ON PHYSICAL HEAT REGULATION AND THE SENSE OF TEMPERATURE IN MAN

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Human physiology has given much of its attention to those systems which control in a multicellular organism the essential internal conditions: to respiration as it provides optimal concentrations of carbon dioxide, hydrogen ions and oxygen, to circulation as it maintains adequate blood flowrates and pressures, and to production and loss of energy as they are balanced through a regulatory mechanism for the maintenance of optimal body temperature.

For the purpose of analysis, three main components may be distinguished with any regulatory system in physiology:

1. Specific sensory-receptor organs register the physical or chemical quantity that is to be regulated. They produce nerve impulses commensurate with the magnitude of this stimulus.

2. One or more effector organs act in response to the stimulus. This results in a return of the physical or chemical quantity registered toward the optimal level whereby the stimulus is reduced or abolished at the site of registration and elsewhere.

3. A coordinating center in the central nervous system receives the afferent nerve impulses. It produces efferent impulses which initiate or maintain the regulatory action of the effector organs.

A physiological control mechanism cannot be considered clarified until its effector organs, center of coordination, and receptor sensory structures have been identified, and until the quantitative relations between causes and effects, that is, between physical or chemical stimuli and physiological responses, have been demonstrated. In this paper an attempt is described to clarify experimentally one of these mechanisms: the so-called "physical heat regulation"* of man. We shall also discuss the registration of temperature and the sense of temperature, functions no less important than the other senses to survival and performance at various intensities of exertion, on earth with its many climates. Such an attempt begins at the present state of knowledge and requires a brief history of the discoveries made in this field.

For the regulation of temperature in experimental animals and man physiologists have detected, at very early times in some instances and more recently in others, the following possible components suited for the sensory, central, or effector assignments:

(a) The human skin contains terminal organs capable of initiating consciously perceived sensations of warm or cold. Moreover, following the discovery in 1904 by Kahn¹ that elevated intracranial temperature is an effective stimulus for the activation of heat loss mechanisms, and the experiments of Barbour in 1912,² pointing to the basal ganglia of the brain as a temperature-sensitive site, thermo-regulatory responses to temperature have been elicited experimentally in animals by Magoun et al. (1938),³ by Hess and Stoll,⁴ and by Folkow et al.⁵ from the pre-

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optico-supraoptic region of the hypothalamus, a primitive part of the forebrain. Finally, C. von Euler (1950) succeeded in eliciting "slow temperature potentials" of highly specific characteristics through artificially induced changes of temperature in the preoptico-supraoptic region of the hypothalamus in cats. These potentials are indicative of receptor cells translating thermal energy into electrical energy, "much as a retinal cell changes the energy of light into an electrical potential."

(b) On the effector side, three mechanisms for altering body temperature have been established: (1) an increase of total metabolic rate in response to cold environment was found by Rubner (1900) (this mechanism shall not be treated in the present paper); (2) in response to warm environment, sweat is secreted by cutaneous sweat glands, and heat is absorbed in its evaporation (measured by Rubner, 1900); (3) furthermore, in response to warm environment, the heat transferring component of blood flow (that is, the flow of blood between the interior of the body and the skin) increases substantially, which facilitates heat loss as long as internal temperature is higher than skin temperature. Thermoregulatory changes in blood circulation have been observed in 1900 by Rubner, and measured in 1936 quantitatively by Burton and Bazett in a bath calorimeter, with the method of determining thermal "conductance" introduced by Burton (1934).

(c) Earlier than the cerebral registration of thermal stimuli, the existence of a cerebral thermoregulatory center was discovered, with a "puncture" technique by Aronsohn and Sachs (1885). Isenschmidt and Krehl (1912) made animals poikilothermic by transecting the diencephalon in its rear and middle part. After a separation of the telencephalon from the brain stem they found that temperature control was essentially intact. The efferent thermoregulatory impulses originate mainly from the caudalateral part of the hypothalamus and adjoining mesencephalic tegmentum, that is, at some distance from the thermally sensitive preoptico-supraoptic tissue.

