in thermoregulation. Due to extensive work by Zotterman, Hensel and Dodt, and by Iggo (76, 78, 152, 153, 154, 156, 157, 159, 179, 292) we now have detailed knowledge about the adequate stimulus for these thermoreceptors and their pattern of firing which allows a fruitful discussion of the roles played by the peripheral and central sets of thermodetectors.

This question concerning the control of the regulating mechanisms is one of the key problems to the understanding of thermoregulation and the effects of different drugs and agents. It is dealt with in the first half of the paper and discussed in connection with the main effector reactions. The other part of this presentation is devoted to a consideration of the standard to which the regulator is locked: whether it is fixed, or whether it is adjustable as suggested by Bergmann (see above) to permit functional regulation at different temperature levels in different situations, such as in fever, during exercise, sleep and wakefulness, in emotions, and during conflicting interactions between different homeostatic mechanisms. This problem concerning the setting of the "body thermostat" is of considerable pharmacological significance since the effect of some of the drugs acting on temperature regulation may be exerted on the mechanisms setting the "thermostat."

The mechanisms subserving homeostasis of body temperature have, for the sake of simplicity, often been called the "body thermostat." The use of the term seems justifiable since it only refers to a self-actuating mechanism of any kind capable of maintaining the temperature of a system at, or close to, a predetermined level independently of considerable variations in the surrounding temperatures. The definition is indeed applicable to the thermoregulatory mechanisms of the homeothermic organisms.

I. THE BODY THERMOSTAT AND ITS GOVERNOR

A. Vasomotor reactions

The conductance of heat from the interior of the body to the surface where it can be dissipated by radiation, convection, and evaporation is intimately related to the blood flow through skin and to some extent the respiratory system. The vasomotor reactions of the vessels of these surfaces are therefore of greatest importance for the maintenance of heat balance.

With alterations in thermal load, the cutaneous blood flow may change more than a hundredfold (56, 59, 63, 106, 248). There is, however, a great difference in this respect between different skin areas (20, 79, 99, 162, 175, 271).

The cutaneous regions which are mainly employed for the fine adjustments of heat balance are those richly furnished with arteriovenous anastomoses (155, 227). These vessels are specialized for central nervous control: they are well supplied with vasoconstrictor nerve fibres and have a very low inherent tone (106). The nerve fibres innervating these cutaneous shunts have been found to have somewhat lower thresholds to electrical stimulation than those fibres supplying "metabolic" vessels of skin and muscle. This suggests that the fibres exercising the precise control of heat loss are larger and conduct at faster speeds than other vasomotor nerves (107).

In cats and dogs the mechanism of cutaneous vasomotor reactions in response to thermal changes was found to be mediated only by vasoconstrictor nerves (108, 109, 110, 270, 272). This also holds for the human hand, where the increase in blood flow in response to body heating can be quantitatively accounted for by the decrease in sympathetic vasoconstrictor tone (12, 24, 120, 226, 240). The existence of vasodilator fibres to the skin vessels has never been conclusively demonstrated nor has it been proved that vasodilatation may be physiologically mediated by antidromic activity in dorsal root fibres. Nevertheless, the cutaneous vasodilatation which occurs in the human forearm in response to body warming and which is associated with sweating could not be imitated merely by blocking the sympathetic fibers supplying this skin area, nor could this thermal vasodilatation be elicited during such nerve block (132); it seems to be mediated by sympathetic nerve fibres. Accumulating evidence, however, indicates that this vasodilatation is caused by the activity of the sweat glands, which are innervated by sympathetic fibres, and mediated by bradykinin, a powerful vasodilator (111). Activity in the sweat glands as well as in the submandibular gland has been found to be accompanied by liberation of an enzyme producing bradykinin in the surrounding tissue fluids (167). In accordance with this idea, only slight vasodilatation is found in the forearm but powerful vasodilatation in the hand. This may be prevented by epinephrine applied electrophoretically. The main cutaneous vasodilatation in the forearm seems not to occur until the onset of sweating (239). The cutaneous vasomotor reactions of the upper arm, calf, and thigh show the same pattern (42). In humans thermal sweating is said not to occur on the palms and soles (196); when there is sweating in these regions in response to excitement, it is also followed by vasodilatation (5).

Vasoconstrictor tone is maintained by structures in the forebrain. Pinkston *et al.* (228), confirming the old observations by Eulenburg and Landois (91), found that forebrain decortication in dogs and cats led to a chronic state of cutaneous vasodilatation with the normal vasoconstrictor response to cold greatly impaired. They concluded that the cutaneous vasomotor mechanisms were governed by cortical structures. This has been amply confirmed by the extensive work of Ström *et al.* (90, 270, 272, 273). When vasoconstrictor tone from forebrain structures has been reduced by destruction or ablation there is less activity left for the thermal inhibitory activity to play on. The hemodynamic

impedance of the cutaneous vessels at each hypothalamic temperature seems thus to be dependent on the state of activity of the forebrain structures involved. Even under the conditions of heavy external and internal load there is usually a high vasoconstrictor tone which has to be completely counteracted in order to produce maximal vasodilatation (272).

This principle of a strong inhibitory drive playing on a strong excitatory drive, may be recognized from the control of shivering (see below). It seems further to be employed in other nervous control mechanisms, *e.g.*, the control of the tonic spinal motoneurone activity (131), and perhaps in the mechanism of impulse generation in thermoreceptors (292). This arrangement probably secures fast reactions and a large range of response in both directions from a resting level.

Kahn (185) showed that moderate warming of the carotid blood in dogs led to a rise in skin temperature and to sweating. Barbour (21, 22) demonstrated wide changes in skin temperature of the rabbit ear due to artificial heating and cooling of structures at the "base of the brain." Hemingway *et al.* (150) heated the hypothalamus in unanesthetized dogs with diathermy with resulting large temperature rise in the ears. These authors interpreted the changes induced in skin temperature as corresponding to changes in cutaneous blood flow. It remained for Uvnäs and his school (90, 108, 109, 270, 272, 281, 282) to study these centrally evoked cutaneous vasomotor reactions with methods allowing greater anatomical precision (207) and direct quantitative measurement of cutaneous blood flow. They found that cutaneous vasodilatation was readily elicited by local heating in the anterior hypothalamus. The thermosensitive structures in the anterior hypothalamus discovered by Magoun *et al.* (207) were found also to be governors of the thermoregulatory vasomotor reactions. Cutaneous vasodilatation proved, in fact, to be very sensitive to local heating of these structures.

However, it is still being debated whether the main thermal control of cutaneous blood flow is exerted from the skin temperature receptors (278), or whether the hypothalamic thermodetectors constitute the principal governor of this regulatory mechanism (32). There are many reports on thermoregulatory vasomotor reactions induced by changes in skin temperature. Many of them may not be valid because rectal temperature is taken as an index of the regulated temperature. There is good evidence that rectal temperature may differ considerably from hypothalamic temperature (26, 32, 81, 154). There is no doubt, however, that cutaneous vasomotor reflexes may be thermally elicited from skin areas (53, 84, 150, 163). Considerable difference in receptive importance of the various surface regions has been reported (20). Most of these reflexes appear to be transient and their significance for maintenance of body temperature is uncertain, although they may have a buffering effect.

A short latency for a thermal vasomotor reaction is commonly taken as evidence that it is reflexly evoked from the skin. It should, however, be kept in mind that it may be very difficult to estimate such latencies especially when indirect methods are used for measuring blood flow (26). Further, it is difficult to exclude the possibility that the described effects are, at least partly, due to "pain" reflexes (273). There seems, in fact, to be a lack of conclusive evidence that

average skin temperature is a factor involved in the control of cutaneous vasomotor reactions. There are, however, reasons to question this view. If average skin temperature were to control cutaneous blood flow, which is one determining factor for the skin temperature, then a small decrease in skin temperature would cause vasoconstriction and thereby a further temperature drop leading to further vasoconstriction and so on towards the limits for this reflex. Similarly, a slight elevation of skin temperature would incite a progressive increase in skin temperature and cutaneous blood flow until, again, the limits of the responsiveness were approached. The obvious consequences of such a positive feed-back arrangement (99) would be oscillations in skin temperature with nearly maximal swings. The fact that such is not the case could be used as a valid argument against the above view. The small rhythmical fluctuations in thermal conductance that occur at "neutral" ambient temperature (154, 155) cannot be interpreted as oscillations due to such a positive feed-back. Benzinger (32) has recently studied the problem of the chief control of physical thermoregulation in man, using new methods and employing a more reliable index for the hypothalamic temperature than the rectal one. These experiments are dealt with below in connection with regulation of sudomotor activity. They showed that physical regulation was apparently governed solely by the hypothalamic thermodetectors.

The cutaneous vessels and peripheral circulation may be directly affected by extreme skin temperatures. Cooled blood has a higher viscosity than blood at normal core temperature. A decrease in blood temperature therefore reduces rate of blood flow even if vasoconstriction does not occur. After correction for this factor, Barcroft and Edholm (25) found local vasoconstriction as a direct effect of cold even in subjects who had been sympathectomized (25, 59, 171).

