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BENGT ERIK ANDERSSON

ON FEVER HUNGER AND THIRST

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ON FEVER, HUNGER AND THIRST

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SVMMARIVM — Describit Auctor quid indagando expertus sit qualis in cerebro locus esset famis, sitis, corporis caloris qualesque essent eorum interactiones.

The decision of the Academy to confer on me the Medal of His Holiness Pius XI has overwhelmed me. I feel extremely honoured and deeply grateful, but also most unworthy of this noble distinction. I shall therefore not regard it as a reward for any work performed so far, but instead try to let it become a spur for future industrious work.

It is a most wonderful and unforgettable experience for my wife and me to come to the Vatican and Rome as guests of this famous Academy, to be received by The Holy Father and to be allowed to attend to the sessions of the Academy. I therefore respectfully ask the Pontificial Academy of Science to accept our sincere and deep thanks.

Die 5 mensis octobris in Academiae Sessione Plenaria anni 1962 clarissimus vir Professor BENGT ERIK ANDERSSON de Academicorum consensu meruit ut coronam auream, vulgo « Medaglia d'oro Pio XI », e manibus Summi Pontificis IOANNIS Papae XXIII acciperet.

Idem post habitas laudes in eadem Academiae Sessione Plenaria die 6 octobris 1962, hanc orationem dixit de studiis suis.

May I also on this occasion direct particular thanks to one of the distinguished members of the Academy, to Professor WALTER RUDOLF HESS. Twelve years ago I was fortunate enough to get the opportunity to spend a few months in his famous institute at the Zürich University, having Prof. HESS as beloved teacher and superwiser. I gained very much from that visit which later became of fundamental importance and inestimable value for my further scientific activities. I am very sorry that Prof. HESS was unable to attend this session.

My talk has been called: On Fever, Hunger and Thirst. Under this general heading I want to review some more recent experiments of ours in the light of what is presently known about central regulation of body temperature and about the control of food and water intake.

A century ago the great French physiologist CLAUDE BERNARD [1] created the concept of « le milieu intérieur » or the internal environment. He pointed out that the external environment of the organism as a whole is not the environment of the individual cells of the body. The environment of the cells is the interstitial fluid and the blood plasma which thus form « le milieu intérieur ». CLAUDE BERNARD also stated that the constancy of the composition of this internal environment is really in a sense the condition of free life. He also emphasized that in spite of the very wide range of variation that occurs in the composition of the external environment, the internal environment by contrast is kept remarkably constant as a result of many compensatory mechanisms. One small part of the brain has since gradually become recognized as a regulator for many of these compensatory mechanisms, namely the hypothalamus.

Phylogenetically seen the hypothalamus is one of the oldest parts of the vertebrate forebrain. It forms the bottom and the lateral walls of the third brain ventricle just above the hypophysis. Although the weight of the hypothalamus is less than

half a per cent of that of the total brain in man, it is now well known that numerous mechanisms of importance for the maintenance of a constant internal environment are controlled or influenced by the hypothalamus. This certainly holds true for the regulation of body temperature and for the control of food and water intake. We have during the latest ten years been studying these particular hypothalamic functions at the Dept. of Physiology of the Royal Veterinary College in Stockholm, where we have used unaneasthetized goats as experimental animals. I shall come back to some of our later studies after having briefly reviewed present knowledge of the importance of the hypothalamus for these regulations.

The importance of the hypothalamus for the regulation of body temperature and for the control of food and water intake has been demonstrated in several ways. Various stimulation and lesion experiments have revealed that different systems or « centers » in the hypothalamus are of importance for each of these functions. Twenty five years ago MAGOUN et al. [2] showed that the most anterior part of the hypothalamus, the preoptic region, is of great importance for the bodily defense against heat. They found that local warming of this part of the brain causes the mobilization of various heat loss mechanisms like sweating, peripheral vasodilatation and polypneic panting. This part of the hypothalamus thus apparently contains nerve cells specifically sensitive to heat, so called central warm detectors. The warm detectors seem to respond to a rise in the temperature of the internal environment by activating various heat loss mechanisms. More direct evidence for the existence of warm detectors in the preoptic region has recently been provided by experiments in which the activity of single nerve cells was recorded [3]. Many nerve cells in the anterior hypothalamus were thus found to react specifically to an increased temperature. It therefore seems fully justifield to use the term « heat loss center » for the most anterior part of the hypothalamus.

Various types of experiments have also shown that the hypothalamus plays an important role in the regulation of food and water intake. After a destruction of the ventromedial hypothalamus experimental animals generally become abnormously fat [4]. This obesity is the consequence of a conspicuous overeating or hyperphagia [5]. One near at hand explanation for the hyperphagia would be that a destruction of the ventromedial hypothalamus intensifies the hunger « drive ». It has clearly been shown, however, that it is not so. The hunger « drive » rather decreases after ventromedial hypothalamic lesions, but the lesioned animals eat excessively because their ability to experience satiety during feeding has became markedly reduced [6, 7]. A satiety system or satiety « center » is therefore apparently located in the ventromedial hppothalamus.

More doubtful is whether the term « hunger center » could be used for the lateral hypothalamus. If was originally shown by ANAND and BROBECK [8] that bilateral damage to the lateral hypothalamus may have the results that experimental animals stop eating completely Conversely, electrical stimulation in this region may cause eating in previously not hungry animals [9]. But the lateral hypothalamus is a passage for numerous nerve tracts and fibres connecting the frontal brain, the basal ganglia and the temporal lobes with the hypothalamus and lower parts of the brain stem. Some of these tracts descending or crossing through the lateral hypothalamus may be concerned with the coordination of eating and drinking motor activities. Other tracts may transmit the urge to eat and to drink to higher organized parts of the central nervous system. If this is so, the lateral hypothalamus may not be regarded as a « hunger center » in a true sense and the importance of the hypothalamus in the regulation of food intake would then essentially be to modify the hunger « drive » by determining the degree of satiety.