From the undisputable pieces of experimental evidence a concept of autonomic physical temperature control was developed and generally accepted by physiology, in which the cerebral thermoregulatory system receives its main afferent thermoregulatory impulses from the thermoreceptors in the skin, and then evokes responses in the effector mechanisms, namely sweat glands and cutaneous vessels. Space does not permit quotation from the numerous original papers, monographs, physiological reviews and chapters on temperature control in the textbooks of medicine or physiology, in which the stimulus of internal temperature has been attributed a role no more important, and more often a role less important than the stimulus of skin temperature in eliciting afferent thermoregulatory impulses to the hypothalamus for vasomotor and sudomotor action. Much of the more recent work on physiological temperature control was designed to quantitate the part played by "reflex" control originating from cutaneous thermoreceptors. In some papers the role of internal temperature has been reduced to a mere influence upon the excitability of the centers for afferent impulses from the skin. In others, which assume a participation of both cutaneous and internal nerve impulses, mathematical equations, models, or electrical analogues have been applied to describe in quantitative terms the role of impulses from the skin. Moreover, attempts have been made to attribute the origin of impulses for the regulatory centers to deep skin receptors which register temperatures intermediate between internal and cutaneous
or gradients between two sets of end organs in the skin, one deep and the other superficially located.\textsuperscript{16}

Progress in methods rather than theoretical considerations gave occasion to the present study with the availability of a new principle\textsuperscript{17} and instrumentation\textsuperscript{18} for human calorimetry. The first objective was to find whether cutaneous or internal temperature or both of them or none of them act as stimuli eliciting the known thermoregulatory reactions to environmental conditions. Secondly, it might be possible to clarify in a quantitative manner the function of this neural mechanism of sensory, central, and effector components. This would then help in finding rational approaches to physiological aspects such as limits of tolerance, protection or adaptation, or to the pharmacology of the vasomotor and sudomotor phenomena, or to pathology and clinics including the problems of fever and hypothermia for surgery. Needless to say that only the higher level of organization is meant by "clarifying" the mechanism, which excludes the molecular aspects of smooth muscle contraction, sweat secretion, nervous transmission, and transformation of thermal stimuli into nerve impulses.

The experimental approach was by functional not anatomical analysis of the apparatus, without blocking measures, with all parts of the system intact and in vigorous thermoregulatory action, by simultaneous and continuous measurements of the responses and the two possible stimuli: \textit{internal} temperature and \textit{skin} temperature.

These two temperatures, unfortunately, move jointly up or down under most physiological conditions and make it thus impossible for the experimenter to decide which one of the two was the stimulus for a response he observed. This difficulty may be overcome by experimental interference, dissociating the internal and cutaneous temperatures from their normal relation. Even so, there would be some interdependence and no plot could be obtained with, say, internal temperatures varying over a wide range, and skin temperature always at the same standard level or vice versa. Yet, such a plot would seem to be required for observation of the vasomotor and sudomotor responses to \textit{internal} temperature without interference from \textit{cutaneous} thermoceptors. The same considerations would apply to the converse: observation of responses to \textit{skin} temperature without interference from \textit{internal} thermoreception. Fortunately, there are two very special cases in which unequivocal answers would be obtained: if the thermoregulatory system of vasomotor and sudomotor responses were completely insensitive to \textit{internal} temperature, responses plotted against \textit{skin} temperature would fall upon one best line, with all deviations random and within experimental errors. Conversely, if the system were completely insensitive to \textit{skin} temperature, the responses plotted against \textit{internal} temperature would fall upon one best line, with all deviations random and within experimental errors.

After a careful study of the literature it became most unlikely that either one of these two special situations existed. However, if it did, the experiments would leave no doubt about it. One of the two plots would be smooth, the other disrupted, if measurements could be obtained at widely varied relations between internal and cutaneous temperatures. If both stimuli were powerful, neither of the two plots would make sense. If one of the two were the true stimulus and the other had some influence upon the response, however weak and of whatever origin, this would
cause a directed, not random, dissociation of the plotted values. Prior to a discussion of the outcome a brief introduction is required on experimental tools and procedures.