Vasodilatation may also occur as a direct effect of cold on the vessels. Lewis (199) described the rhythmical recurring vasodilatation and vasoconstriction in fingers immersed in ice water. These phenomena have been further studied on excised vessels perfused with cold saline solution (13, 14, 15, 87). Cold vasodilatation develops even in generally chilled human subjects and, when present, it is little affected by vasoconstrictor reflexes or by epinephrine (186).

There has been some debate on whether or not vasomotor reactions play an important role in temperature regulation in a cold environment (59). Some of the controversy on these points seems to depend on generalizations from one species to another. The range of environmental temperatures within which the heat production is minimal, *i.e.*, the zone of "thermal neutrality" of Giaja (122), varies widely from species to species. It is 29 to 32°C for the mouse, 27 to 29°C for the cat, 20 to 27°C for the dog, and −40 to +31°C for the Arctic white fox. The differences depend very much on the outer insulation, *i.e.*, the insulation by hair and feathers, and on vasomotor reactions (246). The range of environmental temperatures within which nude man maintains his core temperature without significant rise of heat production is also subject to considerable individual variations (59, 140, 154, 286). This seems to depend on differences in the ability to change the body's own power of insulation, *i.e.*, on the vasomotor reactions of skin and subcutaneous tissue. The skin temperature of women has been found to

change more than that of men, so that they may be colder in a cold environment with lower heat loss than men and hotter in the zone of evaporative heat loss because of a higher temperature threshold for sweating. This lower temperature in cold seems to depend partly on a larger amplitude of vasomotor reaction and only partly on the thicker layer of subcutaneous fat in women (140, 141, 210, 211).

In response to cold, cutaneous blood flow, and thereby also the conductance of the peripheral tissue, decrease to very low levels. This, of course, leads to a considerable heat debt at the same time that heat loss from the internal parts of the body is effectively prevented. A third to a half of the body mass may be excluded from effective temperature regulation by acting as a "suit of clothes" (59, 81). The limbs with their large surface areas relative to mass seem to be of particular importance in this respect. The main improvement in heat economy is, however, gained by the arrangement by which the arteries and veins run closely together, constituting a system for effective heat exchange. Claude Bernard (38) pointed out the significance of this arrangement. This "counter-current" system permits adequate blood supply to the limbs in spite of high temperature gradients (28, 29). The counter-current principle also functions to keep the temperature of the testes down at the lower level necessary for spermatogenesis without any loss of heat (71). In many animal species the counter-current principle is elaborately developed, *e.g.*, in the fins of the whale (247).

Vasodilatation induced during a prevailing heat debt will cause a rapid transient fall in core temperature because constricted vascular beds are opened up and blood perfusing the cold tissue by-passes the counter-current system through the superficial veins. The core thus loses heat at an unusually rapid rate. The compensating increase in heat production will only raise the body temperature at the usual rate. The fall in body temperature may therefore be attributed to an unusual difference between the rates of heat loss and heat gain of the core.

B. Sudomotor reactions

Intimately connected with the thermal vasomotor reactions are the sudomotor reactions whereby the heat loss by evaporation is regulated.

When the ambient temperature is increased, sweating is elicited after a longer latency than that of the increase in cutaneous blood flow. In moderate heat stress there seems to be a "critical skin temperature" of around 34.5°C at which sweating starts (196, 288, 289). This general finding has commonly been misinterpreted to mean that sweating is directly dependent on skin temperature and elicited reflexly from thermoreceptors in the skin. In man or animals suddenly subjected to hot ambient temperature, sweating is not elicited until after several minutes' exposure (196). On moderate hypothalamic heating, however, sweating is actuated promptly, which shows that the long latency is not due to sluggishness in the effector part of the reflex.

There is evidence for direct thermal stimulation of sweat glands at local skin temperatures above 40°C (196, 233). The latency of this direct effect is still longer than could be accounted for by the temporal characteristics of the skin

receptors and the effectors. During exercise, sweating may readily occur at skin temperatures considerably lower than the "critical" 34.5°C (187, 238).

Attempts have been made to correlate sweat rate with temperatures at various sites of the body. The data cited by Robinson (238) point to a linear increase in sweat rate with rectal temperature. Since he found different rates of sweating with different loads of work, the rectal temperature was believed not to be the determining factor for the sweat rate. Nielsen's (220) concept of changing the "set point" of the "body thermostat" has been largely neglected although it was firmly established experimentally and would overcome the difficulties in explaining such results as Robinson's (238) on the basis of internal thermoceptive structures regulating sweat rate.

It has been suggested that sudomotor activity is controlled by hypothetical end-organs situated deeply in the skin which measure temperatures intermediate between internal and superficial (187, 200). The reason for this is probably that rectal temperature has been taken as representative for the temperature that is regulated. It has, however, frequently been established that rectal temperature is not a good measure of "core" temperature, and certainly does not reflect the temperature of the hypothalamus (28, 81, 212). Benzinger (32) has utilized the temperature at the eardrum. By comparing measurements at this point with simultaneous temperature records at other intracranial locations he has been able to verify the temperature measurements at the tympanic membrane as representative of cerebral, and therefore presumably hypothalamic temperatures. They differ considerably from the simultaneous records of rectal temperature, the transient differences especially being of considerable amplitude and long duration.

This technique has provided good opportunities to demonstrate whether thermoregulatory reactions correlate closely with the cranial temperature or whether they show closer correlations with the temperatures of the skin. In this work on man the different aspects of physical regulation, *i.e.*, the regulation of heat loss, was studied quantitatively with the method of gradient calorimetry worked out by Benzinger and Kitzinger (34; see also Hardy, 138). This method permits rapid and continuous recording of total heat loss, which in the steady state is equal to metabolic heat production. It further permits separate measurements of the pulmonary heat losses and of the evaporative part of heat dissipation through the skin. Thus, thermoregulatory sudomotor and vasomotor activities can be recorded separately. Cranial and skin temperatures were made to diverge by the drinking of ice-water. Sweat rate and skin temperature were observed to change in opposite directions while cranial temperature and sweat production paralleled each other faithfully. Similarly, when skin temperature was at its lowest, and internal temperature at its peak, conductance, *i.e.*, cutaneous blood flow, was about three times higher than when internal temperature was minimal. These results suggest that thermoregulatory sudomotor and vasomotor activities are governed only by the hypothalamic thermoreceptive structures.

In steady state experiments the desired divergency between skin and cranial

temperatures was maintained by exercise at different calorimeter temperatures. In these experiments Benzinger (33) plotted sudomotor activity against skin temperature as well as against cranial temperature. He found that one best line fitted all the values relating sweat rate and cranial temperature obtained both at rest and at work, while the plot of sweat rate and skin temperature showed considerable scatter. This evidently means that the internal (cranial) temperature governs the sudomotor part of physical thermoregulation with no apparent influence from the skin thermoreceptors.

When, similarly, conductance was related to skin temperature the values spread about completely inconsistently. Plotted against internal temperature, the conductance values obtained during work corresponded to higher internal temperatures compared with the values recorded at rest. This may be interpreted to mean that during muscular activity there is an increased vasoconstrictor tonus, suggesting a shift of the set point of the body thermostat to a higher temperature level during exercise (99, 220; see below).

C. Shivering and thermal muscle tone

Shivering is a potent thermogenic mechanism whereby the oxygen consumption may be elevated to as much as 500% of resting value (2, 266, 267). The increase in thermogenesis in response to cold is mainly due to increased muscular activity. Whether the rhythmical appearance of rapid phasic contractions characteristic of shivering (75) is already evident at the onset of increased muscular activity, or whether the first response is an initial period of increased muscle tone, "thermal tone" (57, 59, 123), seems to be a matter of great variability between individuals (274). Usually the onset of shivering does not occur until after some heat loss from the superficial areas of the body (267), *i.e.*, when the body, as a result of a hypothalamic response, has increased its own "suit of clothes." The intensity of shivering ordinarily seems to be kept sufficient to prevent further heat loss. However, the regulation of shivering does not always seem to aim at a decrease or repayment of this heat debt (266, 267), even when shivering intensity is far from maximal.

The pattern of shivering seems to be dependent on muscle afferent fibres (75, 182, 202, 225). Muscle spindle activity is influenced in a sensitive way by the hypothalamic temperature (98). In the lightly anesthetized cat kept at a temperature slightly below thermal balance there is a high rate of discharge from the muscle spindles. Warming the temperature sensitive area of the hypothalamus diminished and even abolished the muscle spindle activity due to decreased activity in gamma motor fibres innervating the intrafusal muscles of the muscle spindles.

The spinal pathways mediating shivering in the cat have been found in the lateral white columns (39, 40, 41) close to the rubro-reticulo-spinal tracts, where Granit and Holmgren (128) found a direct pathway from the brain-stem to the spinal gamma motoneurones. From clinical investigations on patients with a variety of spinal lesions, Uprus *et al.* (280) concluded that the pathway mediating shivering was part of the lateral tectospinal or rubrospinal tracts. Their studies

were confirmed and extended by Jung *et al.* (182) who further found that shivering appeared first and most readily in spastic muscles. This is interesting in view of the role for spasticity that is proposed for the external servo-loop of gamma motor fibres and muscle spindle afferents (89, 127). The participation of the different muscles in light and moderate shivering is dependent on their engagement for other purposes (75). This selection of muscles and muscle groups for shivering may prove to be dependent on muscle spindles.