Also the sensation of thirst has apparently its origin in the hypothalamus. Injections of small amounts of hypertonic saline

into the medial hypothalamus [10, 11] or electrical stimulation in the perifornical region [12] may thus elicit conspicuous drinking in previously non-thirsty goats. Destruction of the anterior and medial parts of the hypothalamus may have the opposite effect. Such animals apparently no longer experience thirst, since they refuse to drink water even when severely dehydrated [13, 14].

Although stimulation and lesion experiments have helped to delimit regions or «centers» in the hypothalamus of importance for the control of hunger and thirst, such experiments have generally not revealed how changes in the internal and external environments may influence the activity of these « centers ». Observations in man and experiments in animals have shown that a cellular dehydration apparently is the crucial factor eliciting thirst [15]. The same changes in the internal environment which cause cellular dehydration also lead to the release of antidiuretic hormone from the neurohypophysis. VERNEY [16, 17] has elegantly shown that this release is regulated by cells in the anterior hypothalamus which react specifically to dehydration, so called « osmoreceptors ». It is therefore not unreasonable to suggest that thirst may originate from a similar hypothalamic « osmoreceptor » mechanism, especially since injections of minute amounts of hypertonic saline directly into the hypothalamus have been observed to cause polydipsia [11]. But cellular dehydration is apparently not the sole factor eliciting thirst [18, 19]. Other changes in the internal environment, such as a decreased extracellular fluid volume and, as I shall come back to later, a markedly increased body temperature may also have this effect.

Even more complex factors seem to determine how much we eat. Two components can be separated in the regulation of food intake. There is apparently one short term regulation working to keep the daily energy supply equal to the daily energy expenditure. In addition a long term regulation works to maintain the fat depots, and thus the body weight relatively

constant. Various types of experimental evidence have been presented to show that a so called glucostatic mechanism in the satiety « center » maintains the short term regulation [20, 21]. According to this glucostatic theory of MAYER the degree of satiety is determined by how effectively the cells of the hypothalamic satiety « center » are utilizing the blood glucose. The long term regulation, on the other hand, is thought to be dependent on a so called lipostatic mechanism [22, 23]. According to the lipostatic theory some metabolits of fat are able to activate the satiety « center » and thus to limit food intake. Of special interest in this connection is that there also exists an intimate relation between body temperature and food intake. BROBECK [24, 25] has studied this relation thoroughly in experimental animals and he has come to the conclusion that heat is also an important factor in the short term regulation of food intake. According to BROBECK'S thermostatic theory, hunger is reduced by a rise in temperature in the ventromedial hypothalamus (the satiety « center ») or by stimulating heat sensitive neurons in the anterior hypothalamus (the heat loss « center ») which impinge on the satiety « center ».

In the latest three years we have been studying the thermoregulatory and alimentary response to local warming and cooling of the preoptic heat loss « center » in goats. We have thereby made observations which give direct evidence for BROBECK'S thermostatic theory and which may justify the further extension of this theory to involve also the regulation of water intake [26, 27]. I shall come back to these experiments after having said a few words about the technique we have used and about the thermoregulatory responses to preoptic warming and cooling in the goat.

The technique used has allowed local cooling or warming of the preoptic region and the anterior hypothalamus for long periods of time in unrestrained goats maintained in their normal environment. Cooling was obtained by perfusing permantently implanted silver thermodes (fig. 1, T) with cold water. The