METHODS

A. Calorimetry.—The quantitative principle of gradient calorimetry introduced in 1949\textsuperscript{17} permits continuous and rapid recordings of heat loss, which in a steady state, is equal to metabolic heat production; a ventilatory air circuit with the gradient calorimeter permits the separate measurement of the rate of evaporative water loss as a component. A respiratory air circuit allows the separation of pulmonary heat losses from the heat transfer through the skin. From cutaneous heat loss, $Q$, and the difference between internal temperature, $T_i$, and cutaneous temperature, $T_s$, “conductance,” $C = Q/(T_i - T_s)$ (the thermal index of heat transferring blood circulation), is readily derived. It is therefore possible by gradient calorimetry to obtain rapid and continuous recordings of the two responses—sweat secretion and peripheral blood-flow rate—simultaneously with the potential stimuli, namely, skin temperature and internal temperature. For the calorimetric techniques and their reliability (error ± 1 per cent of human resting metabolism or 0.2 cal/sec), reference is made to a previous publication.\textsuperscript{18}

B. Thermometry.—For the measurement of internal body temperature, a site as well defined and as close as feasible to the hypothalamic heat center was chosen. Into the external auditory canal, 36-gauge twin wires of copper and constantan were introduced. The thermoelectric junction of the wires was placed at the tympanic membrane. Cotton insulation protected the site from undue influence of the environmental temperature. Stable and reproducible measurements, responsive to experimentally induced changes, were thus obtained. The correct location of the junction could be judged from the slight pain and alteration of hearing felt during the hours with the junction in position. These measurements at the tympanic membrane were verified as representing cerebral—and therefore hypothalamic—temperatures, by simultaneous measurements at other intracranial locations (Figure 1a). In collaboration with G. W. Taylor thermocouples were placed a) at the anterior outer wall of the sphenoid sinus; b) at the base of the skull in the anterior ethmoidal region, and c) in the nasopharyngeal recess of Rosenmüller for comparison with d) the tympanic membrane site. Locations a) and b) are supplied with blood from the internal carotid artery by way of the ophthalmic and ethmoidal branches. In location c) the thermocouple sat on the stem of the internal carotid artery. The nostrils were sealed while the choanae remained open. Levels of temperature at a), b), and c) were found practically identical. So were the quantitative changes of temperature (integrated areas) observed at b), c), and d) (Figure 2) after ingestion of ice. The only difference found with d), the tympanic measurement, was a less rapid response due to slower circulation through bone and cartilage. The reading of d) was always the highest (regardless of environmental temperature) because evaporative cooling takes place at the wet surfaces of a), b), and c). None of these differences is disturbing the experiments under consideration. Potentials from single junctions were amplified 100 times with a dc-breaker amplifier. Calibrations were carried out with certified mercury thermometers with the junction firmly attached to the bulb and the thermometer
immersed in water. The readings were reproducible within ±0.01°C. A standard temperature for all reference junctions was established arbitrarily but reproducibly at 38.38° ± 0.005°C, in a 1 kg block of pure aluminum, accommodated in a thermos flask, which was protected by a collapsible polyethylene bag for deep immersion in a 60-gallon water tank. The tank was continuously stirred and regulated at 38.38° ± 0.01°C, using a larger mercury bulb and a fine capillary with platinum contact. The contact operated a relay for intermittent heating. Additional constant heat was applied. The bulb, capillary, and lead wires were also immersed deeply in the tank. Cooling was not required, with a room temperature of +24°C.

Skin temperature was measured in ten chosen places (forehead, cheek, upper arm, chest, back, lateral thigh, medial thigh, calf, dorsal foot, dorsal hand), and integrated by wiring these ten thermoelectric potentials in series, with tenfold amplification (to match the response of internal temperature as measured with one thermocouple and one hundredfold amplification). The deflection obtained on the recorder was 10 cm/C° for all temperature measurements. The skin junctions were isolated with moistureproof resin and placed between two pieces of soft 100 mesh copper wire-screen, 1 × 2 inches. These were firmly attached to each other and to the skin for thermal contact. Copper screen was used for its thermal conductivity and negligible interference with sweat evaporation from the site of measurement.

