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# NEURAL ASPECTS OF TEMPERATURE REGULATION

*1st. Symposium*



Editors  
JOHN P. HANNON  
ELEANOR VIERECK

MBL/WHOI



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*USAF*  
ARCTIC AEROMEDICAL LABORATORY  
FORT WAINWRIGHT  
ALASKA  
1961

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Sponsored by the  
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FORT WAINWRIGHT  
ALASKA

PROCEEDINGS

SYMPOSIA ON ARCTIC BIOLOGY AND MEDICINE

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THE NEURAL CONTROL OF THE  
PHYSIOLOGICAL RESPONSES TO COLD  
HISTORICAL REVIEW

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In the animal kingdom, only birds and mammals have the ability to maintain rectal temperature within a narrow range in spite of wide changes of environmental temperature. This property of homeothermy is not possessed by the lower vertebrates or any of the invertebrates. The homeotherms have physiological responses to cold and warmth under control of the central nervous system which are absent in the poikilotherms.

In analyzing the physiological responses to cold and heat which the homeotherms possess, the following physiological mechanisms are observed: For protection against heat, the homeotherms can (1) dilate their cutaneous vessels and raise their skin temperature to facilitate heat loss and (2) increase evaporative cooling by sweating or panting. For protection against cold, the homeotherms can increase their metabolic heat by (1) shivering and (2) nonshivering thermogenesis and can (3) reduce heat loss to the environment by cutaneous vasoconstriction. The control of body temperatures by cutaneous vasoconstriction and vasodilation is a physiological mechanism functioning continuously throughout the day and throughout life. It is this mechanism which maintains rectal temperature nearly constant in a comfortable environment. Shivering, panting, and sweating are emergency functions which only become active during cold or heat stress.

This system of physiological mechanisms which functions to maintain homeothermy is under the control of the central nervous system which functions with remarkable efficiency as a thermostat to activate, inhibit, and regulate the component functional physiological processes of homeothermy. A survey will now be given of the experimental data which in recent years has served to establish our current concepts of how the central nervous system functions to protect against cold.

For protection against cold, the homeothermic animal can increase its heat production by shivering to a value as much as four to five times the resting heat production. In a recent paper where shivering was studied on man, Iampietro, Vaughan, Goldman, Masucci, and Bass (1960) found the maximal shivering heat production rate to be 442 Cal/hr, and with a resting nonshivering heat production rate of 80, the heat production rate was increased to 5.5 times the resting nonshivering value. This value is, however, maximal and usually the heat production rate observed during shivering is two to four times the nonshivering value. In fact, the regulation of shivering is so well adjusted to temperature regulation demands that the shivering can be mild, moderate, or intense as required. Nonshivering thermogenesis, the term applied to an elevation of heat production caused by cold without shivering, can elevate the oxygen consumption rate from 10 to 20 percent in the larger animals and possibly more in the small mammals and birds. The other physiological protection against cold, the thermal cutaneous vasomotor response, is the nervous control of the diameter of the blood vessels in the skin. Contraction of the smooth muscle of the cutaneous arterioles causes vasoconstriction and reduces blood flow through the skin. The skin temperature is lowered and heat loss from the skin is reduced.

#### Methods of Testing Physiological Responses to Cold

Before the details of the neural control of the physiological responses to cold are described, the methods for testing these responses will be reviewed briefly. The following methods are those which have been used by investigators for testing the functional activity of the various components of the temperature regulating system.

Cold exposure test (test for homeothermy). An animal is placed in a cold environment, usually a cold room having a temperature of from  $0^{\circ}\text{C}$  to  $15^{\circ}\text{C}$ , and its rectal temperature measured at

## HISTORICAL REVIEW

intervals in a 1- to 4-hour test. The presence or absence of shivering is determined visually or by palpation. A normal animal will maintain a rectal temperature within narrow limits of  $0.5^{\circ}$  to  $1.0^{\circ}$  C, whereas a poikilotherm will have a continuously falling rectal temperature. Experiments which impair temperature regulation will have a temperature-time record intermediate between these extremes.

Measurement of oxygen consumption rate. This measurement is perhaps the most useful and quantitative method of measuring shivering and nonshivering thermogenesis. An animal tested for shivering is first placed in a comfortable environment of  $25^{\circ}$  to  $30^{\circ}$  C, and after a time interval sufficient to achieve a steady state, its oxygen consumption rate (designated as  $\dot{V}O_2$ ) is measured. The oxygen consumption rate is usually expressed as milliliters  $O_2$  STPD per kilogram of body weight per minute. The animal is next placed in a cold environment of  $0^{\circ}$  to  $10^{\circ}$  C, and the oxygen consumption rate continuously measured; the oxygen consumption rate will rise and finally reach a fluctuating steady state value. The fluctuation is caused by the irregularity in shivering. The ratio  $\dot{V}O_2$  (cold environment)/ $\dot{V}O_2$  (comfortable environment) is a useful index of the intensity of shivering. Oxygen consumption rate can be measured by one of several methods. A convenient method used in our laboratory has been to measure continuously the  $O_2$  content and the  $CO_2$  content of the gas within a sealed box in which the animal is placed. Carbon dioxide and water are removed by circulation of the gas through absorbing columns.

Mechanical record of shivering. Since a shivering animal produces a well-defined tremor, the presence of shivering can be detected and can be roughly measured quantitatively by measuring the vibration of shivering. A resting animal is placed on a platform which is suspended by wires or supported on springs. The shivering causes a vibration of the platform and can be measured with a piezo-electric crystal, a sensitive pressure transducer, a strain gauge, or more simply with a thread which has one end attached to the platform and the other end to a lever arranged for kymograph recording. With kymograph recording, however, the frequency characteristics of the system are likely to be poor.

Electromyogram. The shivering muscles, which are undergoing contraction and relaxation, produce action potentials which can be amplified and recorded on kymograph paper. The electromyograms as recorded with an AC amplifier consist of a succession of biphasic spike potentials, irregular in frequency and amplitude. Using a suitable rectifier, these biphasic potentials can be converted into an integrated monophasic record whose amplitude is roughly proportional to the intensity of shivering.

The thermal cutaneous vasomotor response. The ability of the cutaneous vessels to constrict in the cold and dilate in the heat can be measured conveniently in dogs by measuring their ear skin temperature. In a cool environment of 15° to 20° C, cutaneous vasoconstriction is indicated by a low ear skin temperature of 2° to 3° C, above environmental temperature. Vasodilation, in this environment, caused by central or peripheral heating, is indicated by a rise in the ear temperature which will reach values as high as 34° C. This test is simply an indicator of cutaneous vasoconstriction and vasodilation, and is roughly quantitative.

Other methods of measuring cutaneous blood flow are the (a) photoelectric plethysmograph (Hertzman, et al., 1946); (b) the impedance plethysmograph (Nyboer, 1960); (c) the venous occlusion plethysmograph (Abramson, 1944, and Freeman, 1945); and (d) the opening of a cutaneous vein and measuring the blood flow rate of the blood lost by hemorrhage. The photoelectric plethysmograph and the impedance plethysmograph cause negligible discomfort to the animal or human subject, but the measurements are only approximate. The venous occlusion plethysmograph, while it gives quantitative values of blood flow rate, does not measure cutaneous blood flow alone, but the blood flow of the extremity. The assumption is required that the venous occlusion obstructs all of the venous outflow from the extremity and does not interfere with arterial inflow. The measurement of the cutaneous bloodflow by hemorrhage is suitable only for animals under anesthesia.