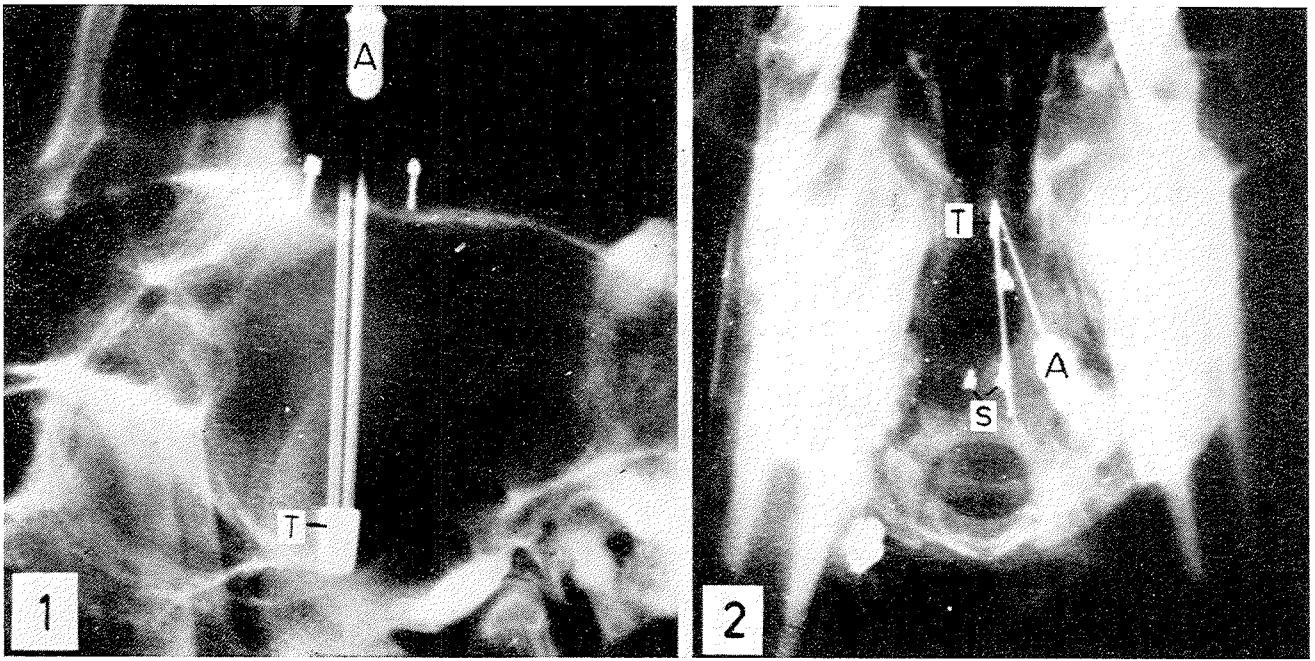

FIG. 1 — *X - Ray pictures of the head of a « thermode goat » taken from the side* (1) *and from above* (2).
T = The body of the silver thermode implanted medially in the preoptic region.
A = A needle applicator for temperature recording having its thermosensitive tip close to the lateral surface of the thermode.
S = Dental root screws used for fixation of dental cement to the skull bone.

degree of central cooling was measured by help of needle applicators for temperature recording (fig. 1, A) having their thermosentisive tip placed close to the lateral surface of the thermodes. The same thermodes were originally also used for local warming by perfusing them with warm water. In later experiments, however, a special technique of high frequency warming between two bilaterally implanted silver plates has made it possible to raise and to maintain at a constant level the temperature of the preoptic region of the goats for long periods of time (fig. 2).

The thermoregulatory response to preoptic cooling and warming in the goat clearly demonstrates the importance of both peripheral cold receptors and central warm detectors for the regulation of body temperature. Thus in the calm goat, fully accustomed to the experimental conditions, local cooling of the preoptic heat loss « center » induces shivering in a cold environment only (fig. 3), or during local stimulation of peripheral cold receptors. But if these goats are subjected to mild stress or to an infusion of adrenal cathecholamines, cooling of the heat loss « center » may elicit shivering in a thermally neutral or even warm environment [28]. It thus seems as if the central warm detectors of the heat loss « center » serve not only to activate various heat loss mechanisms but also serve as a brake on the shivering mechanism. However, only when there is a simultaneous, stimulatory « drive » on the shivering mechanism from peripheral cold receptors or from other sources (emotional excitation, sympatico - adrenal activation, pyrogens etc.), only then does an inactivation of the central warm detectors by cooling elicit shivering (For tentative scheme see fig. 4).

The task of the heat loss « center » is apparently not only a purely nervous control of physical thermoregulatory mechanisms. We have recently made experiments which indicate that this « center » also participates in the control of hormonal factors involved in temperature regulation [29, 30, 31]. It is well known that several endocrine factors are of importance for the maintenance of a constant body temperature. It has thus

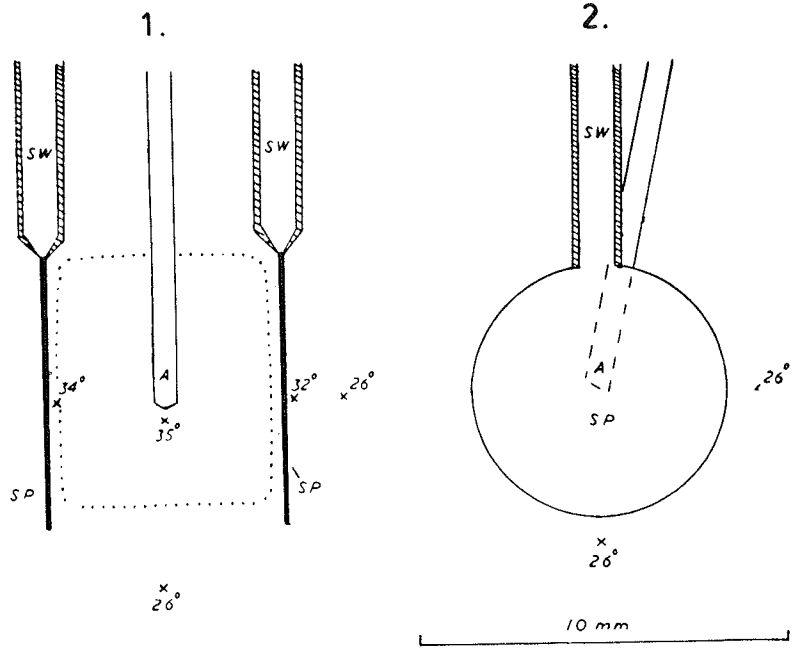

FIG. 2 — *Arrangement for high frequency warming of the preoptic region and anterior hypothalamus of unanaesthetized goats.*

1 = Frontal view. 2 = Side view.

A = Needle applicator for temperature recording.

S P = Uninsulated silver plates.

S W = Insulated silver wires.

The temperatures refer to the temperature gradient found during warming between the plates in an egg white medium at 25°C. The maximal temperature rise was obtained centrally between the two silver plates.
The area limited by dotted lines indicates the shape of a coagulation obtained in egg white when the central temperature was raised to 70°C.