An independent check on this way of measuring and integrating average skin temperature was carried out by calorimetry: through experimental interference, human heat loss may be altered so that it changes sign, going through zero. At these instants, the driving force of human heat loss, namely, the temperature gradient between internal and skin temperature, must also be observed to be zero, if all the independent calorimetric and thermometric measurements are correct. Figure 2 shows that this was indeed the case, except for a shift by 0.1°C—or 1.2 percent of the difference between air and skin temperatures—toward air temperature, under extreme conditions. With this applied as a correction, average skin temperatures as measured are considered reliable within ± 0.1°C centigrade. This seems satisfactory compared with a range of 12°C over which skin temperature varied between the limits of our experimental conditions of environment. The independent confirmation by calorimetry should eliminate from the discussion of the experiments reported here the never-ending argument, whether or not skin temperature was correctly measured, and correctly integrated over the entire surface of the body.

C. Means of Influencing Separately Cutaneous and Internal Body Temperatures.—To influence skin temperature, levels of environmental temperature were varied between experiments on different days over a range from +10° to +45°C in 5°C steps.

This covers on the hot side, the range in which a nude resting subject can maintain a thermal steady state for an indefinite period with his physical heat regulation. In order to obtain reproducible steady states, waiting periods of one to two hours were often required, and some of the experiments including work periods lasted up to seven hours. The subject wore bathing trunks. He was suspended in the supine position on wire-screen as described in reference 18. Wall and air temperatures in the calorimeter were kept alike. Ventilatory air was supplied at a rate of 800
liters/minute with a water vapor pressure of 6.3 mm Hg throughout. The resulting relative humidity in the calorimeter was of the order 25 per cent with the resting subject, or 50 per cent during exercise. In this way it was ascertained that full wetting of the skin never occurred during the experiments. Any loss of water by dripping sweat without evaporation would have been physiologically meaningless and technically incorrect, since the measurement was based on the heats of evaporation and condensation. Whenever, as in these experiments, the water secreted from the sweat glands is immediately and completely evaporated, the heat of evaporation represents directly the rate of sudomotor action. Respiratory air was separately supplied with a flow rate of 100 liters per minute at a temperature of 37.5°C with 50 per cent relative humidity throughout, regardless of environmental temperature. These conditions were established to avoid a direct influence of the variations in environmental temperature, upon the chest organs. For similar reasons nose breathing was maintained throughout, with a breathing mask by which the subject inhaled from, and exhaled into the constant 100 liter air stream of the respiratory circuit. The excess air of the circuit does not enter the calorimeter. The water vapor content of the air in the calorimeter was measured at one-minute or five-minute intervals, and rates of change, if any, were applied as a correction to the calorimetric readings.

For influencing artificially the temperature prevailing at the internal thermoceptive system, physical exercise proved to be most useful. Steady states may be obtained by exercise with increased metabolic heat production and loss. This leads to elevated steady levels of internal temperature, whereas skin temperature is influenced very little, and often, so it was found, in the opposite direction (skin cooler during exercise). Two levels of physical exercise were used: 6 calories and 12 calories of work output per second, which was measured by means of a special ergometer, to be described elsewhere. With an efficiency of approximately 25 per cent for the mechanochemical conversion of energy in muscle, the 6 or 12 cal/sec work levels resulted in 25 to 50 cal/sec increase of metabolic rate over the resting level of approximately 20 cal/sec.

While muscular exercise appeared to be the method of choice for a separation of internal and skin temperatures in steady states for a high reproducibility in quantitative observations, a different technique was found to be useful with nonsteady states and rapid changes.

By repeated eating of ice-water emulsions, internal temperature may be thrown into a cycle of fluctuations covering with its amplitude more than one-third of the entire range of physiological control. Although under these conditions, there is not enough time for every measurement to arrive at its final and entirely reproducible level, the ice procedure is suited to show in one experiment without further evaluation, which of the two, skin or internal temperature as a stimulus, is answered by the effector mechanisms of human heat loss.