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### Apparatus Used for Testing Cold Responses of Animals

In studying the responses of homeothermic animals to cold, the animals used for testing have been mainly men, dogs, cats, and rats. The advantages and limitations of using men are well known. Of the various animals available for study, there are certain anatomical and physiological characteristics of dogs, cats, and rats which make them useful for special purposes. Dogs and cats have a well-developed shivering mechanism which is similar in all respects to that of man. The presently well-known control for starting, stopping, and regulating shivering in these animals is identical with that of man. This is not true for the physiological response to heat. Where metabolic, circulatory, and respiratory investigations are being made and where adequate samples of blood for analysis are needed, the dog is the animal of choice. In addition, the dog can be trained to lie motionless on a table or platform without restraint. This is a most important characteristic where studies are made of mild shivering, or in attempts to separate the metabolism of shivering from nonshivering thermogenesis. The cat is particularly valuable where studies of the nervous system are required. The neuroanatomy and neurophysiology of the cat are probably as well, if not better, understood than that of man. This is a result of the popular usage of the cat for studies of the nervous system because of the uniformity of the shape of the head of the cat for stereotaxis studies, and the ease, convenience, and cost of the cat in handling and maintenance. For such considerations, the monkey, although useful, is much less popular. The rat, due to its omnivorous diet, is useful for nutritional studies. It shivers well in the cold and is a fairly good homeotherm. Apparently, however, the rat differs in its response to cold from the larger animals, relying on nonshivering thermogenesis.

The apparatus which has been found the most useful for studying shivering in the dog (Hemingway and Hathaway, 1941) is shown in Figure 1. The trained dog lies on his side in a double-walled box with either cold or hot water being circulated through the space between the walls. A glass window in the cover permits observation of the animal. The shoulders and chest of the dog are supported by a fixed platform, while the hind legs rest on a platform suspended

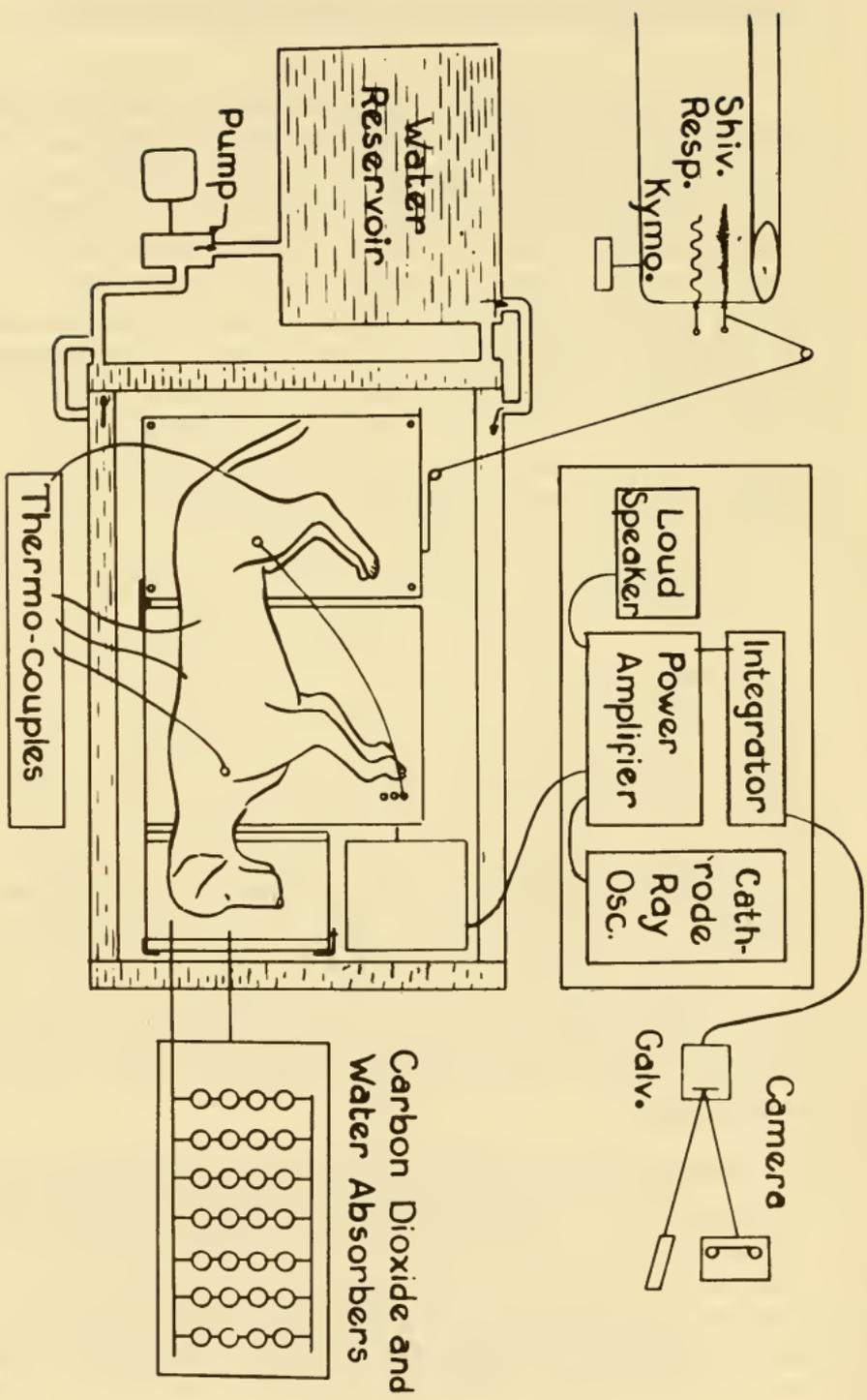


Figure 1. Apparatus for studying shivering in the trained unanesthetized dog.

## HISTORICAL REVIEW

by steel wires but hinged to the fixed platform. When shivering starts, the movable platform vibrates, and the vibration is recorded to give a mechanical record of the tremor of shivering. The head of the dog is sealed within a chamber through which gas of the closed respiratory system is circulated with an airtight pump (refrigerator pump). Respiration and oxygen consumption rates are recorded from a spirometer of the closed circuit system. Thermocouples are used to record skin and rectal temperatures. Electrodes sealed to the skin with collodion are used for recording of the electromyogram. Trained animals will lie for as long as 3 hours in this apparatus and endure cold sufficient to produce shivering without attempting to move. A record of the start of shivering as revealed by the record of rectified action potentials is seen in Figure 2. Before shivering, there was slight background electrical activity due to respiration and the heart beat. When shivering started there was a sudden rise in the rectified action potentials which was coincident with the appearance of visible shivering. For this animal, there was no increase of electromyographic activity preceding visible shivering.

The apparatus used in studying shivering in cats is shown in Figure 3. A cat is not capable of being trained to lie in a relaxed resting condition such as is a dog. A carefully selected cat will, however, sit with little voluntary movement for an hour or two in a confined box such as is shown in Figure 3. The cat sits on a platform supported by springs or rubber stoppers and shivering is recorded by a strain gauge attached to a movable platform. The box which contains the cat is sealed airtight and the gas within the box is circulated by means of a sealed pump. The box having a glass cover is placed within a refrigerator, also with a glass cover, so that the cat can be observed. The gas of the enclosure is circulated through cooling coils immersed in ice water in the refrigerator. Continuous analyses are made of the  $O_2$  and  $CO_2$  content of the enclosed gas. This apparatus permits a measurement of oxygen consumption rate, but not a measurement of respiration. Thermocouples and electromyographic electrodes record temperatures and muscle action potentials respectively.