The clinical neurological investigation (182) mentioned above, showed further that the normal shivering pattern requires the intact functioning of the cerebellum which in animal experiments has proved to be essential for the linkage between alpha and gamma motor activity (127, 129). It may be concluded that the gamma motor system and the muscle spindle reflexes play an important role in the increased muscular activity and for the origin of the shivering pattern. The precise mechanism of the latter is, however, not known.

Richet (234, 235), experimenting on dogs anesthetized with chloralose, found that after transection of the spinal cord shivering was immediately confined to muscles rostral to the transection. He therefore concluded that shivering is not a spinal reflex, as had been generally believed, but depends on supraspinal control. Sherrington (252) confirmed this in chronically paraplegic dogs and showed that long after complete subsidence of all depression from the spinal shock following the transection there was no shivering in the paraplegic region. Even when he chilled the paraplegic region by immersion of this part in ice-cold water there was no shivering in the muscles innervated from behind the lesion. Rostral to the lesion, however, vigorous shivering was soon elicited at falling core temperature, although the skin over these regions, especially ears, nose, and feet, felt warm as compared with those of normal dogs chilled in the same way. These experiments of Sherrington are well known and often cited. His conclusion, however, that shivering may be elicited without "cold" stimulus to the skin receptors but is probably "of deep origin from direct cooling of a central (diencephalic) thermotaxic mechanism," has been considered invalid since the cold blood from chilled paraplegic regions could stimulate the skin receptors rostral to the transection. It is curious, however, that some interesting and important details of this work of Sherrington have been largely neglected and forgotten. Thus he observed shivering in a cold immersion experiment on a cervical spinal dog with surface temperature above 34.3°C in the non-paraplegic region. The vasoconstrictor outflow had, of course, been interrupted as well. At that occasion the room temperature was 24°C. Similar experiments were carried out at room temperatures ranging from 30°C up to 67.5°C. In spite of this hot air being in contact with the skin of the non-paraplegic region, shivering was initiated soon after immersion of the paraplegic region in ice-water, when the internal temperature had fallen to 37.1°C. The temperature of the skin receptors must, under these circumstances, have been above 37.1°C, which is rather a high skin temperature, and it seems utterly impossible that the shivering could have been initiated from skin receptors at such a high surface temperature.

However, at that time the knowledge about the adequate stimulus of the

peripheral temperature receptors that we possess to-day was lacking. Sherrington, therefore, phrased his conclusion in the following way: "Shivering under these circumstances is, on older views of the nature of the adequate skin-stimulus for 'cold,' difficult to explain as reflex but is yet not precluded from being reflex on the view propounded by Ebbecke for the nature of the adequate skin-stimulus for 'cold' sensation. Shivering under these circumstances may, on the other hand, be possibly of deep origin from direct cooling of a central (diencephalic) thermotaxic mechanism."

Ebbecke's theory (83) on adequate skin-stimulus for "cold" stimulation has, however, been disproved by the fundamental work on thermoception carried out by Zotterman, Hensel, and Dodt (76, 78, 152, 153, 154, 159, 292). It can thus be concluded that shivering does not necessarily depend on signals from temperature sense organs of the skin. This view is supported by a somewhat different type of experiment. Cats under pentobarbital anesthesia supplemented with ether were flayed with the exception of the head. As the ether wore off the cats were able to increase their body temperature several degrees centigrade by means of intense shivering. All the cut nerve endings were treated with lidocaine and the skin of the head was kept warm by radiant heat (author's laboratory, unpublished). The work of Chatonnet and Tanche (64) lends further support to this conclusion.

It has, however, been demonstrated beyond any doubt that shivering and thermal muscle tone can be very effectively inhibited by moderate warming of the thermoceptive structures in the anterior hypothalamus (98, 99, 113, 136, 150). The hypothalamic threshold temperature for inhibition of shivering is lower than that for vasodilatation. This excludes the possibility that shivering in these cases might have been inhibited by increased skin temperature due to hypothalamically induced vasodilatation.

Further, it has been shown conclusively that shivering can be inhibited and released merely by changing the skin temperature in man (182) and lower animals (99, 136).

The available data show, in summary, that shivering is inhibited if core temperature has risen above the prevailing control level for temperature regulation even at low skin temperatures. Similarly, shivering may be inhibited by a warm skin even when the core temperature has dropped slightly below that level. Whether shivering can be elicited or not in response to cooling the hypothalamus below the temperature level for that balance is a matter of conjecture. This is easily understandable from what has been said above. The effect of changing the hypothalamic temperature is dependent on the prevailing skin temperature. The reason why on one hand Hammel *et al.* (136), Kundt *et al.* (195), and Hensel and Krüger (158) were able to provoke shivering by hypothalamic cooling, while on the other hand, Ström (270), Freeman and Davis (113) and Brendel (49, 50, 51) were unable to do so, may be explained by differences in skin temperature, or by the effects of anesthetics, or both. This dual dependence on hypothalamic and skin temperature has recently been confirmed in a quantitative way by Benzinger *et al.* (35). They found the hypothalamic temperature to be ten times more effective than the skin temperature in increasing heat production.

Probably due to methodological inadequacy, Blatteis (43) was recently unable to show any apparent relation between deep body temperature and the mean temperature of skin or brain in lightly anesthetized dogs.

Electrical stimulation of the heat sensitive hypothalamic structures may also inhibit shivering and elicit heat dissipation reactions, with a considerable fall in body temperature as the result (9, 10, 11). On the other hand electrical stimulation of septal structures may cause increased shivering (3, 8). Removal of the motor cortex has also been reported to promote shivering (228). It appears, thus, as if the occurrence or absence of shivering is due to a change in balance between simultaneously acting excitatory and inhibitory drives. The excitatory drive does not depend entirely on afferent inflow from peripheral thermoreceptors.

It was shown above that the cutaneous blood flow, as well as sweating, is mainly a function of internal (hypothalamic) temperature. Skin temperature, therefore, is a function not only of ambient temperature but also of that of the hypothalamus. This provides the central thermoceptive device with two ways for its control of shivering: 1) a rather direct projection of the temperature sensitive structures in the anterior hypothalamus on those (hypothalamic) structures subserving thermoregulatory co-ordination, and further on the descending pathways for shivering mentioned above, and 2) a reflex loop formed by efferent vasomotor and sudomotor fibres influencing the temperature of the skin and thereby the rate of discharge from the cutaneous thermoreceptors which project back to the thermoregulatory relays in the hypothalamus. This latter external loop of control may be of some importance in man, where thermal vasomotor and sudomotor reactions operate over almost the whole surface of the body. In animals such as the cat and rabbit, on the other hand, most of the heavily furred skin areas of the trunk and thighs are not engaged in thermally induced vasomotor reactions (99). Shivering could, however, readily be influenced from these skin areas but was unaffected even by large changes in skin temperature of, *e.g.*, the ears, although these skin areas are important thermoregulatory effector organs due to their strong vasomotor reactions. This separation of receptive and effector function seems to be an important principle in avoiding positive feed-back in the regulatory system.

Whether this contribution from skin receptors is mainly due to a facilitatory action by the cold receptors or to inhibition from warmth receptors is not immediately evident from the way in which shivering is influenced, nor from what is known about the discharge patterns from the two types of receptors. Carbon dioxide decreases the discharge frequency from the cold receptors and increases impulse frequency from the warmth receptors. Moderate hypoxia in a similar way causes a decrease in impulse frequency from the cold receptors and an increase from the warmth receptors (77). Since shivering is depressed by both hypoxia and hypercapnia (99) these data do not help in solving the question. Menthol, however, produces an increased firing rate only from cold receptors, (160) and it has been reported to facilitate shivering. This would indicate that the cold receptors are of importance for the cutaneous effect on shivering. Human subjects treated with menthol over extensive parts of their body surface felt very

cold. In response, however, the body temperature rose only 0.3 to 0.4°C (221), indicating the dominance of the hypothalamic thermodetectors over the skin receptors.

D. The hypothalamic thermodetectors' control over motor and cortical activity

When internal temperature is increased most animals at first become less active, lie down, stretch out, show signs of increasing drowsiness, and may go to sleep (237). Further increase in body temperature arouses restlessness and signs of severe distress in some species, *e.g.*, the rabbit (*cf.* 98).

These changes in behavioural activity may be faithfully imitated merely by moderate local hypothalamic heating in conscious animals (94, 119, 150). Kahn (185) observed the quieting and "almost narcotic effect" of moderate heating of the carotid blood in cats and dogs.

The thermally induced alterations in behavioural activity correspond to characteristic changes in cerebral cortical activity and in the activity of the gamma motor system (98) controlling the muscle spindle activity (130, 127). Slight increase in body temperature or in local hypothalamic temperature leads to synchronization of the electrical activity of the neocortex and desynchronization of the activity in the hippocampal cortex, thus giving rise to EEG patterns characteristic of drowsiness and sleep. It further leads to a progressive inhibition of the gamma motor activity whereby the muscle spindles are correspondingly silenced, which in its turn reflexly lowers the excitability of the large (α-) motoneurones.