RESULTS

A. Observations with Rapid Changes.—Figure 1 is a photograph of an original recording, 8 X 16 inches. In this experiment with a male subject (age 53, height 180 cm, weight 72 kg) in a hot environment (+45°C) in the gradient calorimeter, the following quantities were simultaneously recorded over time: (1) average skin
temperature; (2) internal (cranial) temperature; (3) rate of water evaporation. Three times (arrows at zero, 27 and 50 minutes) the subject, through eating hastily 450 g of an ice-water emulsion, lowered his internal temperature by approximately 0.6°C. Each time, the ice was consumed in approximately three minutes. Internal temperature reached a minimum after approximately ten minutes and then re-

Fig. 1.—Effects of periodic changes of internal temperature, induced by repeated oral ingestion of ice in hot environment (+45°C). The effects upon rate of sweating and skin temperature were simultaneously recorded. For identification the area between the lines for internal temperature (upper line) and rate of sweating (lower line) has been shaded.

Fig. 1A.—Intracranial measurements of temperature. X-rays in lateral and mento-vertical views show thermocouples placed at the anterior ethmoidal site, b), in Rosenmueller's recess, c), and at the tympanic membrane, d). Site a), the anterior wall of the sphenoid sinus, is indicated, without thermocouple, by dotted rings. The recording, taken immediately after the X-ray, shows the three responses practically identical in quantity although less rapid at the tympanic membrane and with a minor influence of evaporative cooling at the "wet" sites b) and c). Subject: T.B.
turned swiftly to normal. In this way, a repeated cycle of internal temperature with considerable amplitude was artificially induced. The cycle is reflected in every one of the physiological measurements.

The essential observation is, that the curve for rate of sweating reproduces like an image, the internal cranial temperature. It seems difficult indeed to avoid the conclusion, that internal temperature was the stimulus, and sudomotor activity was the response. For there is no other, no physical connection between the temperature at the tympanic membrane and the rate at which the sweat glands in the skin are pouring out water. Skin temperature, different from internal temperature, was paradoxically related to the rate of sweating. Whenever skin temperature rose, the rate of sweating dropped and vice versa which would be nonsensical as a thermoregulatory response. It is impossible to explain the repeated increases of skin temperature as a direct, physical effect of cooling the abdomen with ice, and it is also impossible to consider the changing skin temperature as a cause or stimulus for the observed changes in sudomotor activity, since the response would not make sense. The role of skin temperature is therefore recognized as passive, with the sequence of events as follows: Eating the ice reduced internal temperature, which depressed the sudomotor action, and made the temperature of the drying skin rise for mere physical reasons in the intensely hot environment, by radiation, convection, and conduction. The opposite changes took place in the opposite phases of the cycles.

Conductances as indices of the rate of peripheral circulation were computed from the cutaneous and internal temperatures and from the heat loss through the skin, simultaneously recorded though not shown in Figure 1. Conductances at the peaks of internal temperatures were found to be three times as high when compared with the conductance values at the minima of internal temperature. Although precision cannot be claimed for measurements of conductance in nonsteady states, it became

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**Fig. 2.—Calorimetric check on measurements of average skin temperature.** Periods are shown during which total cutaneous heat loss and the gradient between internal and cutaneous temperatures are inversed. In the lower part of the figure, the broken line represents the rate of cutaneous heat loss after correction for cyclic changes of humidity in the calorimeter. The phase-shift is caused by lag of tissue temperatures behind the calorimetric measurements of sweating.
obvious from these observations that both sudomotor and vasomotor activities responded to internal, not cutaneous, thermoception. With simultaneous and rapid recordings of the essential quantities it thus became quite improbable after a single experiment, that the thermoreceptors of the skin participate at all in human physical heat regulation by sudomotor and vasomotor activity. In view of the importance of the issue it was felt, however that tests should be extended over the full range of human tolerance to heat, to rule out any influence of skin temperature on sudomotor activity, to study peripheral blood flow in a similar way, and to arrive at a complete and quantitative understanding of the basic mechanism underlying the physical heat regulation of man. Experience showed that ultimate precision and reproducibility can only be attained in steady states, where the heat flow rate is uniform throughout the system, and differences of temperature are observed only in space, not in time.