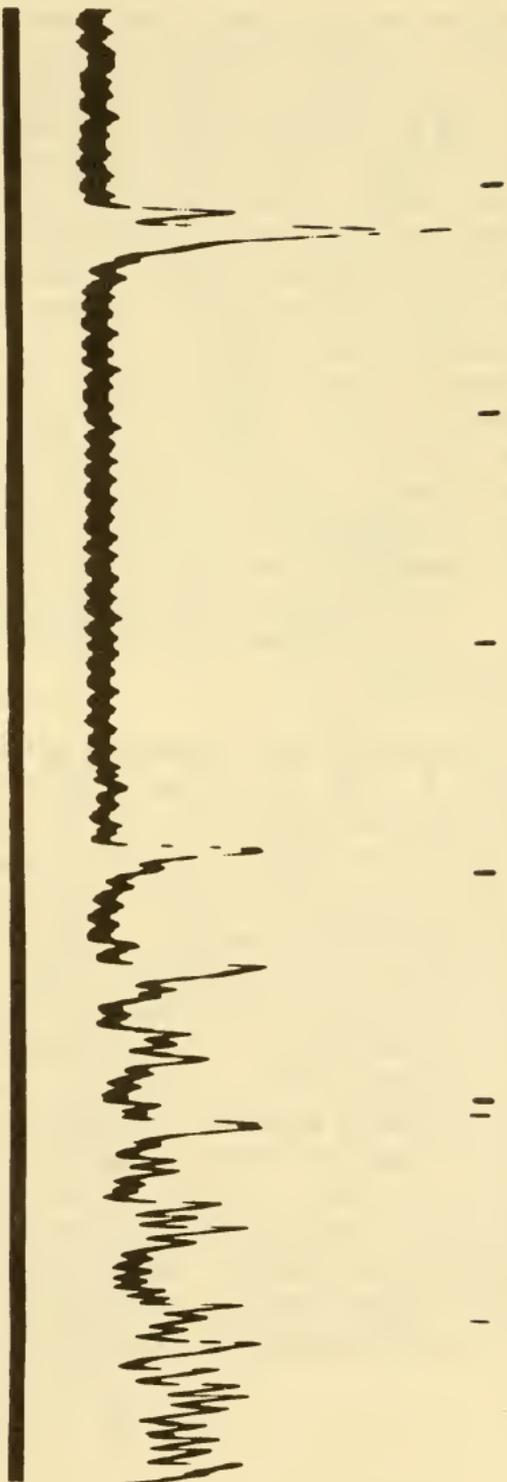


Figure 2. Record of rectified electromyographic potentials obtained from skin electrodes on a dog. The background activity is due to action potentials from the heart and respiratory muscles. The beginning of shivering is characterized by a sharp increase in current. Time in minutes. Record reads from left to right.

## HISTORICAL REVIEW

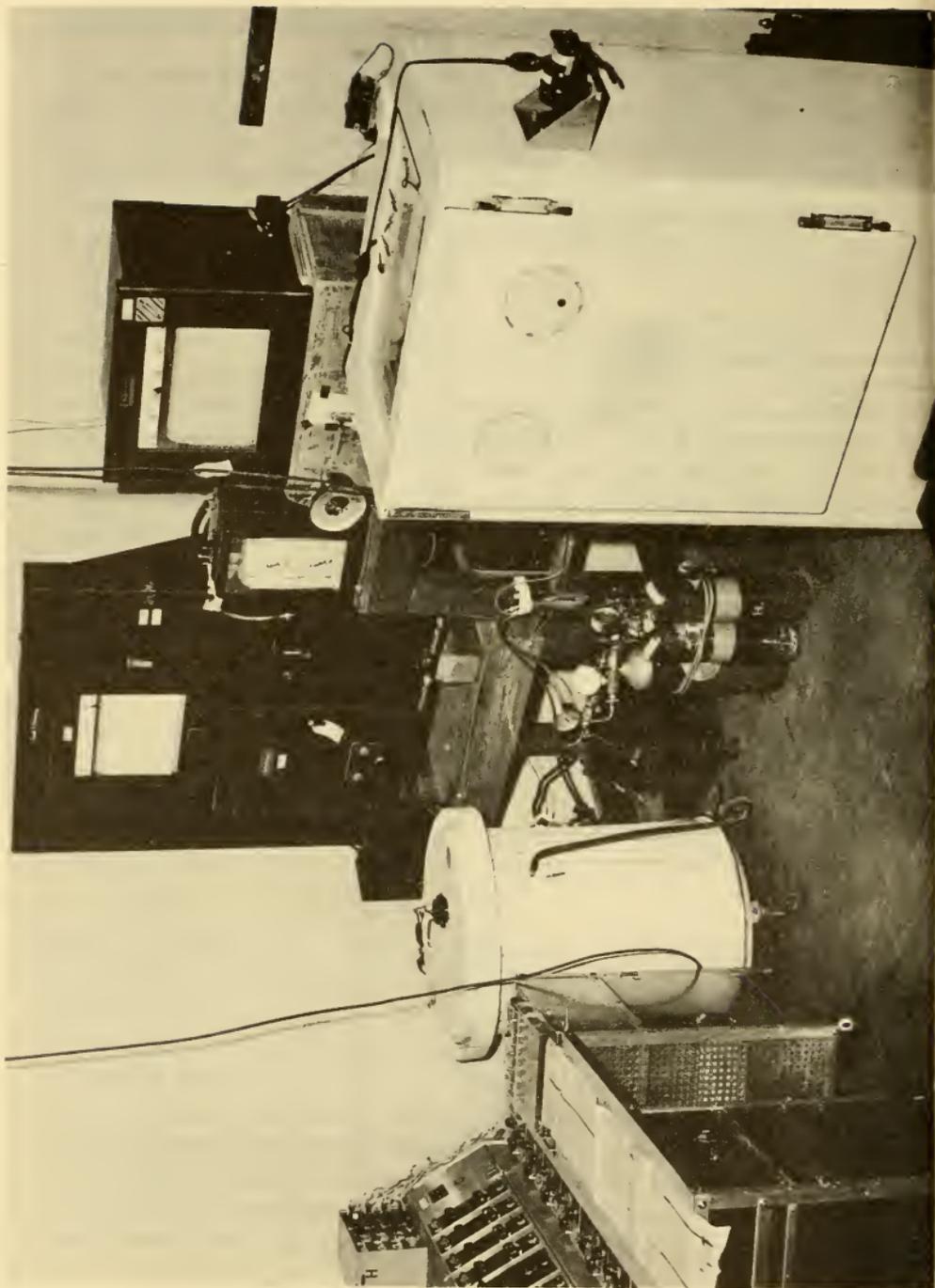
### Current Concept of Nervous Control of Temperature Regulation

The current concept of the nervous control of temperature regulation is that the control is effected through a modified reflex system, somewhat similar to the control of respiration. This modified reflex system consists of afferent pathways, a center, and efferent pathways to peripheral effector organs with, at least for shivering, a "feed-back" pathway for control of shivering rhythm.

Afferent system. Afferent impulses from cutaneous thermal receptors, to be described later at this Symposium by Professor Hensel, travel via afferent nerves through the dorsal roots, the spinothalamic tracts, and the fifth cranial nerve to reach the thalamus. From the thalamus, which functions as a distributory center for afferent impulses, the impulses are relayed to the cerebral cortex and hypothalamus. This theory of the thalamus functioning as a distributory center may not be strictly valid since animals with a larger part of the thalamus destroyed regulate their body temperatures efficiently. This is the so called "peripheral" control of body temperature, and requires further study.

There is considerable evidence from experiments on brain cooling and heating that the temperature regulating activities can be motivated or suppressed by temperature changes of the brain without any temperature change of the skin. This leads to the conclusion that there is a "central" or "centralthermostatic" controlling system.