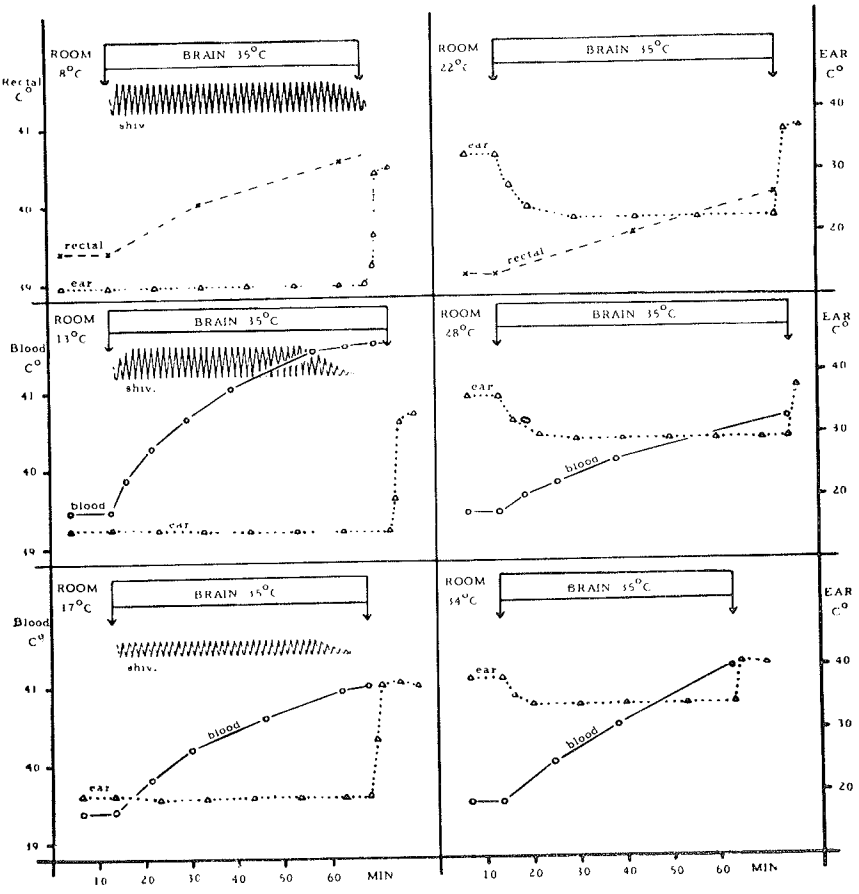

FIG. 3 — *Thermoregulatory responses to local cooling of the preoptic heat loss « center » at different room temperatures in a calm goat, accustomed to the experimental conditions. Shivering was only seen at room temperatures below* 18°C.
The brain temperature was recorded 4 mm lateral to the cooling thermode. (From ANDERSEN et al. [28]).

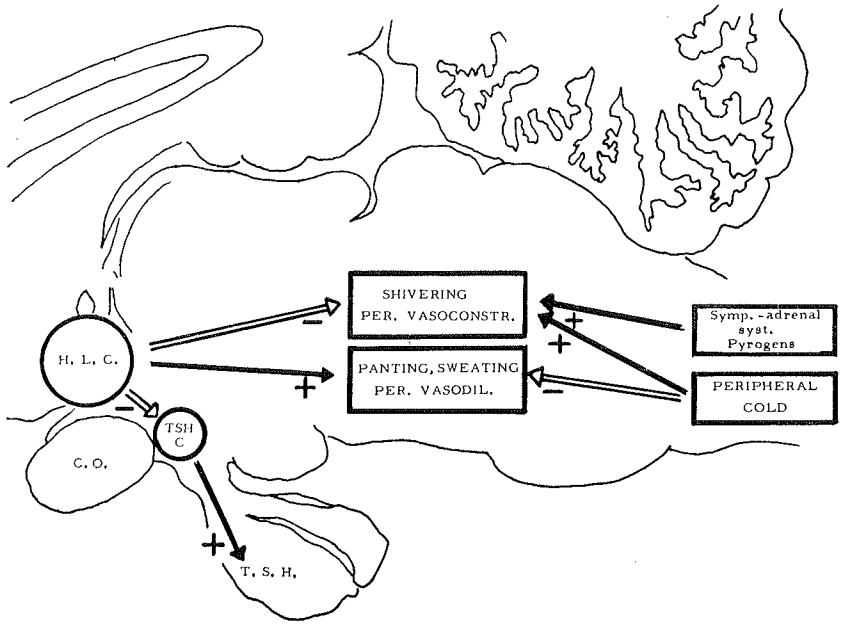

FIG. 4 — *Tentative scheme to explain the termoregulatory responses to cooling and warming of the heat loss « center » in the goat.*

H.L.C. = Preoptic Heat Loss « Center ».

TSC / C = Anterior hypothalamic « center » for release of thyrotrophic hormone (TSH) from the hypophisis.

C.O. = Chiasma opticum.

For further explanation see text.

been shown that both adrenal and thyroid hormones participate in the cold defense. Cold exposure is, for example, known to activate the release of thyroid hormone by way of the hypothalamo — pituitary axis [32, 33] and probably also the release of adreno-cortical hormones in the same way. Following the onset of cooling of the heat loss « center » goats develop a marked hyperthermia even in the absence of detectable shivering (fig. 5) [27]. This hypethermia persists throughout periods