A low body or brain temperature is accompanied by a desynchronized neocortical and a synchronized hippocampal activity which is characteristic of wakefulness and alertness. This thermal situation promotes a high gamma motor activity, maintaining the excitability of the motoneurones at a high level (98).

It has already been pointed out above that a good correlation has been found between thermally induced changes of muscle spindle activity and the conditions under which shivering occurs, and that there is a close relationship between the central nervous structures necessary for shivering and those involved in controlling muscle spindle activity.

The cortical and the motor responses thus paralleled each other closely. They proved not to be causally dependent on each other, but were probably jointly controlled by the activating relay systems of the brain-stem from which much of the activity of the body is governed. It was thus concluded that the thermoceptive structures of anterior hypothalamus described by Magoun *et al.* (207) project onto the activating brain-stem system of Moruzzi and Magoun (216). Since changes in activity mean changes in heat production, this projection incorporates the activating relay systems of the brain-stem and their control of the general level of activity into the feed-back system subserving homeostasis of body temperature.

Other interoreceptors probably also project onto these brain-stem relay systems and utilize it for refined adjustments in the corresponding homeostatic mechanisms. The baroceptive inflow from the carotid sinus, for instance, likewise

projects onto the brain-stem relays and thereby exerts a general damping influence on cortical and motor activities (46, 74).

In this way much more of the whole body than merely the thermoregulatory effector organs, as they are usually considered, is under feed-back control opposing the inherent temperature instability of living tissues due to the temperature dependence of the rates of chemical reactions. The temperature coefficient for the human metabolic rate has been estimated to be $Q_{10} = 2.6$ to 2.9 (80, 118). Impairment of temperature regulation may therefore lead to either hypothermia or hyperthermia, the effect depending upon the type of destruction, *i.e.*, whether the effectors for heat loss or for heat preservation were left on. From the poikilothermic organisms one may collect many examples of specific thermally induced reactions against overheating, which emphasizes the biological importance of preventing a self-perpetuating temperature rise (116).

E. The power of the regulating system

From the data presented so far it is evident that the hypothalamic thermodetectors exert an influence on potent thermoregulatory effector organs in such a way that a feed-back regulatory system is formed. There has, however, been some doubt about its physiological significance.

In order to be able to analyze negative feed-back circuits, such as those in a regulator or in a feed-back amplifier, as to the function of their different parts or to estimate their regulating power or "gain," it is necessary to break the feed-back loop at a suitable place. For instance, the detector device may, in some way, be prevented from "feeling" the result of the effector mechanisms and, instead, subjected to steady, predetermined external stimuli giving rise to corresponding "error signals" to the effectors. The end result of their activity in response to the different stimuli is measured, and the ratio of response to stimulus is then a measure of the regulating power or "gain" of the system.

Such experiments have been done in the past on the blood pressure regulating system governed by the carotid baroreceptors (192). When the pressure in one isolated carotid sinus is artificially set to different levels, the systemic pressure changes in response. If the baroreceptors of the aortic arch and the other sinus region are left intact there will be only transient responses. If, on the other hand, these other baroreceptors are denervated there will be lasting responses (165, 192). An elevation of endosinus pressure of 20 mm Hg would reduce the systemic pressure by some 20 mm Hg. This gives a "gain" of about 1. A similar type of experiment has recently been tried on the thermoregulating system (94). The hypothalamic area containing the thermoceptive structures was warmed diathermically with a multi-electrode set to a few tenths of a degree centigrade above the previous control level and kept constant at that temperature. This necessitated a continuous slight increase in the heating current to match the falling body temperature. The resulting temperature decrease was 8 to 10 times greater than the hypothalamic temperature elevation which provoked it. Since the hypothalamic temperature was measured by one of the heating electrodes,

the average tissue temperature was lower than that recorded. This gives a still higher value for the "gain."

The temperature regulator governed by the hypothalamic thermodetectors thus proved to have a regulating power of more than ten times. It should be remembered that the regulation governed by the skin thermoreceptors was left intact to oppose the action of the one tested. If the thermoregulatory feed-back mechanism were more powerfully governed by the skin receptors, there would have been almost no fall in body temperature in response to hypothalamic warming just as there is no shift in systemic blood pressure in response to changed endosinus pressure as long as other baroreceptors are left intact in their regulatory circuits.

The power of the regulator may also be expressed as the initial change in the rate of heat loss or heat production ($Cal/m^2/sec$) in response to a unit change in core temperature (30, 32).

F. The governor. Conclusions

The main conclusions concerning the detector device for thermoregulation may be summarized as follows. Temperature regulation seems to be governed by the thermodetectors of the anterior hypothalamus and is not necessarily dependent on the skin temperature receptors for the elicitation of adequate regulatory reactions. Only modifications in the performance can be attributed to the skin receptors. Their co-operation in the control of shivering is believed to minimize the phase-lag that is bound to occur between variations in heat loss and the compensatory thermoregulatory achievements. The skin receptors may be of importance for the behavioural aid in thermoregulation which aims at a "comfortable" skin temperature by creation of a suitable microclimate and by adjusting voluntary muscular activity so as to avoid large heat debts (59, 177, 178, 291). The cutaneous thermoreceptors are thus considered to have only a subordinate role in the regulation of the internal temperature, but to be of importance for the control of heat debt.

The question whether the thermoceptive structures in the hypothalamus generate impulses in response to temperature changes or whether they only modulate a train of incoming impulses cannot be answered with certainty as yet. It appears, however, that these structures do not depend on impulses from the cutaneous thermoreceptors. On the basis of current neurophysiological views, we must consider these thermoceptive structures as containing thermo-electric transducer properties transforming, in some way, thermal energy into electrical energy in terms of changes in polarization of neuronal membranes. The above question is thus only a question of thresholds, *i.e.*, whether these changes in membrane potential are in themselves sufficient to initiate impulses or whether their thresholds need the excitatory effect of impinging impulses in order to discharge impulses in proportion to the prevailing temperature. As a likely index of this thermo-electric transducing effect, slow d.c. potentials have been recorded from the thermoceptive impulses in response to temperature changes. These slow "thermo-potentials" (92) were interpreted as "generator potentials" (126).

This interpretation was strengthened when similar slow potentials were obtained from the medullary chemoceptive structures in response to CO_2. These structures were shown to have properties similar to peripheral receptors (96, 97).

G. Pharmacological aspects, general

The power of the temperature regulating mechanism, discussed above, suggests that drugs and agents may exert actions on the thermoregulatory effector systems without causing significant changes in body temperature. Whether a drug acting on a thermoregulatory effector organ will cause a change in body temperature or not depends mainly on two factors: 1) on the temperature threshold of the affected effector mechanism relative to the temperature thresholds of the other synergistic effectors, and 2) on the prevailing stress on temperature regulation by such factors as environmental temperature and muscular activity. The vasoconstriction induced by sympathomimetic agents, for instance, reduces the capacity for heat loss and provokes a mild hyperthermia. If this increase in body temperature were solely dependent on the vasomotor actions of these drugs, it would not be expected to exceed the temperature threshold for sweating. Most of the sympathomimetic agents have, however, other actions as well, and might influence the setting of the body thermostat (see below) and change the temperature threshold for sweating to a somewhat higher level. The anhidrotic action of atropine, on the other hand, which blocks thermal (as well as emotional) sweating at comparatively small doses in man (68), apparently does not affect body temperature of a subject resting at comfortable ambient temperature. In a hot environment, however, hyperthermia may develop in response to moderate doses of atropine in spite of the simultaneously occurring vasodilation. This temperature elevation may lead to heat stroke (174). The condition of impaired capacity for heat loss under atropine resembles that of a patient with congenital absence of sweat glands, as described by Richardson (233a). At rest, this patient exhibited an almost normal water vaporization from the skin. During exercise and with exposure to external heat the elimination of water did not increase, with hyperthermia as the consequence. The water vapor permeability of the non-sweating skin, however, is also claimed to decrease under the influence of atropine (54). Unfortunately, this effect of atropine was not brought to a test in the above-mentioned case.

In somewhat larger doses (about 1 mg hypodermically in man) atropine has been found to increase the metabolic rate (265), probably by an increase in muscular activity. Increased liveliness and restlessness were the main effects observed in response to injections of atropine in doses up to 150 μg into the lateral ventricle of the unanesthetized cat. Larger doses (200 to 300 μg) lead to a condition in which the cat lies panting in the cage, often fully relaxed, with all four paws outstretched, the eyes open, and blink and pupillary reflexes present. The condition "resembles that of a panting cat lying in the sun in hot weather" (105a).

Ethyl alcohol provokes both vasodilation and sweating, leading to a considerable increase in the rate of heat loss. This may not be compensated by increased

heat production, because of the depressant or narcotic action on central nervous structures. The hypothermia which may develop as a consequence is augmented by the fact that the rate of oxidation of ethyl alcohol is decreasing rapidly with falling body temperature (180a).