Temperature regulating center. The term "center" for such activities as respiration, vasomotor activity, or temperature regulation has been justly criticized as a term which has a vague meaning and uncertain anatomical localization. Nevertheless, the term serves a useful purpose in the original sense as used by Sherrington when applied to a region in the brain which serves to integrate, coordinate, and regulate the afferent influences for motivation, inhibition, and regulation of the motor effects. An anatomical center may subserve more than one physiological function. The term "center" will be used here for want of a better substitute.



# HISTORICAL REVIEW

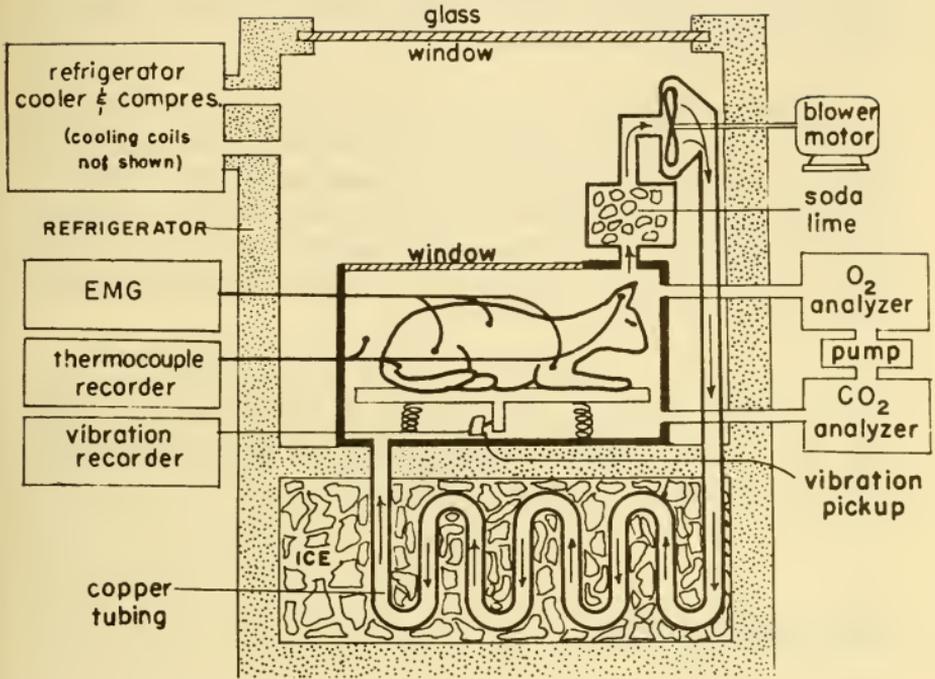


Figure 3. Apparatus for studying shivering in cats.

## HEMINGWAY, A.

All evidence indicates that the region of the brain most effective and important for temperature regulation is in the hypothalamus, and that this part of the brain must be functional and connected through nervous pathways with the lower motor centers. However, temperature regulation can be influenced by activities of the cerebellum, the cerebrum, and the midbrain.

Efferent system. The efferent system for temperature regulation involves several pathways. Shivering pathways essential for effective shivering travel downward through the midbrain and medulla to the lower motor neurons. A possible pathway for these impulses will be described later. Panting involves pathways of the respiratory system. Cutaneous vasomotor activity and sweating are mediated by fibers of the automatic nervous system.

Feedback. The rhythm of shivering is controlled by proprioceptive activity (Perkins, 1945; Lippold, Redfearn, and Vuco, 1958). The level in the central nervous system at which this feedback control is integrated is as yet undetermined.

### Experimental Evidence

This concept of the neural mechanisms controlling temperature regulation is based on a large amount of experimental evidence accumulated mainly in the past 50 years. Some of the experimental data which have contributed to our understanding of how the nervous system controls temperature regulation, especially shivering, will now be reviewed.

The experimental methods used by neurophysiologists in studying functional activity of the nervous system have consisted of the following four procedures: (1) Studying physiological response to cold after transections, (2) studying lesions of the central nervous system, (3) studying the responses evoked by electrical stimulation of various points of the brain, and (4) recording of electrical activity associated with a particular physiological activity. Examples of these procedures with their role in temperature regulation will now be given.

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Transections of the central nervous system. In locating centers within the central nervous system which are essential for function, one of the oldest procedures has been the central nervous system transection. Transections can be made at all levels in the central nervous system, excluding regions above or below the lesion from functional activity. Transections between the fourth cervical level and the lower medulla cannot be made without artificial respiration because of the failure of spontaneous respiration. In the classical work of Sherrington (1923-24), spinal cord transections were made in dogs and the animals were studied long after spinal shock had subsided. Sherrington found that shivering and cutaneous vasoconstriction failed in the cold in the structures innervated from the spinal cord below the lesion.

When the cerebral cortex is removed by a brain transection just below the thalamus and the animals allowed to recover from the operation, there is no appreciable reduction in shivering. These observations, first made by Dusser de Barenne in 1920, have been confirmed by Pinkston, Bard, and Rioch (1934) and more recently by Birzis and Stuart at the University of California. Bard and Rioch (1937) found that ablation of the cerebral cortex resulted in a warm skin in a cool environment with more rapid onset of severe shivering. This cutaneous vasodilation in a cool environment occurred after removal of the ansate cortex. In spite of a warm skin, the piloerection occurred.

Whereas a brain transection removing the cerebral cortex from the brain stem has only a slight effect on temperature regulation against cold, a midbrain transection made between the diencephalon and mesencephalon (the decerebrate preparation) has a profound effect on temperature regulation. The decerebrate preparation is (for all practical purposes) poikilothermic, as shown by experiments of Bazett and Penfield (1922), Keller and Hare (1932), and Bard and Macht (1958). However, a few investigators have reported a slight residual tremor which can occur after transection in muscles innervated from levels of the central nervous system below the lesion. Dworkin (1930) found that shivering which was insufficient to prevent a fall in the rectal temperature of rabbits in the cold, occurred in medullary and midbrain preparations. Thauer and Peters (1937a and 1937b), using rabbits, found that after

a 5-day recovery period from a trauma of surgery, there is an increase in the ability of animals to resist cold. These observations while somewhat limited in scope, and contradictory to the majority of the results of others, would lead to the rather important generalization that a controlling mechanism for defense against cold occurs in the brain stem below the hypothalamus. In order to investigate this question further and to extend the work to other animals, a study of chronic decerebrate cats has been made in our laboratory. In these animals, the entire forebrain above a plane extending from the superior colliculi to the mammillary bodies is isolated from the brain stem by transection followed by removal of a 2 mm wedge of midbrain tissue. Considerable nursing care is required for these animals for the prevention of hypo- and hyperthermia and cage sores. Hand feeding is required. However, with this time-consuming effort, the animals can be maintained for periods of several days to several months. These animals have been studied carefully by the methods already described. It has been found that in two of nine animals, a tremor only remotely resembling shivering can be induced by cold exposure and stopped by warmth. However, this tremor is valueless in protecting an animal against cold. The tremor does not raise the oxygen consumption rate and does not prevent a fall in rectal temperature in the cold. Professor Philip Bard of Johns Hopkins University, who has made extensive studies of the chronic decerebrate cat and has been interested particularly in the temperature regulation impairment caused by decerebration, has also observed this cold-induced tremor in the chronic midbrain preparation (1958). The occurrence of the cold-induced tremor in the chronic decerebrate cat, while it serves no useful purpose in temperature regulation, does raise the question of the extent in the central nervous system of the controlling mechanism for body temperature regulation.