B. Steady-State Observations.—(1) Sudomotor activity: On eight different days between October 23 and November 14, 1958, a subject (not the same as in experiment Figure 1, male, age 33, height 175 cm, weight 72.5 kg) rested or worked at either one of the two levels, 6 or 12 cal/sec, respectively, in the gradient calorimeter at constant levels of environmental temperatures of +10, +15, +20, +25, +30, +35, +40, and +45°C. Each state of rest or exercise was maintained until after an hour or more, all thermometric and calorimetric observations had reached steady levels and maintained these levels for a period of 10 to 20 minutes with negligible changes. The measurements in these steady states were used in Figures 3 to 7 for plots of internal temperatures, skin temperatures, rates of water evaporation, and indices of heat transferring blood flow (conductance). Attention is again called to the fact that full wetting of the skin did not occur in these experiments. Whatever water was secreted by the sweat glands was immediately evaporated from the skin. Therefore, the rate of evaporation as measured was identical with the intensity of sudomotor action.

In Figure 3 the rates of sweating in the various steady states were plotted against the skin temperatures. The line drawn through the points of observation at rest (dots) shows a reproducible relationship between skin temperature and rate of sweating, well known from everyday experience. This must, however, not be interpreted as a relation between stimulus and response. For during exercise the rates of sweating (triangles) observed at the same skin temperatures fell widely off the curve. They were higher by 35 cal/sec as an average, or 50 cal/sec at the maximum. This dissociation was accomplished simply by increasing metabolic activity through exercise, which affected skin temperature very little, and changed internal temperature very much. Obviously, skin temperature cannot be the stimulus, since its relation to the rate of sweating is inconsistent.

In contrast, the relation between internal temperature and rate of sweating is consistent for both work and rest observations as shown in Figure 4. Every conceivable effort had been made, and documented as to its efficiency, in Figure 3, to force skin temperature to show its hand in human heat control. These efforts failed. The firm relation between internal temperature and sudomotor activity—a stimulus-response relation—was not disrupted by the drastic changes of skin temperature, nor by the drastic action taken to produce those changes, anywhere in the physiological range of tolerable environmental conditions.
In looking back on Figure 3 it now becomes apparent that a meaningless though reproducible relationship must exist between sudomotor activity and skin temperature at rest: since sudomotor action as a response is consistently related to internal temperature as a stimulus, while internal temperature in a resting man happens to be reproducibly related to his skin temperature, a coincidental relationship must be observed at rest between skin temperature and sudomotor action. This relation is readily broken by any measure dissociating internal from cutaneous temperature. The relation thus shown to be coincidental, was certainly one of the reasons why a stimulus-response relationship between skin temperature and thermo-regulatory action had been invariably assumed. Another even more attractive reason will soon become apparent with the measurements of heat transferring blood flow.

(2) Heat transferring blood flow: The measurements of thermal conductance are shown in Figures 5 and 6. While for the rate of sweating, irrelevance of skin temperature could be clearly demonstrated, this is not physically possible for blood flow to the skin. Directly, without reflex action, the temperature of the skin has an influence upon the state of dilatation in cutaneous vessels. It is an everyday experience, that the skin may change its color locally when stimulated by heat or cold. Several authors have shown that such changes take place after transection of cutaneous nerves (for example, Breslauer; Hyndman and Wolkin). It must therefore be expected that in observations during exercise, when for any
given internal temperature the temperature in the cutaneous vessels is comparatively low, cutaneous blood flow rate will be lower than in corresponding observations at rest (when for any given internal temperature, skin temperature is at its maximum value). This modifying influence of skin temperature, though clearly visible in Figure 6, does not obscure the more important relation between internal temperature and vasomotor action. It is an image of the relation between internal temperature and sudomotor action, shown in Figure 4, with sudden increase from a sharply defined threshold, which is approximately 0.15°C lower than the threshold observed with sudomotor activity. While rigorous reasoning could be applied with Figure 4 for sudomotor action, common sense reasoning would accept from Figure 6 as a fact that vasomotor action is likewise a response to the stimulus of internal temperature, modified, but certainly not determined by some direct effect of skin temperature upon the state of dilation in cutaneous vessels.

The nature of the side effect cannot be judged from present data. The literature (Hyndman and Wolkin,\textsuperscript{20} Krogh,\textsuperscript{21} DuBois\textsuperscript{22}) suggests several contributions: (a) direct action of temperature upon the vascular muscles, (b) chemically mediated dilatation, (c) axon reflexes.