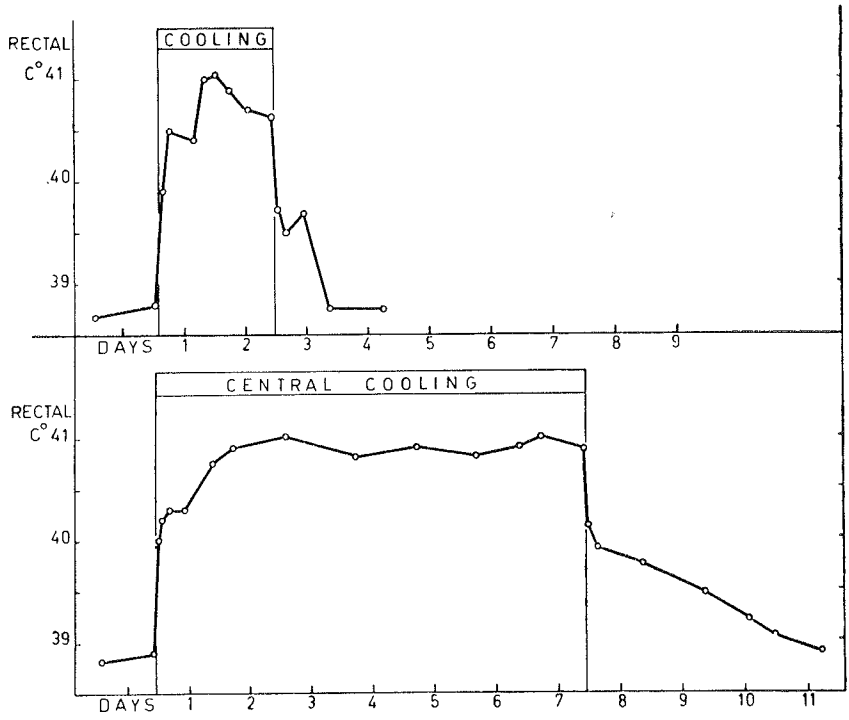

FIG. 5 — *Examples of persistent hyperthermia obtained by cooling the anterior hypothalamus of a goat.*
The hyperthermia developed in the absence of detectable shivering.
(From ANDERSSON et al. [27]).

of seven days, indicating an increased metabolism of non-shivering origin. Studies of the thyroid activity in these animals have revealed that local cooling of the heat loss « center » leads to a conspicuous release of hormone from the thyroid [29]. The thyroid activation is comparable to, or even greater, than that observed when the same animals are subjected to rather severe general cold stress (fig. 6). If the hypothalamic control of anterior pituitary function is disturbed by lesioning the median

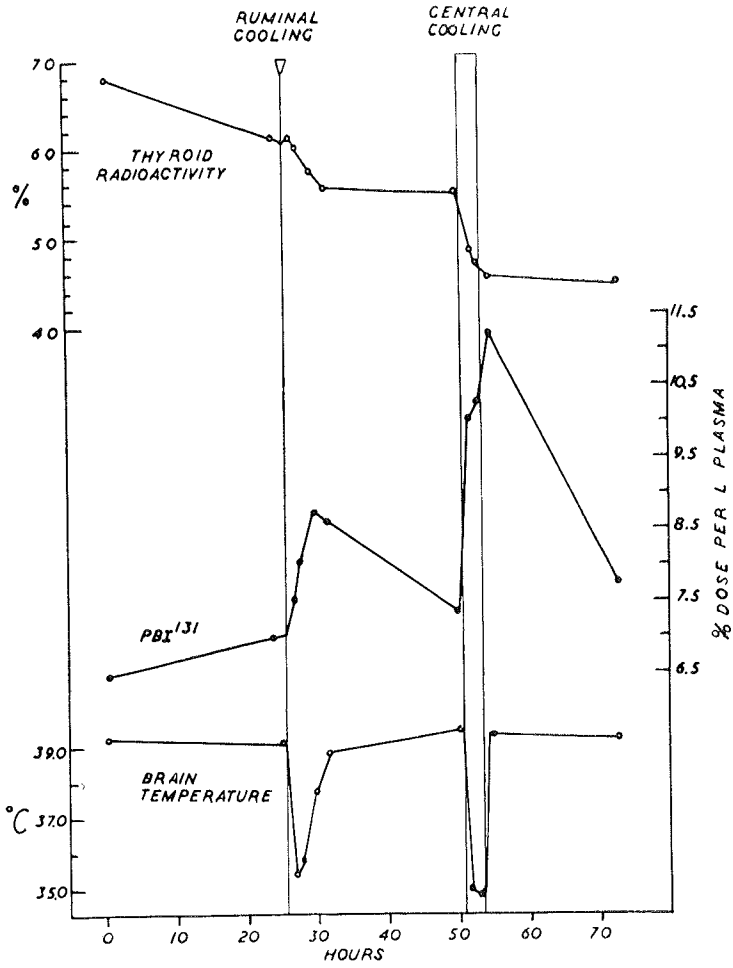

FIG. 6 — *A comparison of the thyroid activities caused by general cold stress (Ruminal cooling) and by local cooling of the preoptic heat loss « center ». (Central cooling).*
Radioactiv iodine (I^{131}) was used to study thyroid activity.
PBI^{131} = Plasma protein bound I^{131}.
(From ANDERSSON et al. [30]).

eminence, this thyroid response to cooling the heat loss « center » is eliminated [35].

Moderate local warming of the heat loss « center » has the opposite effect to cooling [31]. It blocks the thyroidal response to a general cold stress (fig. 7) and also seems to inhibit the