Lesions of the central nervous system. The transection technique for separating completely the central nervous system into two unequal parts with no intracerebral or intraspinal nervous connection between the two parts has served a useful purpose in anatomical localization of the level in the central nervous system for control

## HISTORICAL REVIEW

of a particular function. However, the site of injury is extensive and excessive loss of function occurs. In recent years, most of the investigative work seeking to understand the extent and activity of various regions of the central nervous system has consisted of making small discrete lesions and testing the animal before and after the operation to determine loss of function caused by the lesion.

In the older work, the puncture technique was used. This consisted of first exposing the surface of the brain, inserting a probe or small scalpel, and destroying mechanically from the surface inward, a region adjacent to the surface. This was the method used in the classical work of Isenschmid (1912, 1914), whose work first definitely localized within the hypothalamus, the control for temperature regulation. The anatomical site of lesions in the brains of rabbits produced by the puncture technique of Isenschmid is shown in Figure 4. The stippled areas of the brain cross-sections represent the regions destroyed by the puncture. The clear unstippled areas represent intact brain. Below each of the four sections of Figure 4, the interference with homeothermic function caused by the lesion is indicated. In the section designated "abolished", there was no temperature regulatory function - the animal was poikilothermic. In the section labeled "undisturbed", temperature regulation was normal. If one superimposes the "undisturbed" section in the lower left-hand corner over the "abolished" section of the upper right-hand corner (since both of these sections are at the same level), it will be found that a small region in a transverse plane at the caudal border of the mammillary bodies, dorsolateral to the mammillary bodies and at a position laterally about one-fourth of the distance from the wall of the third ventricle to the lateral surface, must be intact and have neural connections with more caudal portions of the central nervous system for maintenance of homeothermy. The role of this particular region in temperature regulation will be discussed later in the Symposium by Douglas Stuart. In more recent years, a similar technique has been used by the neurophysiologists of the Army Medical Research Laboratory at Fort Knox, particularly Keller and Batsel (1952) and Keller (1956). Using electrocoagulation, a region of the brain was destroyed which resulted in converting a dog to a poikilothermic state (or nearly poikilothermic), producing a preparation called the "poikilothermic dog". The region destroyed was at the junction of the mesencephalon and diencephalon and included the region found earlier by Isenschmid to

BODY TEMPERATURE REGULATION ALTERATIONS

2 - 10 days post probe lesions

(Isenschmid - 1914)

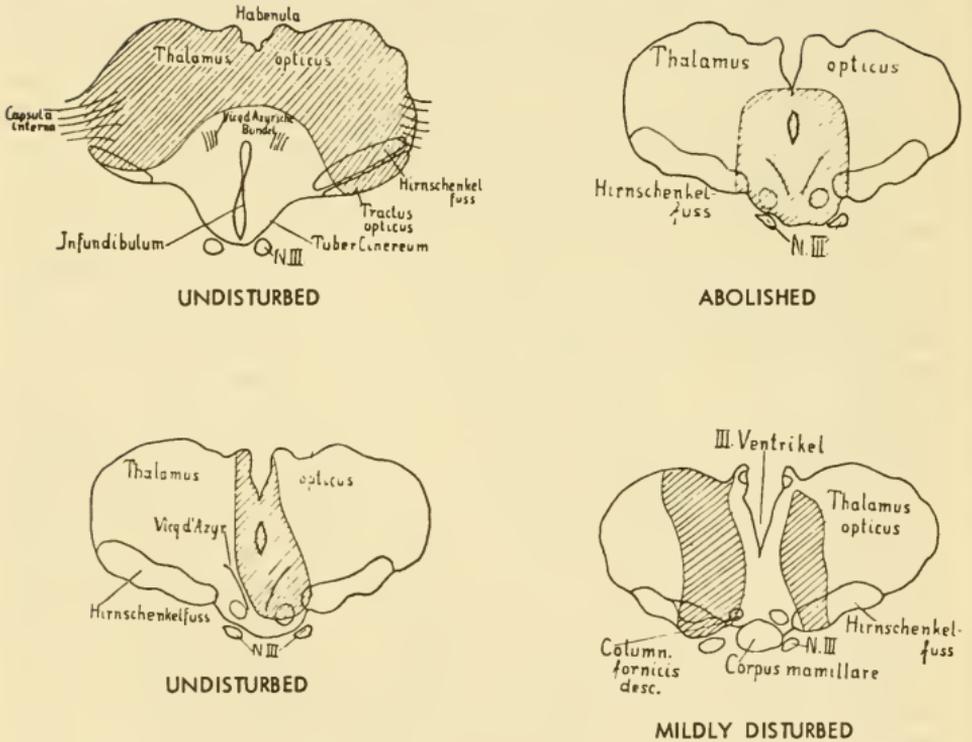


Figure 4. Effect on temperature regulation of lesions in the brain of a rabbit. The part of the brain destroyed by the puncture is indicated by the stippled area. The lesions in the two left-hand sections left temperature regulation undisturbed as determined by a cold exposure test. The lesion represented in the upper right-hand figure abolished temperature regulation, making the animal poikilothermic. Data of Isenschmid and Kiehl (1912).

## HISTORICAL REVIEW

be essential for homeothermy. However, the Fort Knox workers, in contrast with earlier workers, were able to keep their animals alive for many months and make homeothermy tests long after the traumatic shock of the operation had subsided.

The most popular technique for producing localized lesions in the central nervous system has been the electrolytic lesion produced at the tip of electrodes placed in the brain of anesthetized animals from the Horsley-Clark head frame. With this procedure, it is possible to make a lesion of a desired size at any desired location within the brain. The cat is the animal of choice for these studies due to the uniformity of the size and shape of the head. The first study of impairment of temperature regulation caused by these discrete lesion was made by the Ranson school of investigators. The earlier work of this group has been reviewed by Ranson in his classical 1940 paper. Examples of the type of lesion made by this method from work of Birzis and Hemingway are shown in Figure 5. In this figure, the regions of the brain destroyed are small areas in the lateral pons with the level of the section being shown in the upper half of the figure. This lesion abolished shivering in a cat. The advantage of this method of producing a lesion over the transection and puncture technique is that regions remote from the brain surface can be destroyed with little injury to surface structures.

Using the Horsley-Clark method of producing bilateral lesions at different levels in the brain stem of the anesthetized cat, Birzis and Hemingway (1956) have found that a region of the brain stem essential for shivering comprises a long pathway extending from the posterior hypothalamus to the medulla. This pathway starts downward from a position just dorsal to the junction between the medial edge of the cerebral peduncle and the lateral border of the mammillary bodies. As it descends through the midbrain, it courses dorsolaterally to the red nucleus, and in the pons it deviates laterally, reaching a superficial position immediately adjacent to the transverse pontine fibers. It retains its lateral position in the upper medulla. This pathway through the brain stem is shown in Figure 6. The pathway consists of the region within the elliptical figure drawn on the sections. It will be noted that this pathway does not involve the corticospinal tracts. Figure 7 shows the site of lesions which destroyed the corticospinal tracts and adjacent areas of the