From what has been mentioned above it seems apparent that body temperature alone is a poor index of pharmacological actions on thermoregulatory mechanisms. Estimating the change in regulating power might prove to be a more suitable method for studying drug action on temperature regulation. Calorigenic methods have been used. Benzinger *et al.* (33), for instance, studied the effect of acetyl-beta-methylcholine (methacholine) on man in the gradient calorimeter. Intramuscular administration of 10 mg of this agent provoked a rise of the evaporative heat loss to more than 80% above the resting level. Later, heat loss fell slightly below the resting level and heat was retained again. Concomitantly, there were no significant changes in radiant skin temperature. It was not reported, however, whether or not this disturbance decreased the regulating power to such an extent that the body could not maintain its core temperature.

Other cholinomimetic agents such as pilocarpine, furtrethonium (Furmethide), and acetylcholine have similar peripheral sudorific actions.

In this connection it might be of interest to note that Burn and Dutta found it probable that "the maintenance of body temperature depends on a mechanism in which acetylcholine plays a part" (55a).

Behmann and Bontke (30) have studied quantitatively heat production in dogs during steady levels of hypothermia of various degrees. Thereby they obtained a measure of the regulating power expressed in heat production per unit rectal temperature. This enabled them to study in a quantitative way the effect of different depths of anesthesia. Anesthetics in full doses abolish all thermoregulating power, and since they also abolish the vasoconstrictor tonus body temperature falls (147, 277). In the cat, pentobarbital in smaller doses will, however, raise the threshold temperatures for the thermoregulatory reactions to higher levels, *i.e.*, it will produce a regulated "fever" (57, 88, 98, 99). Ethyl carbamate (urethane) lowers the threshold temperature for thermoregulatory events in cat (92, 133, 207). Morphine in small doses may have a similar effect, setting the regulator to a lower temperature level, as it were (146).

Changes in oxygen consumption or carbon dioxide production have also been used as indexes of the pharmacological actions of drugs on temperature regulation. The pyrogenic action of 2,4-dinitrophenol is to increase the metabolic rate, for which reason it was used, or widely misused, as a weight-reducing agent (70, 206). The oxygen consumption may be raised to more than ten times the normal in intact mammals. The accompanying temperature elevation may be lethal, and is not influenced by adrenergic blocking agents, curarization, thyroidectomy, or adrenalectomy (276), but is depressed by cyanide (100), large doses of quinine (222), and other drugs. There is accumulating evidence that dinitrophenol accelerates tissue metabolism and heat production by uncoupling phosphorylation from oxidation both *in vitro* and *in vivo* (203, 217, 218, 219). There are other nitro compounds with similar actions. Of considerable interest, however, is a

group of substances containing only carbon, hydrogen and oxygen which have metabolism accelerating actions very similar to those of dinitrophenol. To this group belong vulpinic acid, usnic acid, and humulone, as well as the well-known anticoagulants 1,3-indandiones and 4-hydroxy-coumarin (256, 257, 258, 262, 263).

The calorigenic action of epinephrine has been much debated. This subject was reviewed by Griffith (134), who concluded that an increase in metabolic rate of the organism as a whole by epinephrine may be accepted as an established fact, although "the case for adrenaline being a direct stimulant (or depressant) of cellular respiration has not been proven." This calorigenic action and the epinephrine hyperthermia seem to be caused by the integrated sum of both peripheral and central actions, the most important of which are the hyperglycemic action, the vasomotor effects, and the direct actions on central nervous structures (see below). Epinephrine has been found to provoke higher temperature elevations after intraventricular or intracisternal injection than when injected intravenously (104). The blood-brain barrier is an effective impedance against penetration of catecholamines into central nervous structures with the exception of parts of the hypothalamus (241, 285a). This may explain partially the observations that the catecholamines do not provoke arousal reactions more readily when injected arterially in the vertebral or carotid arteries than when injected intravenously (59a, 99, 207a).

During cold-acclimatization, the calorigenic effect of epinephrine, and especially norepinephrine, increases considerably (175a, b). In rats the calorigenic response to norepinephrine has been found to be a function of the amount of norepinephrine infused per unit time and also to be related to the duration of the cold exposure. The metabolic response to norepinephrine in the course of acclimatization was found to be related to changes in the thermoregulatory pattern. In particular it bears a striking inverse relation to the electromyographic record of muscular activity as a function of time of exposure to the cold environment. Accordingly, rats were found to increase their excretion of norepinephrine very rapidly in response to cold, with an almost maximal response within 24 hours. Epinephrine excretion showed a gradual increase to a maximum in 6 to 8 days, and a rapid decline thereafter (198a).

Effects of epinephrine and norepinephrine on the threshold temperatures for thermoregulatory events, and the possible role of the catecholamines for the setting mechanism are discussed below under "The setting of the body thermostat."

Tetrahydro-β-naphthylamine produces several adrenergic-like effects. Its thermogenic effect is well established. The metabolic rate is increased and the rate of heat loss is decreased by vasoconstriction. The calorigenic effect seems to be at least partly of peripheral origin, since it has been reported to occur in the spinal animal and, interestingly enough, to be dependent on the thyroid (190, 191). The "tetra" hyperthermia is not antagonized by salicylates or antipyrine but may be abolished if the vasoconstriction is overcome, *e.g.*, by nitrates or barbiturate anesthesia (6).

Other sympathomimetic agents such as ephedrine, amphetamine, methylene blue (100), and cocaine have pyretic effects which are attributed at least partly to vasoconstriction (265) and which occur mainly in a warm environment. Methylene blue hyperthermia is accompanied by increased electrical activity of the cerebral cortex. Racemic ephedrine (racephedrine, Ephetonin) may cause a fall in body temperature (265). Caffeine may cause a slight hyperthermia, probably through its central stimulating action, since it increases wakefulness and muscle tone; CO_2 tension is reduced, and the sensitivity of respiration to CO_2 is increased (236).

Histamine in doses of 50 mg/kg body weight decreases body temperature of rats and mice at a room temperature of 20°C (105a, 222a). Guinea pigs were much more sensitive, while rabbits did not show any changes in body temperature in response to histamine (222a). This effect is probably due to the increased heat loss by the cutaneous vasodilatation. Oxygen consumption was found to be depressed transiently (105a). At an ambient temperature of 30°C, histamine in the same doses caused hyperthermia and increased oxygen consumption (105a). The calorigenic effect of histamine was absent from adrenalectomized animals. These effects of histamine on body temperature were all prevented effectively by diphenhydramine or tripelennamine (105a).

The effects of drugs are, of course, temperature dependent (117, 118, 118a, 186a), the temperature coefficient, Q_{10}, being 2 to 4 for most pharmacological actions (117, 118). The metabolic rate when 2,4-dinitrophenol is administered, for instance, is greatly increased at ambient temperatures above 20°C but is depressed below 16°C (186a, 275). This may be attributable in part to the fact that the narcotic effect inhibits shivering. Accordingly, Tainter has suggested that external cooling might be the best treatment of acute dinitrophenol poisoning. Further, reserpine does not potentiate pentobarbital unless the body temperature is allowed to fall. This temperature dependence may be of considerable importance since the peripheral parts of the body, including a considerable mass of muscle tissue with its accompanying blood vessels and nervous structures, may be subject to large temperature variations (25). The vasomotor nerve endings may be of special importance in this respect.

Shemano and Nickerson (250, 251) have very rightly pointed out the importance of the environmental temperature on drug induced effects on thermoregulation. They have suggested the use of "the critical ambient temperature," the temperature above which hyperthermia and below which hypothermia is produced, as a measure of the effects of drugs on temperature regulation. Chlorpromazine, for instance, was found to elevate this critical ambient temperature to 36°C, while with 2,4-dinitrophenol it was lowered to 20°C. The insensitivity of this index is, however, indicated by the finding that the critical ambient temperature was hardly affected by drugs such as ergotamine, dihydroergokryptine, lysergic acid diethylamide, and 5-hydroxytryptamine, all of which are known to affect systems involved in thermoregulation in different ways (see below). Of greater interest seems to be the rate of change of core temperature at different ambient temperatures as compared with corresponding values for untreated con-

trols. Shemano and Nickerson (251) have recently presented such data for pentylenetetrazol.

II. THE SETTING OF THE BODY THERMOSTAT

It is of interest to find in the old literature (37, 200) that even at the time when the first concepts on thermoregulatory principles were enunciated it was clearly appreciated that the body temperature is not regulated to a fixed temperature level, but to different levels under different conditions. This concept of setting the body thermostat was substantiated by Nielsen (220) and has recently been subjected to animal experimentation. Euler and Söderberg (98) arrived at the conclusion that the activating brain-stem system of Moruzzi and Magoun (216) is closely interconnected with the thermoceptive structures in the hypothalamus. Against the background of these concepts it may prove possible to find some common denominators for many of the pharmacological observations on the influence of various agents on thermoregulation.