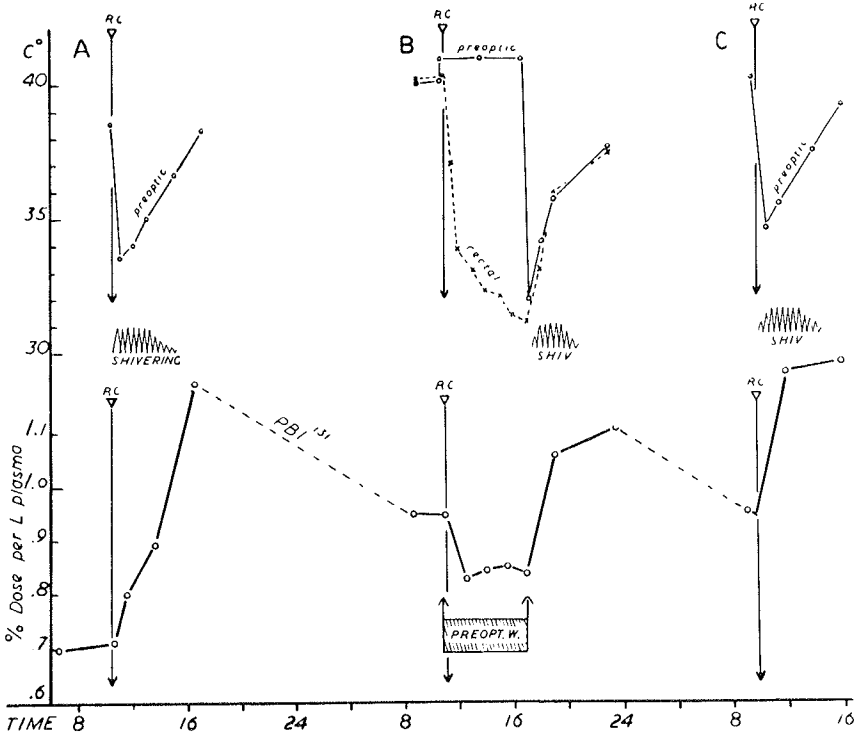

FIG. 7 — *Blocking of the thyroid response to cold by local warming of the pre optic heat loss « center ».*

A = Thyroid response (increase in plasma protein bound Iodine, PBI^{131}) to ruminal cooling (R C).

B = Inhibition of this response by preoptic warming (preopt. w.) to 40.8°C. Note subsequent rise in PBI^{131} and onset of shivering when preoptic warming is stopped.

C = Ruminal cooling repeated without preoptic warming. Response as in A. Time of day recorded on abscissa.

(From ANDERSSON et al. [31]).

normal resease of hormone from the thyroid (fig. 8). It may therefore be assumed that heat loss « center » even at a normal body temperature exerts a certain inhibitory tone on the release of thyrotrophic hormone (T.S.H.) from the hypophysis. The strength of this inhibitory tone seems to increase in relation to the rise of the temperature of the heat loss « center », i.e. in relation to the degree of activation of central warm detectors (see fig. 4).

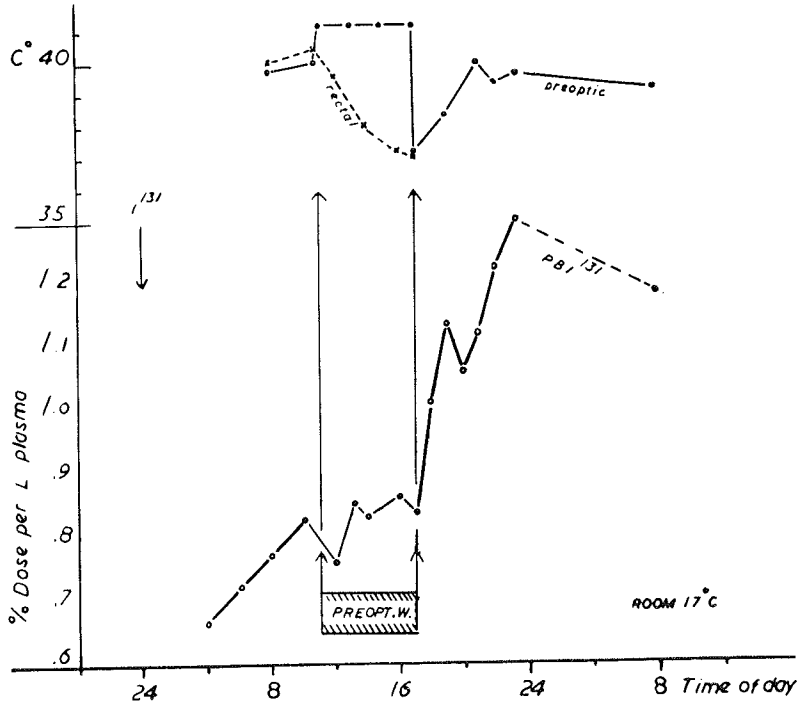

FIG. 8 — *Diminished release of protein bound iodine (PBI^{131}) into plasma during preoptic warming, followed by an increased release and a rise of body temperature on cessation of warming of the preoptic heat loss «center».* Time of day recorded on abscissa.
(From ANDERSSON et al. [31].

We have also reason to believe that other humoral mechanisms of importance in the cold defense are also inhibited in a similar manner by the heat loss « center » [34]. In preliminary experiments the temperature of this « center » has been raised 1 to 2 degrees centigrade and maintained at this level when the goats are placed in a cold environment. Due to the mobilization of heat loss mechanisms and to the inhibition of shivering and other cold defence mechanisms, the core temperature of the animals falls relatively rapidly below 30° C. The hyperglycemia which otherwise is seen to develop at this low body temperature does not appear as long as the heat loss « center » is kept active by local warming. But as soon as anterior hypothalamic warming is stopped, hyperglycemia rapidly develops (fig. 9). The heat loss « center » thus seems to inhibit the apparently humoral mechanisms responsible for the hypothermic hyperglycemia. Further studies may reveal to which extent the pituitary - adrenal system and the adrenal medulla may be involved in the development of this hyperglycemia.

According to the title this lecture should also deal with fever. The increased body temperature which develops during local cooling of the preoptic heat loss « center » may not be regarded as fever in a true sense. It is rather the normal bodily response to a lowered temperature in this part of the brain. Fever, on the other hand is the hyperthemia appearing f.ex. during infections and intoxications and it is the consequence of some abnormality in the regulation of body temperature. During infections and intoxications so called pyrogen substances are formed in the organism. It is also possible to isolate certain polysacharides from bacterial substrates which have a pronounced pyrogenic action. When such exogenous pyrogens are injected into man or animals they cause fever but it takes half an hour to 90 minutes before the pyrogenic action becomes apparent. These substances apparently need to react with some unknown factor in the blood before they become active [36, 37].