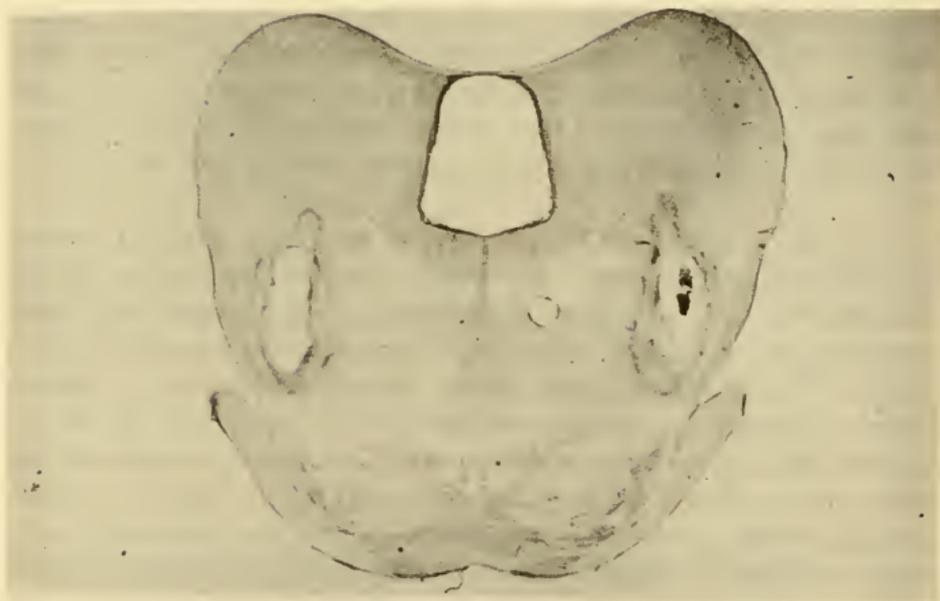


Figure 5. Electrolytic lesions which abolished shivering in the brain of a cat. The lesions are laterally located in the pons. The electrodes were inserted from a Horsley-Clark stereotaxic frame. Birzis and Hemingway (1956).

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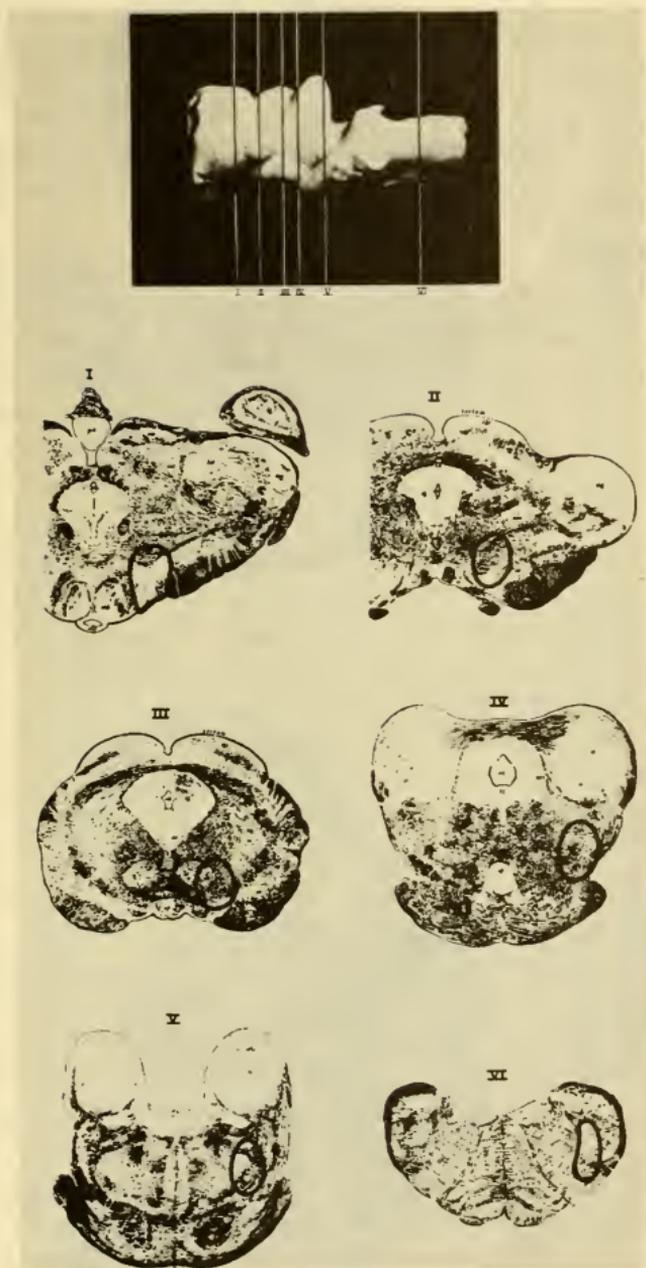
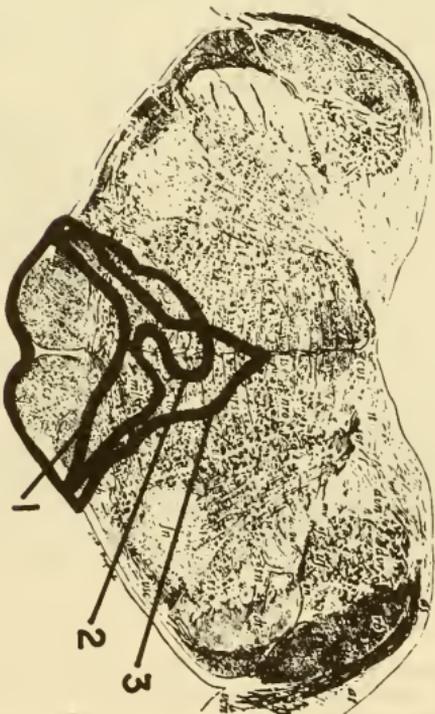


Figure 6. Site of lesions at various levels in the brain stem of cats, extending from hypothalamus to medulla oblongata, which abolished shivering. The site of each lesion is encircled.

PYRAMIDAL TR. LESIONS

PYRAMIDAL TR. LESIONS



SHIVERING RETURNED

1 — 1 HR

2 — 15 MIN

3 — 1 HR

SHIVERING RETURNED

1 — 1.5 HRS

2 — 30 MIN

3 — 1.7 HRS

Figure 7. Lesions in six cats which destroyed the corticospinal tracts in the medulla oblongata but did not prevent

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medulla of six cats. Shivering persisted in these animals after the lesion. It would be an attractive hypothesis to propose that the pathway described, which was found to be intact for shivering to occur, was the efferent pathway from the hypothalamus to the lower motor center for control of shivering. However, this hypothesis must be proposed with caution and final decision awaited for confirmatory evidence, preferably using unanesthetized animals.

Electrical stimulation. A method currently used in electrophysiology for determining the site of control of a particular function is to stimulate a point within the central nervous system and to observe the physiological response to stimulation. This technique has been used effectively in studies of respiration to determine location of the inspiratory and expiratory centers in the central nervous system. If stimulation of a point in the medulla oblongata invokes inspiration, then the point stimulated can be assumed to be located in the inspiratory center. This technique has been used by a number of observers in studying shivering. Akert and Kesselring (1951) in reviewing the extensive diencephalic stimulation data from the laboratory of Hess found a number of instances where stimulation of regions in and adjacent to the hypothalamus produced a tremor resembling shivering. The tremor was produced by low frequency stimulation of eleven points in eight cats. Six of these points were in the septum pellucidum, three were in the caudate nucleus, one in the thalamus, and one in the posterior hypothalamus. Birzis and Hemingway (1957) were able to produce a tremor similar to shivering when nineteen points in the midbrain of four cats were stimulated. These points were on the pathway described previously which was established by lesion experiments; the region dorsolateral to the red nucleus and a region in the lateral pons where stimulation evoked shivering is shown in Figure 8. From the record below the figure, the onset of shivering after stimulation is shown. This is a continuous record of muscle electrical activity (electromyogram) in two muscle groups. After stimulation of a point near the red nucleus, there was a brief latent period followed by shivering. With cessation of the stimulus shivering subsided during a brief after-discharge period of approximately five seconds. Interest in the septum pellucidum as a controlling center for shivering was again aroused by the work of Andersson (1957). He, like Akert and Kesselring, was able to induce shivering by stimulation of points in the septum pellucidum of goats. The role of the septum pellucidum in shivering