It was concluded above that the activating relay system of the brain-stem is employed in thermoregulation through the influence exerted by the hypothalamic thermoceptive structures. The activating brain-stem system is, however, "energized" by many nonspecific projections, which all contribute to determine the level of activity. Supposedly these other projections would then influence the thermoregulatory effector systems. In fact, the temperature levels at which both heat-dissipating and heat-producing reactions are initiated were found to be raised to a significantly higher level in response to different stimuli such as electrical stimulation of the midbrain tegmentum, nociceptive stimuli, and twisting the pinna, all of which proved to activate the cerebral cortex as well as the gamma motor system. As a consequence the body temperature rose to the higher level. Similarly, with the application of stimuli which inhibit the cortical and gamma motor activity, the threshold temperatures for these thermoregulatory effects were lowered, followed by a slight fall in internal temperature.

These results suggest that the state of activity maintained in the brain-stem activating system, or part of it, constitutes a thermally independent reference mechanism for thermoregulation. That is to say the temperature level towards which thermoregulation aims is different in different situations.

A. Fever

From his extensive studies on fever, Liebermeister in 1875 (200) concluded that the temperature in febrile patients is still precisely regulated, although at a higher level: "It is of the nature of fever that the heat regulation is set to a higher temperature level" which can be "reset" to normal values by the use of antipyretics. This has been confirmed repeatedly (80). If we accept this concept of fever as a setting of the body thermostat to regulate at a higher temperature level, then we would expect the underlying heat production to show an initial transient phase of large amplitude during the phase of temperature rise and a second phase of only slightly increased metabolic rate when the temperature stays level. DuBois (80) studied quantitatively the metabolic rates in febrile

patients and demonstrated such an initial "spike" of increased heat production, which amounted to 300 to 400% of resting metabolic rate, followed by the phase of steady temperature level when the metabolic rate was only increased by some 15% per degree centigrade above normal resting levels. This level corresponds roughly to what is to be expected from the change in metabolism simply due to the temperature coefficient for metabolism.

Fox and Macpherson (112) made comparative studies on thermoregulation in febrile subjects and in healthy subjects under thermal stress. Both quantitatively and qualitatively the thermoregulatory events were found to be the same with the exception that they all occurred at a higher temperature in the febrile patients. In accordance with this view, Thauer (277) presented data indicating that animals in which the thermoregulatory mechanisms are impaired cannot develop endotoxin fever (154).

The pathogenesis of fever has recently been extensively reviewed by Atkins (19) and Cranston (65) and falls outside the scope of this paper.

The available data on temperature regulation in health and in fever seem to suggest that pyrogens probably act on the hypothalamic thermoregulatory structures. Hashimoto (143, 144) subjected this hypothesis to experimental test. Cannulas aimed for the diencephalic heat sensitive structures were implanted chronically into rabbits. Pyrogens injected by this route proved more potent in producing fever than on systemic injection. Subarachnoidal or intraventricular injection of pyrogen in cats and dogs (253) elicited fever much more readily than when given subcutaneously or intravenously (249). Recently, selective heating of the anterior hypothalamic area in unanesthetized dogs has been shown to prevent pyrogen induced fever or to bring the febrile temperature down to normal (7, 136). This is an elegant confirmation of Barbour's (21) and of Hashimoto's (143, 144) finding that heat directly applied to the base of the brain is a potent antipyretic.

B. Antipyretics

Antipyretic effects have been demonstrated in response to direct intracerebral application of chloral, antipyrine, and quinine, and to local heating (22, 143, 144). The action of these drugs proved to be more effective when applied in this way than on systemic administration (19).

Salicylates and other antipyretics such as acetanilid, acetophenetidin, antipyrine, and aminopyrine have little or no effect when the body temperature is within normal range. In fever they change the heat balance mainly by increasing heat dissipation (22, 23). Heat production is lowered "passively" with the falling body temperature (see above). The antipyretic effects are not exerted peripherally. In monkeys with hypothalamic lesions the antipyretic action of acetylsalicylic acid was suppressed. Although sweating is very prominent the antipyretic action is not confined to this mode of heat loss. Even when sweating has been abolished by atropinization there is still a marked antipyretic effect, due to vasodilatation (135). Salicylates as well as the other antipyretic drugs mobilize water and cause hydremia which promotes heat loss by increased conductance

as well as by increased sweat rate (22, 23, 135). A similar though weaker antipyretic effect was evoked merely by lowering the osmolality of the blood by administration of glucose solutions (22).

Quinine was earlier believed to have an action similar to the antipyretic drugs mentioned above, although Hashimoto (143, 144) found that local temperature changes of the basal nuclei of the brain did not affect heat balance during quinine action as they do in untreated animals, and still more markedly during simultaneous treatment with salicylate or antipyrine.

The antipyretic effect of quinine is not very prominent, except in cases of malaria. The striking effect in this disease is due to its specific antimalarial action.

The weak antipyretic effect that quinine has in other febrile conditions seems to be due to a mainly peripheral, general inhibitory effect on metabolism (60, 61, 62) and suppression of skeletal muscle activity (82, 222).

C. Exercise

Nielsen (220) showed that the elevated body temperature during muscular exercise is, within a wide range, independent of the ambient temperature and precisely regulated, the temperature level being proportional to the intensity of the work. Nielsen suggested that this "setting of the body thermostat" to an elevated temperature during exercise would improve performance. Asmussen and Bøje (18) presented convincing evidence in support of that view, which was later repeatedly confirmed (238).

D. Diurnal variations

The diurnal variation in body temperature was first described by Hunter in 1778 (176): "When man is asleep, he is colder than when awake; and I find, in general, that the difference is about one degree and a half, sometimes less."

At the transition from sleep to wakefulness and from wakefulness to sleep, skin temperature and internal temperature may move in opposite directions (193). This is difficult to explain without postulating a change in reference for the thermoregulatory mechanism, probably linked to the mechanisms controlling sleep and awakening (73).

Both mammals and birds show diurnal temperature variations. Those species which are active during daytime have their temperature maxima in early afternoon and minima early in the morning, while those active at night have a reversed temperature rhythm (17, 161, 166, 181, 215, 254, 259). The diurnal temperature variation is largely independent of ambient temperature, the mealtimes, and to some degree also of the type of occupation during the 24 hours. It seems to be linked to diurnal rhythmicity of other physiological activities, and to depend on endogenous factors synchronized to revolution of the earth by some timing device of remarkable precision (16, 55, 285).

In human beings the average diurnal variations were greater for men (1.49°C) than for women of the same age group (1.20°C). The amplitudes varied from 0.7 to 2.1°C (213). The corresponding diurnal variations in heat production for human beings is around 10 $Cal/m^2/hr$. A temperature elevation of the same

magnitude, 1.2 to 1.5°C, due to exercise would require a work intensity corresponding to some extra 100 Cal/m²/hr (230). This shows that the daily temperature elevation does not depend on the increased muscular work or any of its correlates.

E. Emotions

A similar change in reference temperature for the thermoregulation or resetting of the body thermostat is also known to occur in response to various emotional stimuli. A rise of up to 2°C has been reported and may develop quickly with vasoconstriction, increased muscle tonus, and shivering, just as in fever. This emotional hyperthermia may stay level for some time and terminate with sensation of heat, vasodilatation, and sweating (85, 114, 134, 189).

In this connection it may be of interest to mention that moderate increase in rectal temperature in subjects at rest in a hot environment (*e.g.*, a hot bath) may be associated with some discomfort and with inefficiency in mental tasks (45, 204, 224). A similar rise in temperature during exercise is associated with less discomfort and no evidence of mental disability (26). It is suggestive to postulate that the degree of discomfort is dependent on the difference between the actual internal (brain) temperature and the reference temperature toward which the regulation aims. On this assumption the internal sensations associated with thermal stress would depend on the same principles as the feelings of hunger and thirst. These sensations are considered to be mainly of central nervous origin, and depend on the discrepancy between the prevailing blood levels of some factors (heat, glucose, water) and the "wanted" values (52).

F. Interactions between homeostatic mechanisms

The different effector systems engaged in thermoregulation are employed for other purposes as well. Accordingly, their activity varies considerably in response to many requirements other than those of the thermotaxic structures. This means that the thresholds of the different effectors for thermal activation may change with the prevailing situation, and thereby the mutual order in which they are engaged (1, 99). Heavy loads on more than one homeostatic mechanism may lead to what appears to be resetting of the regulators.

Osmoregulation provides a further example of the principle that a governor may be reset to different "wanted" values under different conditions. Verney (284) found that the water content of the blood is regulated with considerable precision by diencephalic osmoceptive structures (67, 93). These detector devices determine water intake (thirst), diuresis, and internal water shifts. The regulation of the water content of the blood is, however, intimately connected with thermoregulation. Movement of the body water is, in fact, an important effector system in the regulation of body temperature. A higher water content is maintained under conditions when heat loss activities are mobilized, whereas in cold the water content is regulated to a lower level than in rest in thermal neutrality. The water shifts as thermoregulatory reactions are initiated by local temperature changes of the base of the brain (21, 22, 23). Diathermic heating of the hypo-

thalamic thermodetectors has been shown to reduce diuresis with such a short latency that it must be regarded as a direct thermoregulatory effect (261).

From the above it would be expected that cooling the body would increase the threshold for thirst and decrease a prevailing desire for water. Common experience seems to support such a view, although conclusive experiments appear to be lacking as yet.