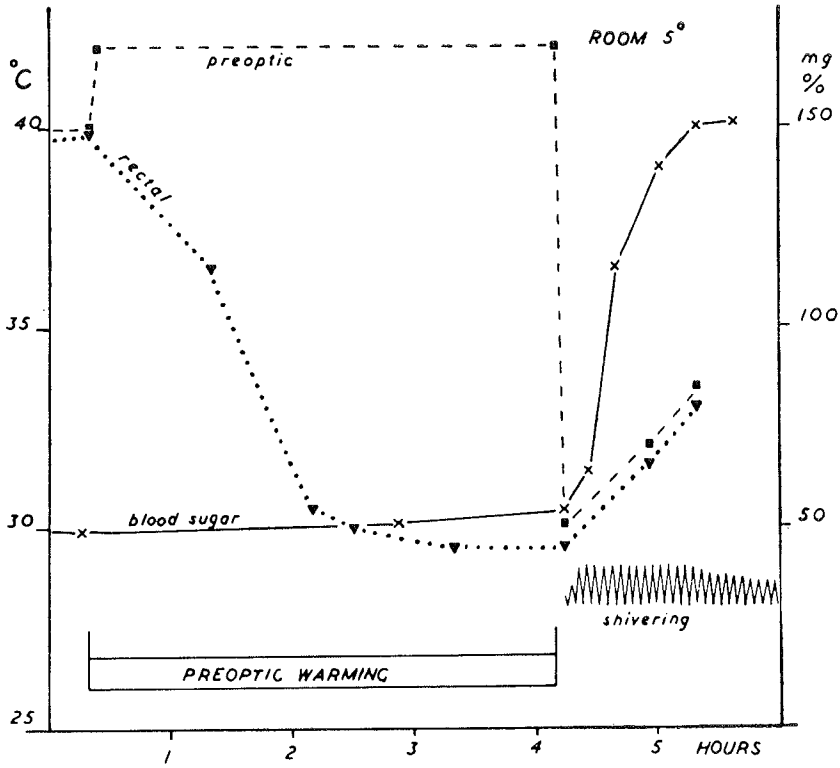

FIG. 9 — *Pronounced hypothermia elicited by local warming of the preoptic heat loss « center » in a cold* (5°C) *environment.*
Polypnea and peripheral vasodilatation were present during the steep decline of rectal temperature. Shivering and hypothermic hyperglycemia did not appear until after cessation of preoptic warming. The preoptic region was uniformely warmed between two bilaterally implanted silver plates (to 41.8°C).
(From ANDERSSON et al. [35]).

The site of action of the pyrogens within the central nervous system is not known. The expression has commonly been used, that pyrogens raise the set point of the bodily thermostate. For this reason it has been suggested that pyrogens should act primarily by depressing the sensitivity of the preoptic heat loss

« center ». But experiments in dogs [38] and goats [28] show that the heat loss « center » participates in temperature regulation even in animals which are under the influence of pyrogens. Local cooling of the heat loss « center » is thus found to cause a very marked potentiation of the febrile action of an exogenous pyrogen. It may therefore well be that the pyrogens exert their febrile action by facilitating cold defense mechanisms at a lower level of the brain stem.

I mentioned earlier that during the studies of central regulation of body temperature in the goat we have also focused our interest on the food and water intake of the animals and on their alimentary behaviour, and that our observations may easiest be explained in the light of BROBECK'S [24, 25] thermostatic theory. Warming of the anterior hypothalamus has thus been found to inhibit food intake and to elicit thirst (fig. 10). Cooling of the same region of the brain has to a certain extent the reverse effect. The food intake of the animals is generally not increased, but it remains at a normal level during long periods of anterior hypothalamic cooling, even though there is a rise in the body temperature to above 41° C. In the goat this is a critical temperature at which food intake is otherwise almost completely inhibited [39]. The water intake is initially totally inhibited and later markedly reduced during periods of anterior hypothalamic cooling (fig. 11).

The importance of the anterior hypothalamus for the thermal inhibition of food intake is further indicated by the effect of bilateral lesions in this part of the brain. A goat in which the heat loss « center » had been destroyed by proton irradiation developed adipsia but continued to eat its normal ration of hay with apparently good appetite, even when its body temperature was raised above 41° C [26]. Rats with corresponding lesions, when heat stressed eat twice as much as their controls but drink less water [40]. Due to the higher food intake the body temperature of the lesioned rats rises two to three degrees centigrade above the controls and may reach lethal threshold.