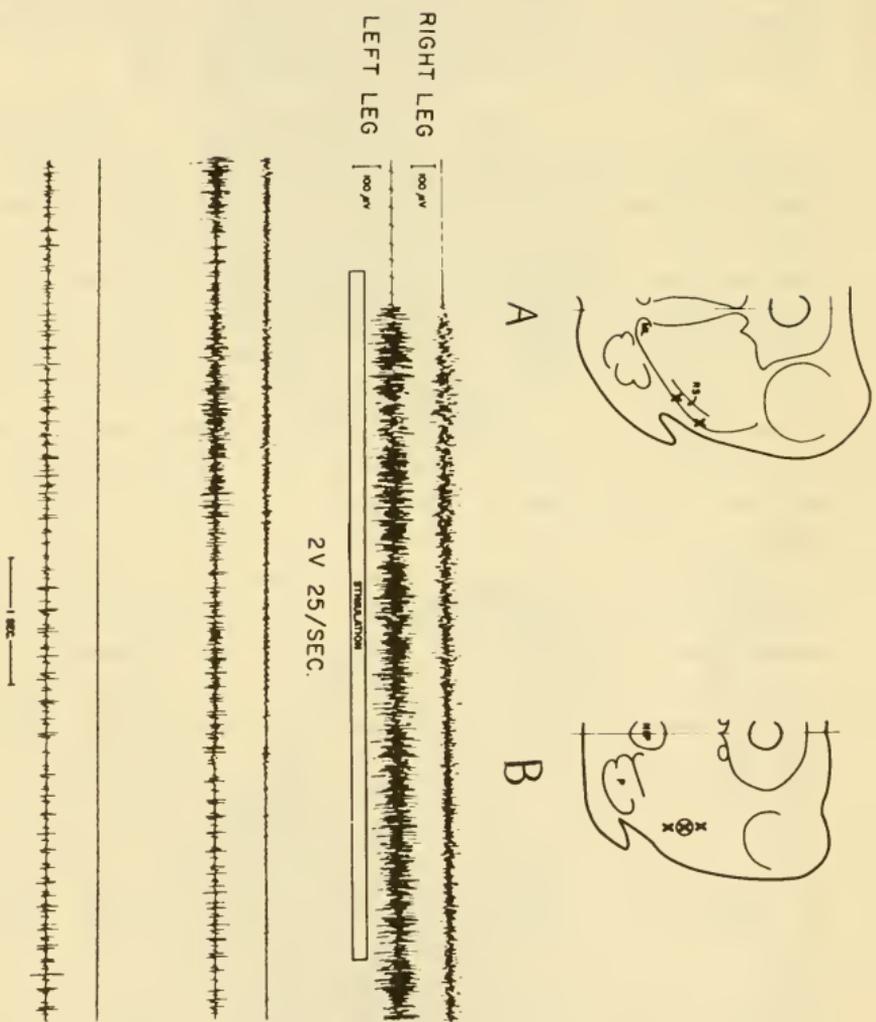


Figure 8. A and B. Transverse sections of the brain of cats where shivering was induced by electrical stimulation at the points marked X. Lower part of figure is a record of shivering (electromyogram) induced by stimulation of a point (encircled) shown in B.

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and its possible relation with the posterior hypothalamus will be discussed in the work of Stuart later in this Symposium. Shivering cannot only be induced by electrical stimulation of points in the brain but it can be suppressed, if it has started spontaneously by cold, by stimulation of other points. Kaada (1951) was able to inhibit shivering by electrical stimulation of points on the cerebral cortex while Hemingway, Forgrave, and Birzis (1954) found that spontaneous shivering could be stopped or attenuated by electrical stimulation of points widely distributed in the hypothalamus. A particularly active suppression region as determined by low stimulus threshold was found in the pre-optic region.

Electrical stimulation of various points in the brain has revealed that shivering can be started or, if proceeding spontaneously, stopped by electrical stimulation of points within the brain. The points for shivering suppression are more widely distributed than the points for shivering stimulation. The most active point for suppression is found in the pre-optic region, while the most active point for stimulation, as Stuart will report later, is in the posterior hypothalamus. Other points of higher threshold for both suppression and stimulation can be found throughout the brain.

At the present time, only a tentative "working" hypothesis of the control of shivering in the cat can be made resulting from interpretation of the stimulation experiments. The active region in the posterior hypothalamus for stimulation may be a primary center for starting and control of shivering, but its function may be under subsidiary influence of secondary centers, particularly in, or rostral to, the feline septum. The widely distributed suppression effects may be interpreted as due to the existence of an inhibitory mechanism for shivering. Shivering, if not too intense, can be suppressed voluntarily, which may involve the cortical suppression control of Kaada. Shivering is also inhibited by voluntary movement. When a voluntary movement is made by a limb, shivering ceases. It seems that in the control of the skeletal musculature, shivering is a function of secondary importance to locomotion. This is reasonable in consideration of animal safety and maintenance that first priority should be assigned to movement for flight, fight, and defense. When the skeletal musculature is needed for these life-saving functions, shivering can be temporarily suspended in favor of emergency action. This

would serve to explain the existence of a widely distributed shivering suppression mechanism which can be immediately initiated when needed.

Recording of electrical activity. A new tool in electrophysiology which has been used rather extensively in the last 10 years is the use of microelectrodes and semi-microelectrodes for recording of electrical activity of the cells of the central nervous system. These electrodes have a diameter of from  $0.2\mu$  to  $50\mu$  and are, in diameter, of the same order of magnitude as nerve cells and their processes, i.e.,  $0.5\mu$  to  $20\mu$ . When placed in contact with a nerve cell (or nerve fiber) which is actively functioning, the electrical of the cell is transmitted to the electrode (Freeman and Hemingway, 1959). The electrical potential of the active cell consists of a series of rapid transient potentials called "spike" potentials. These potentials are amplified and transmitted to a cathode ray oscilloscope and photographed. Birzis and Hemingway (1957) were the first to record well defined spike potentials associated with shivering. These potentials appeared with shivering and disappeared with cessation of shivering. Records of these potentials are shown in Figure 9. These potentials were recorded from electrodes placed on the "shivering pathway" whose boundaries were determined by lesion experiments as described earlier in this paper. A semi-transection made just caudal to the point from which the potentials were recorded did not prevent or change these spike potentials (see Figure 10). This is evidence that the potentials were action potentials of fibers carrying shivering impulses downward in the central nervous system to lower motor neurons, that is, they were part of the efferent fiber system controlling shivering. These spike potentials associated with shivering were extensively studied by Freeman and Hemingway (1959), who found that the action potentials could be recorded from the "shivering pathway" previously described and extended from the fields of Forel in the posterior hypothalamus to the olive in the medulla oblongata. By using a high amplification and rapid sweep of the cathode ray oscilloscope, a characteristic change of potential pattern was discovered in proceeding from the fields of Forel to the olive, which permitted a tentative interpretation of these potentials (based on a theory proposed by Lorente de Nô) as spike potentials travelling downward in the brain. There were, however, two disturbing factors of this study. The impulses seemed to arise from the fields of Forel and travel down-