In the case of rivalry between different homeostatic mechanisms, it seems as if the set point of the regulators could be adjusted so as to meet the situation in the least "dangerous" way. Grande *et al.* (125), for instance, found that during exercise temperature rises to higher, but still well tolerated, levels in dehydrated men than in adequately hydrated subjects and that there is a correspondingly lower sweat rate. The results of Pearcy *et al.* (223) indicate that the diminished sweating during dehydration is probably not mediated by the antidiuretic hormone. Schmidt-Nielsen *et al.* (245) found a considerable rise in the core temperature of the dehydrated camel during daytime heat. These authors arrived at the conclusion that this temperature elevation is due to an adjustment of the regulator and not to regulatory failure.

It has already been mentioned above that increased afferent inflow from the baroceptors of the carotid sinus has an inhibitory influence on the activating brain-stem system (46, 74). It is suggestive, then, that a drop in blood pressure may influence the thermal balance in the direction of a rise in body temperature. In support of such a conclusion it has been found that partial blockade of the baroceptor reflex by small doses of ergotamine (105, 243) not only activates cortical activity but also lowers the threshold temperature for shivering (99).

During work in a hot environment the vascular system is subject to regulatory adjustments of partly opposite directions. There is a competition for available blood between the thermoregulatory increase of cutaneous blood flow and the demand for increased blood flow through the active muscles. A rise in core temperature not only evokes cutaneous vasodilatation: it may also lead to a decrease in the blood flow through the skeletal muscles (259) either by inhibition of the sympathetic vasodilator tonus or increased vasoconstrictor tonus or both. Muscular exercise, on the other hand, leads to active vasodilatation of muscle vessels (281, 282, 283) and increased vasoconstriction of the cutaneous vessels.

During muscular exercise the homeostasis of blood pressure depends strongly on the baroceptive reflexes (102). Under these conditions the baroceptors are considerably sensitized by the action of catecholamines (197) which are liberated at a much higher rate during work (101, 171). This increased baroceptive activity would, according to the above, inhibit motor activity and muscular exercises and depress body temperature. However, the catecholamines have been found to exert an arousing action on the activating brain-stem system (48a, 74, 208, 209, 242, 242a, 287) as well as a stimulating effect on some other central nervous structures (95, 112a, 142, 183, 229). These activating effects of epinephrine and of other stimuli associated with muscular work can evidently alter the blood pressure level as well as the temperature level at which the damping action is brought into play. In accordance with this, infusion of epinephrine and nor-

epinephrine has been found to arouse cortical activity and to raise the threshold temperatures for thermoregulatory events, with an elevation of body temperature as the result. From crossed-circulation experiments it was concluded that these effects of the catecholamines were at least partly exerted on central nervous structures and not mediated by liberation of glucose (99).

Thermoregulatory needs may be brought into conflict with the regulation of pulmonary gas exchange. The alveolar ventilation is governed to a large extent by the peripheral and the medullary chemoreceptors (96, 97). The rate/debt relation depends, however, among several factors on the needs for heat loss, since evaporation from the respiratory tract is of primary importance as a means of heat loss in most animals. Thermal polypnea is independent of the vagus nerve. Heat load will evoke thermal polypnea and, in some species, panting (44, 137, 201, 255). This pattern of respiration is often inadequate for metabolic needs and may lead to increasing hypocapnia (27, 69). As a compensatory reaction, panting is now and then interrupted, demonstrating the rivalry between the two regulatory mechanisms (92). Another example may be obtained from the simultaneous occurrence of hypoxia and heat debt. The hypoxic hyperventilation will cause an undue heat loss and an increased heat debt. Furthermore the hypoxia inhibits shivering, whereby repayment of the heat debt is prevented (121, 148, 194). Accordingly, hypoxia lowered, and breathing pure oxygen raised the threshold temperature for shivering (99). Hypercapnia had an effect similar to that of hypoxia (99, 214). In man the increase in oxygen consumption produced by cold was found to be smaller when breathing pure oxygen than when breathing air (58), although shivering was not affected (115). The above effects of the respiratory gases on the threshold temperatures of shivering may be referred chiefly to the afferent inflow from the peripheral chemoreceptors, since hypoxia had a much stronger effect than hypercapnia. Further, lobeline, which has a stimulating effect mainly on the carotid and aortic bodies (103, 164), in small doses (0.3 mg/kg, i.v., in the cat) inhibited shivering as readily as did hypoxia (99).

G. Further pharmacological aspects of the setting mechanism

The effects of drugs on the setting of the body thermostat have not been systematically studied except for antipyretics, a few other agents mentioned above, and *bemegride* (Megimide). The last-mentioned substance apparently does not influence the threshold temperatures of the thermoregulatory reactions (260). There are, however, available data which indicate that several other drugs may have such effects.

It has already been discussed above that *pentobarbital*, *urethane*, and *morphine* in critical doses may act as if they were changing the reference for the body thermostat.

Another centrally depressant agent which seems to have a similar action is *magnesium*. Schütz (247a) demonstrated that magnesium lowers the body temperature of rabbits and concluded that the effect was caused by a direct action on the central temperature regulating structures. This conclusion was based partly on his observation that magnesium-induced hypothermia was not coun-

teracted by calcium. The validity of his conclusion was questioned on the ground that magnesium has general anesthetic as well as "curare-like" actions. Suomalainen's finding that the ratio of magnesium to calcium is elevated in the serum of hibernating hedgehogs (273a) inspired Heagy and Burton (145) to analyze the mode of action of magnesium on temperature regulation, using unanesthetized dogs under different thermal conditions. Following intravenous injection of magnesium chloride they found a decrease in body temperature whether the experiment was carried out at hot, cold, or normal room temperature. At warm ambient temperature the effect was caused by increased panting, at normal room temperature by vasodilatation and panting, and in a cold environment by a decrease of shivering and of voluntary motor activity. In a cold environment, magnesium did not elicit vasodilatation. The authors concluded that the combined actions of magnesium "change the level of *effective* regulation in favour of a lower body temperature rather than merely depressing the temperature-regulating mechanism." It is well known that calcium antagonizes most of the actions of magnesium. This is true for both the anesthetic and the curare-like actions. Hall and Whalen (135a) took advantage of this antagonism in their study on the antipyretic action of magnesium and its site of action. They found that calcium had no effect on panting caused by magnesium but prevented the respiratory depression that occurred at high magnesium levels, thus confirming Schütz's original observation (247a). Magnesium panting, Hall and Whalen concluded, is due to direct stimulation of the panting mechanism, and not merely to the general depressant action's causing a "release phenomenon." Further experimentation using intracranial injection led these authors to conclude that heat and magnesium have a common anatomical site of action, *i. e.*, the hypothalamic thermoceptive structures. It still remains uncertain, however, whether shivering is depressed mainly by the same mechanism or whether the curare-like action of magnesium is the dominant factor for this effect.

Inhalation of magnesium oxide may produce fever and leukocytosis. Fumes of zinc oxide and other metallic oxides have similar effects, known as "metal fume fever," "brass chills," "zinc shakes," "galvo-fever," or "brass-founder's ague" (145a). The mechanism of action is not understood.

The *ergot alkaloids* have been found to influence temperature regulation. The actions seem to be exerted centrally since they are suppressed by general anesthesia. Both ergotamine and dihydroergotamine depress body temperature in small doses; in higher, especially in toxic, doses ergotamine provokes hyperthermia while dihydroergotamine causes hypothermia. The ergotoxine alkaloids (*i.e.*, ergocristine, ergocornine, and ergokryptine) raise the body temperature in all doses, while the dihydrogenated forms lower it. There seems to exist a parallelism between the rise in temperature and other signs of general excitation (243a).

Chlorpromazine has been found to have many interesting and varied modes of action; these include adrenergic blocking, antiserotonin, and weak antihistaminic properties, but probably only in preparations with an intact and functioning brain-stem activating system. Chlorpromazine has been used as an adjunct

for inducing hypothermia, since it has been reported to lower body temperature. However, the use of phenothiazine derivates in surgical hypothermia seems to be on the wane (86). Chlorpromazine is said to depress both shivering and vasoconstriction in response to cold. Moderate doses of chlorpromazine (10 mg/kg body weight) may cause a decrease in body temperature; the concomitant reduction in heat production was found to be very small or absent (4), and there was no significant increase in heat loss for a given surface area (198). This suggests a proper regulation at the lower temperature level, possibly utilizing the same mechanisms that cause the setting to a low temperature level during natural sleep. Chlorpromazine may not have a direct action on the activating system of the brain-stem (47, 48, 151, 188) but rather on the energizing afferent input to this system. The importance of an intact brain-stem for mediation of the effects of chlorpromazine has, however, been shown by Ingvar and Söderberg (180). They found that the drug reduces cerebral vascular resistance and concomitantly induces spindles and slow waves in the electroencephalogram. At spinal levels it seems to have insignificant effects. The marked effect on posture and on shivering (151) is probably due to its effect on the supraspinal control of the gamma motor system (98, 99).

In the rat, chlorpromazine provoked a rapid decline in body temperatures of approximately 4°C, followed by a steady core temperature for at least 6 hours which was still not back to control levels 24 hours after injection (170). The hypothermia produced in various laboratory animals was found to be largely independent of the ambient temperature (73a). In pigeons, it was found to evoke a slight but long-lasting hypothermic effect (169).