Whatever their nature, these protective side reactions from the part of the vascular system would continue to function, if the organism were deprived of its hypothalamic regulation of temperature. They may represent the lowest—and
phylogenetically oldest—level of organization in the physiological control of heat. The separation of resting and work observations in Figure 6 tends to confirm observations made by Thauer,23 that a certain defense against heat stress is maintained in animals with low transsections of the brain stem. These mechanisms would, however, be inadequate to maintain by themselves a constant human body temperature. They seem small in comparison with the steep rise of conductance above the threshold of internal temperature as shown in Figure 6, and the rise of sudomotor activity as shown in Figure 4. One reason for the efficiency of the hypothalamic mechanisms is that vasomotor and sudomotor action are working in a "tandem" arrangement: The increased conductance facilitates heat-transfer from the interior to the skin. Through evaporation of sweat the heat transfer continues on out, from the surface of the body to the environment. Therefore, one of the two responses cannot work efficiently without the other. The various direct influences of temperature upon the state of dilatation in cutaneous vessels, so readily observed if not measured at the surface of the body, must have contributed largely to the unproved hypothesis on human temperature control through reflexes from cutaneous thermoceptors.

When conductances are plotted against skin temperatures (Fig. 5) the values measured during exercise (with relatively high internal temperatures) fall far above the curve drawn through the observations at rest. The explanation is, of course, the same as given with Figure 3 for the rate of sweating. In the following summary and in Figure 7 only observations at rest were used for demonstration of the vasomotor response. Observations under both working and resting conditions were used for sudomotor activity.

(3) Summary of steady state observations: It is now possible for physiological considerations to give in one graph a quantitative description of the basic mechanism* underlying the physical heat regulation of man: at rest in cool environments (with internal temperatures between 36.0 and 36.6°C) both mechanisms were inactive. Water evaporation was negligibly small. Conductance usually re-
mained below 5 cal sec\(^{-1}\) deg\(^{-1}\). No further reduction indicating vasoconstriction was observed with increasing cold stress. In warm environment the rate of sudomotor action rose from a sharply defined threshold at 36.9°C, responding in the order of one calorie per second to every increase by \(1/100\)°C. The rate of heat transferring blood flow rose earlier, with a significantly lower threshold of internal temperature. Above the threshold, conductance responded with 0.25 cal sec\(^{-1}\) deg\(^{-1}\) to the order of \(1/100\)°C of change in internal temperature, and to smaller changes at higher levels. Through the two responses as described, internal temperature was maintained within a 0.5°C range, in spite of variations in metabolic output from 20 to 70 cal/sec and variations of environment from comfortable to hot, near the limits of tolerance. (The mechanism of chemical heat regulation, active though not presented in the low temperature range of the experiments shown in Fig. 7, shall be described in a later study.)

The experimental results of Figures 1, 4, 6, and 7 may be summarized in one sentence, and the contents of Figures 3 and 5 in another: (1) the mechanism underlying human physical heat regulation has been described as a response to internal temperature by vasomotor and sudomotor action; (2) the absence of a contribution by skin temperature—and therefore by afferent impulses from cutaneous thermoreceptors—to the autonomic mechanism of human physical heat regulation has been demonstrated. A number of conclusions follow inevitably from these findings.

CONCLUSIONS

1. The first conclusion is concerned with the nature of the preoptico-supraoptic region of the hypothalamus as a terminal sensory (-receptor) organ, not merely a site of synaptic interconnections: While it had been established beyond doubt, that thermoregulatory responses\(^3\) and action potentials\(^4\) may be elicited from this region, it had not been conclusively ruled out, and indeed postulated by a number of authors (for example, in references 12, 13, 24) that afferent impulses from the skin are a prerequisite to such thermoregulatory responses. With Figure 3 and 4, the exclusion of this prerequisite is added to the findings of Kahn (1904), Barbour (1912), Magoun (1938), Folkow (1949), and C. von Euler (1950) in which the nature of certain hypothalamic tissue as a sensory receptor organ was elucidated step by step. Figure 7 gives a quantitative description of the function of this organ.

2. The second conclusion is concerned with neural pathways: No path connecting the thermoceptor cells of the skin via thalamus with the hypothalamic thermoregulatory system seems to be required to account for human temperature regulation in a warm environment. As far as this task is concerned, the preoptico-supraoptic receptor cells are terminal sensory neurons.