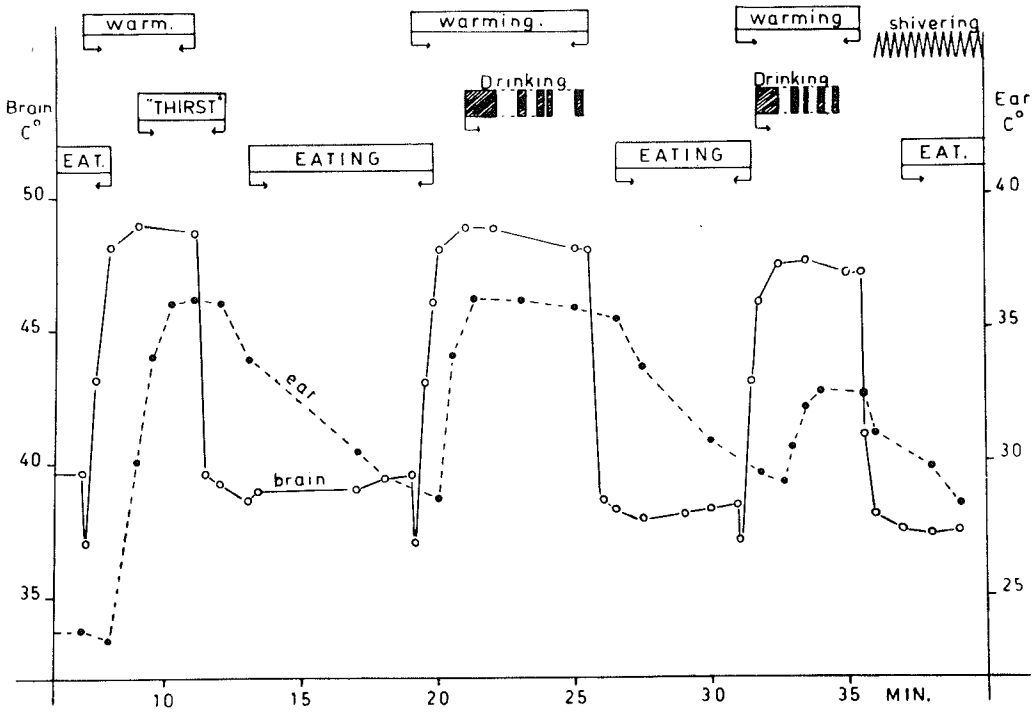

FIG. 10 — *Alimentary response to local warming of the anterior hypothalamus in a previously hungry goat.*
Brain temperature = The temperature of the surface of the silver thermode (perfused with warm water during the periods of central warming).
The goat was fed hay at the beginning of the experiment and had free access to water except during the first period of central warming. During the periods of central warming eating stopped simultaneosuly to the onset of peripheral vasodilatation (rise of ear surface temperature), and started again when the ear surface temperature had begun to fall after discontinuation of central warming. The perfusion of the thermode with warm water induced a strong urge to drink.
(From ANDERSSON and LARSSON [26]).

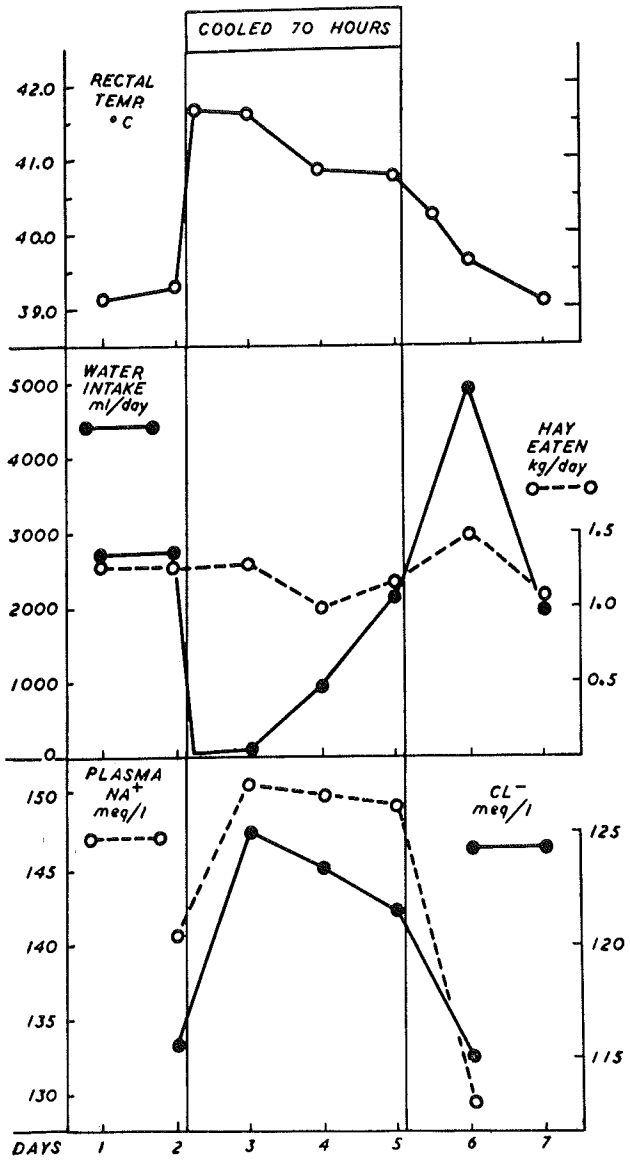

FIG. 11 — *Production of core hyperthermia and inhibition of drinking by local cooling of the preoptic region.*
The goat continued to eat the normal amount of hay in spite of a rise in core temperature to 41°C. Water intake was totally blocked during the first 40 hours of preoptic cooling and remained low during the rest of the cooling period.

Local warming of any part of the central nervous system may act as a non-specific stimulus; local cooling, on the other hand, may inhibit all neuronal activity in the close vicinity of the thermodes. Presently the possibility can therefore not be excluded that the alimentary effects of hypothalamic warming and cooling may be more or less non-specific and not solely due to a stimulation or an inactivation of neurons specifically sensitive to heat. Since the heat loss « center » apparently also controls endocrine factors of importance for intermediary metabolism, the possibility remains open for discussion that changes in the hormonal status of the animal during preoptic warming and cooling may effect an « appestate » mechanism related to carbohydrate and fat metabolsim.

Nevertheless, taken together, the alimentary effects of anterior hypothalamic lesions and those due hypothalamic warming and cooling indicate that a thermostatic mechanisms in BROBECK'S [24, 25] sense really exists. It may, however, mainly serve as an emergency mechanism, acting when the body temperature reaches a critically high level. It may then prevent additional caloric supply by inducing satiety and secure the extra supply of water necessary for urgent heat loss mechanisms by inducing thirst.

I wish to apologize if much of what I have said in this lecture has been difficult to follow and to understand. I should therefore like to finish by showing a short film which better illustrates some of the hypothalamic functions I have been talking about. The film shows some earling experiments performed in our laboratory. Electrical stimulation of different regions of the hypothalamus is here used to elicit eating, drinking and the mobilization of various heat loss mechanisms in goats. The technique of stimulation is principally the one originally developed by Professor W.R. HESS in Zürich [41, 42].

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