Mephenesin and *meprobamate* do not have apparent effects on thermoregulation at neutral ambient temperatures. These drugs reduce spontaneous activity and decrease skeletal muscle tone without causing other prominent central nervous symptoms. Mephenesin is effective in abolishing decerebrate rigidity. It acts at spinal levels, where polysynaptic reflexes are inhibited (36); supraspinal control of spinal reflexes is also readily abolished (128, 184). It may affect thermoregulation at cold ambient temperature, since shivering is prevented. Otherwise, neither mephenesin nor meprobamate seems to affect body temperature, although this does not seem to have been fully studied. Other centrally-acting muscular relaxants with similar modes of action, such as 2-amino-5-phenyl-1,3,4-thiadiazole and 2-amino-5-(2′-thienyl)-1,3,4-thiadiazole, also show an insignificant effect on body temperature (205).

Reserpine is often classified together with chlorpromazine, although these drugs differ considerably in their modes of action (72, 169, 170). Reserpine has been found to liberate catecholamines and 5-hydroxytryptamine from their various stores in the body (59b, 171a, 284a), peripherally as well as in the brain; accordingly, its actions may be dual: peripheral and central. The effect of reserpine on thermoregulatory mechanisms may be an example of its dual action. It lowers the body temperature (19a, 170), although in the rat, at least, it temporarily increases oxygen consumption considerably (170). This means that heat loss mechanisms are brought into action very effectively. The heat loss is

possibly due to peripheral depletion of norepinephrine from the vasomotor nerve endings, which would prevent vasoconstriction. Accordingly, the toxicity of reserpine has been claimed to be very much greater at cold ambient temperature than in warm environments (72).

The calorigenic action may be a central effect. It has been reported that the sympathetic outflow may be uninfluenced or even increased after administration of reserpine (284a), and it has been found that reserpine elicits persistent stimulation of the adrenal medulla, giving rise to a pronounced hyperglycemia (52a). Whether the central effects of reserpine on thermoregulation are due to interaction with norepinephrine, 5-hydroxytryptamine, or both, is an open question. Reserpine may liberate not only catecholamines and 5-hydroxytryptamine but also histamine, and possibly other active products.

Some effects of *epinephrine* and *norepinephrine* on threshold temperatures have been mentioned, and their possible role for the setting mechanism has been suggested above. Evidence has been presented that the blood level of epinephrine may be increased in fever (99a). Epinephrine and norepinephrine do not readily penetrate the blood-brain barrier, with the exception for the hypothalamic region. The brain is, however, easily penetrated by several lipid-soluble phenylethylamines and other drugs with adrenergic-like actions, such as methylphenidate (Ritalin), pipradol (Meratran), amphetamine, tetrahydro-β-naphthylamine, and lysergic acid diethylamide, which may possibly stimulate central adrenergic receptors and provoke their hyperthermic effects by this mechanism (52a, 242a).

5-Hydroxytryptamine (5-HT) has been found to produce hypothermia in mice (20 mg/kg) (105b) and in rats (5 mg/kg) (170, 250) at an ambient temperature below thermal neutrality. In the pigeon it also causes a fall in body temperature (169). In the rabbit, however, this substance was found to provoke mild hyperthermia (19a). Toh (279) has reported that extremes of temperature will selectively lower the brain content of 5-HT, an effect which is prevented by barbiturates.

5-Hydroxytryptamine, like epinephrine and norepinephrine, does not readily penetrate the blood-brain barrier. Its precursor, 5-hydroxytryptophan, however, reaches central nervous structures without difficulty, where it is rapidly decarboxylated to form 5-HT. The central actions of 5-hydroxytryptophan are presumed to be due to the formed 5-HT rather than to immediate actions of the precursor itself. It has therefore been considered advantageous to administer the precursor in order to study the effects of 5-HT. When tested on rabbits, 5-hydroxytryptophan was found to produce hyperthermia. This effect was roughly proportional to the dose given (173).

The amounts of free 5-HT in the brain may also be increased by agents which inhibit its inactivation *e.g.*, monoamine oxidase (MAO) inhibitors, especially if the MAO inhibitor is administered in combination with reserpine. Thus, after pretreatment with the MAO inhibitor, iproniazid, reserpine provoked hyperthermia as well as excitation, mydriasis, and piloerection. The hyperthermia observed in response to catecholamines, 5-HT, phenylethylamine, tyramine, or mescaline was also found to be potentiated by iproniazid (19a). Similar results

have been obtained with MAO inhibitors belonging to the class of *Harmala* alkaloids (228a). These effects of 5-hydroxytryptophan and of iproniazid plus reserpine have striking similarities to the effects of *d*-lysergic acid diethylamide (19a, 173).

d-Lysergic acid diethylamide (LSD) in comparatively large doses may produce depression of certain central nervous activities, while smaller doses have excitatory effects on the same structures, including at least parts of the brain-stem activating system (180, 231, 232). Following intravenous injection, LSD provokes a rapid rise of temperature in rabbits, cats, and dogs, with both vasoconstriction of the cutaneous vessels of the ears and increased heat production (172, 173, 244, 268). In the rabbit this is one of the most sensitive and constant actions (172, 173). The hyperthermia is not affected by conventional antipyretics but is prevented by sodium pentobarbital anesthesia, and there seems to be no indication that LSD acts directly on the thermosensitive structures of hypothalamus. Significant temperature change has been denied to occur in man in response to moderate doses (264), while in pigeons LSD induces hypothermia with decreased oxygen consumption and increased heat loss. In birds, LSD was found to be more potent in producing hypothermia than was chlorpromazine, which had a rather weak effect. Both 5-HT and reserpine also induced hypothermia in pigeons (169). However, 5-HT did not act as a synergist with LSD when given together with this compound, but apparently competed with the action of the latter drug. Reserpine was also found to antagonize the LSD effect. The mutual interaction found between 5-HT and LSD, in spite of the fact that both induced hypothermia in the bird and hyperthermia in mammals, may indicate that these agents exert their actions on the same central nervous structures (168, 169, 173). In this connection it is of interest that a cross-tolerance has been demonstrated to develop between 5-hydroxytryptophan and LSD, indicating their mutual relationship (173). The hyperthermic response to both LSD and 5-HT is greatly diminished by prior administration of the 2-bromo analogue of LSD (BOL 148). This block was found to be competitive and quite specific (173).

It is currently believed that catecholamines, 5-HT, or both may be mediators of activity of brain-stem structures and involved in the regulation of somatic, autonomic, and cortical activity (241). It is inviting, therefore, to think that these putative central neurohumors, as well as drugs interfering with their actions or metabolism, might also exert an influence on the setting mechanism of the body thermostat. Now that we possess rather precise methods for studying the effects of drugs on the different components of the thermoregulatory mechanism, it is to be expected that this hypothesis and the frequently questionable and scattered data presented above may eventually be replaced by well-established facts.

III. CONCLUDING REMARKS

This presentation has been concerned mainly with those aspects of thermoregulation which seem to be of significance for the understanding of drug actions on the body thermostat.

The importance of the ambient temperature on the effects of drugs has been stressed, as well as the facts that only the temperature of the core is subject to precise control and that the heat content of the body is not well regulated.

The occurrence of heat debt in a cold environment, when the peripheral parts of the body act as insulation for the core, may involve important problems of temperature dependence of drug action. During the presence of heat debt, drug induced vasodilatation will cause a rapid lowering of body temperature which may be due merely to changes in relative temporal characteristics for heat loss and heat gain of the core.

It should be kept in mind that rectal temperature is not always a reliable index of the temperature that is regulated. Changes in core temperature may not be a valid index of drug influence on thermoregulatory events. On this index the power of regulation may conceal the effects.

Actions on the effector systems should be investigated after the detectors have been cut out of action to prevent the compensatory effects of the feed-back loops. Drug induced actions on "central" thermoregulatory structures may be due to effects on three different mechanisms: 1) the hypothalamic thermodetectors, 2) the "reference" mechanisms and the setting mechanisms for the body thermostat, 3) the hypothalamic relays for the co-ordination of the regulation.

The following suggestions have been made concerning the methods of studying the site of drug actions on temperature regulation: 1) determinations of changes in threshold temperatures of the thermoregulatory reaction, 2) estimation of changes in regulatory power, either a) in terms of changes in heat loss or heat production (Cal/m^2/sec) per unit temperature change of the detector, or b) in terms of change in body temperature per unit temperature change of the detector. The determination should be carried out at different ambient temperatures.

The brain-stem activating system seems to be involved in the mechanisms determining the setting of the body thermostat. Drugs which influence the activity of this system appear to have an influence on the temperature level of effective regulation. Of special interest in this respect are epinephrine, norepinephrine, and serotonin, as well as drugs affecting the metabolism of these neurohumors.

The many interesting problems concerning acclimatization and seasonal variations in non-muscular chemical heat production have been left out of this presentation mainly because so very little is known about the factors controlling these events. It is of importance, however, to keep in mind that the response pattern to drugs may change considerably with the season and the state of acclimatization.

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