3. The third conclusion concerns the function of the skin as a sense organ for temperature: The skin seems not to have one main function hitherto ascribed to it—to serve as sensory component, in the autonomic system of human temperature control by sudomotor and vasomotor action.

4. The fourth conclusion is concerned with the total mechanism—or rather mechanisms—of physical heat regulation: The role of the skin is altered, not de-emphasized, and recent discoveries on the cutaneous thermoreceptors (Hensel,\(^13\) Zotterman\(^24\)) appear no less important in a different context. The sense of temperature in the skin with its afferent impulses, and the thalamocortical neural
mechanism in which these are received and translated into highly coordinated motor activity, are forming another independent and complete thermoregulatory system. Virtually all skeletal muscles may serve in it as the effector component. By way of conditioned reflexes in that system, a reasonable preconditioning of human body temperature is accomplished, even under the most adverse climatic conditions. Highly effective measures such as locomotion from cold, stormy or shady areas into warm, calm or sunny ones, initiation or avoidance of physical exercise, plunging into cool or warm waters, production and application—or removal—of clothing, covers and shelters, and changes of posture such as stretching out in warm, or curling up in cool, environments, would be hardly possible without a sense of conscious temperature perception in the human skin. Since the effector mechanisms of this conscious and voluntary control system are powerful, its range of operation is extraordinarily wide. The range becomes virtually unlimited, when human activity calls upon exterior sources of energy for thermal protection.

However, the precision of the higher reflex system in controlling temperature is restricted. For the ultimate performance—stability of internal body temperature—the thermoreceptors of the skin are not located in the proper place. Therefore, beginning from a reasonably narrow preconditioned range of internal temperatures, a second, independent and self-sufficient system of temperature control is taking over. The activity of the second, subcortical, hypothalamic mechanism is not associated with the subjective attribute of free volition, for the effector organs, in warm environment, are the sweat glands and cutaneous blood vessels. This situation made it possible in warm environment to observe hypothalamic regulation originating from preoptic-supraoptic cells without any interference from cortical regulation, originating from thermoceptors of the skin. With chemical heat regulation in cold environment this will be difficult. There, skeletal muscle is the common effector organ for both the hypothalamic and the cortical mechanisms. The measurement of metabolic activity by gas analysis or calorimetry cannot distinguish between hypothalamic stimulation of shivering or metabolism in muscle, originating from preoptic-supraoptic cells and cortical stimulation of metabolism with movements more or less coordinated, originating from cutaneous thermoceptors. Perhaps a differentiation will be possible by light general anesthesia that would eliminate the cortical component. The heat loads handled by sweat glands and cutaneous blood vessels are impressive. In the experiments shown, sweating performed the dissipation of four times a human metabolic rate of heat. It poured out water at a rate of more than two gallons per day. Conductance increased from five to thirty-five units. The increase was equivalent to more than two tons of blood circulated through the skin in twenty-four hours. And yet, these figures are modest and the autonomic system appears to be of limited capacity when compared with the loads that higher nervous activity can balance, first by insulation and then by refrigeration or heating, in the field, in shelters or craft on land, sea and air, and ultimately in space vehicles.

As far as precision is concerned, however, the hypothalamic, involuntary mechanism is superior. It is the combination of two human sensory systems for temperature, and of two complete and independent mechanisms of heat regulation working in concert, that provides at once the wide range of climates that can be conquered, and the almost incredible precision of temperature control in man.
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* By "physical heat regulation" is meant the maintenance of a normal body temperature in warm environment, through acceleration of heat loss on the various physical avenues of heat transfer. By "chemical" heat regulation is meant the maintenance of a normal body temperature in cold environment, through acceleration of metabolic, or "chemical," heat production which balances the inevitable physical losses. Physical heat regulation is, and "chemical" regulation is not, the topic of this paper.

† The biochemical problem of the molecular mechanism by which any stimulus is translated into a nerve impulse emanating from a sensory cell remains, of course, unsolved not only for the sense of temperature but likewise for all other senses at this time.

7. Rubner, M., Arch. f. Hygiene, 38, 120 (1900).