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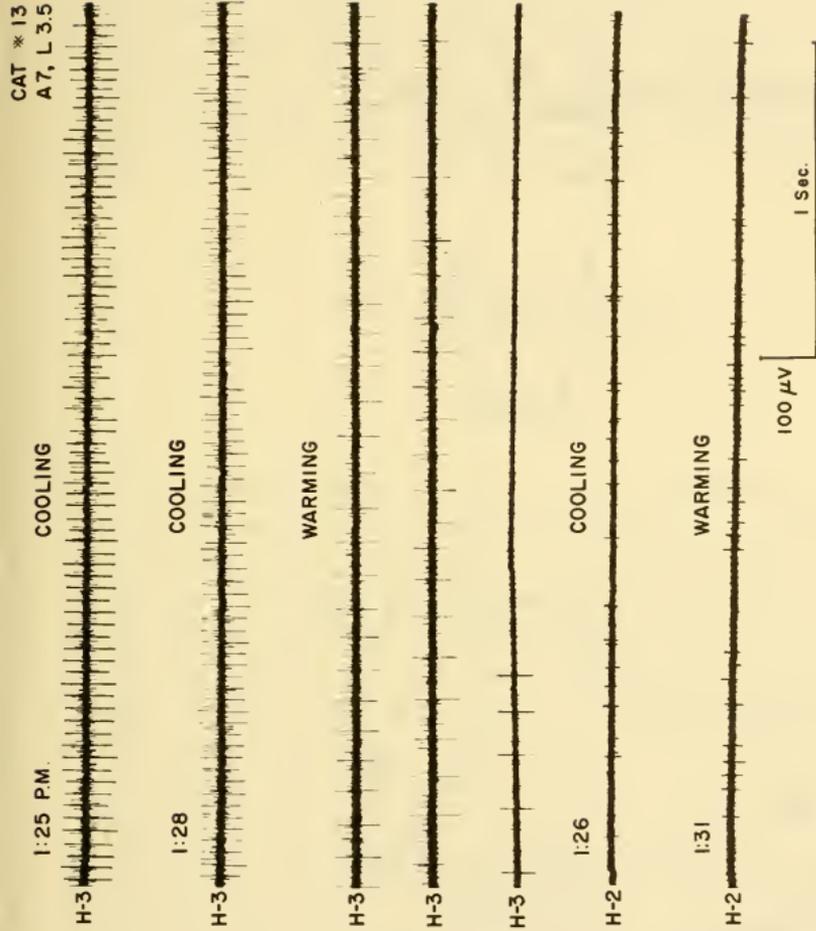


Figure 9. Spike potentials recorded from the midbrain which appear and disappear with shivering. The upper five records (H-3) were all made from the same point where a unit "fixed" when shivering was induced and the potentials disappeared on warming. The lower two records, designated H<sub>2</sub>, were from a point 1mm distant from the point H<sub>3</sub>. The slight discharge was not affected by heating and cooling.

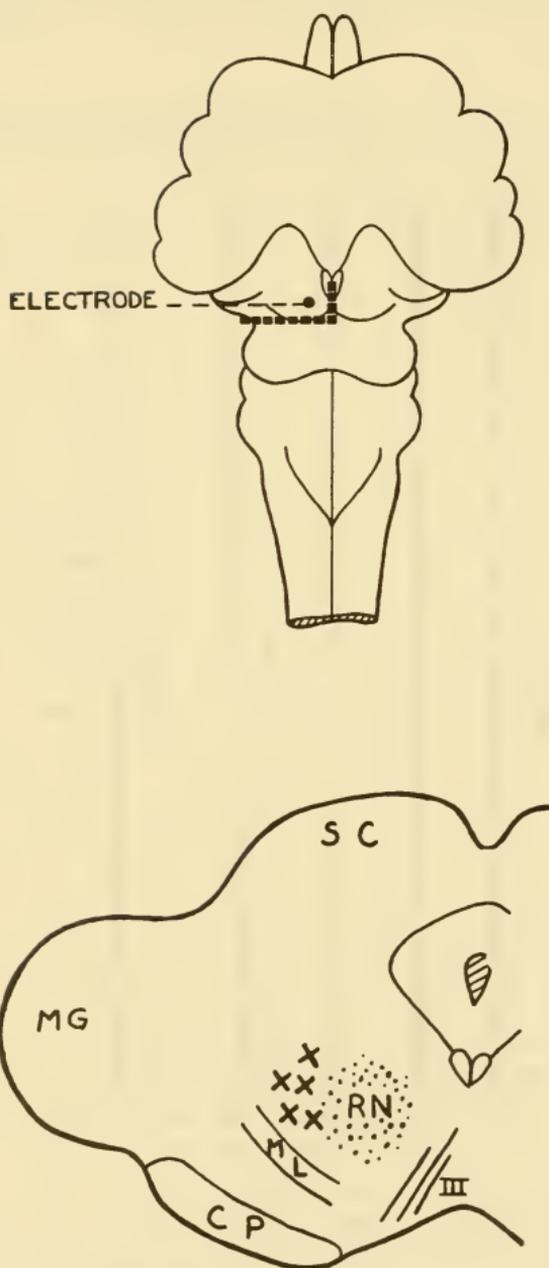


Figure 10. The site of the electrode from which shivering spike potentials appeared. The potentials were obtained after the hemisection and saggital section shown by the dotted line.

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ward. If these impulses were the efferent action potentials controlling shivering which arose in the fields of Forel, then destruction of the fields of Forel should abolish shivering. In a study of small lesions made bilaterally to destroy the fields of Forel, shivering persisted (Stuart, Freeman, and Hemingway, 1959). Another disturbing feature was that the duration of the spike potentials was not exactly the same as the duration of shivering. The potentials seemed to persist after shivering had ceased. These observations reveal that any interpretation that the large well defined spike potentials of the midbrain which come and go with shivering form the efferent control of shivering must be proposed with caution. Further research is needed. This work will be discussed by Dr. Freeman.

## ACKNOWLEDGMENTS

The history of the search for an understanding of the neural control of the responses of the hypothalamus to cold has revealed that considerable progress has been made since the days of Isenschmid in 1912-1914. In acknowledging useful contributions to this field of study, the work of Sherrington, Bard, Keller, Ranson, Clark, Magoun, Thauer, and Hensel has advanced our knowledge over that known in 1914. For the studies conducted at the University of California, which have been briefly reviewed in the latter part of this report, the Arctic Aeromedical Laboratory in Alaska has played a major role by encouragement, scientific liaison, and financial support. It is a pleasure to acknowledge their cooperation and to commend the staff, particularly Colonel Quashnock, Lt. Colonel Herbert, Drs. Hannon and Eagan, for their contributions to the field of environmental physiology by arranging this Symposium.

DISCUSSION

DR. CLARK: I would rather not ask a question. I would like to get into this shivering pathway because there is some of Dr. Keller's work that has been misinterpreted. If I could take a few minutes, I would like to go over this.

If you make a complete transection through the midbrain and then put the animal in the cold as indicated by one of Dr. Hemingway's diagrams, you are going to get a progressive loss in body temperature with time. As you quite well know, when you are attempting to make lesions like this, you fail quite frequently. Now, say you leave a little bit of the cerebral peduncle. The temperature may go way down. These animals shiver; there is a little of the cerebral peduncle left. We do not know how the fibers go through there; we do not know where they come from; but we are attempting to get an anatomical basis for this finding. We have seen it in both cat and dog, but when the entire brain stem is transected except for a little of the pyramid, there is still shivering.

DR. STUART: How long after transection were such preparations studied?

DR. CLARK: I think the longest time has been seven or eight months. You probably would not see it until the animal is at least two months postoperative.

DR. HEMINGWAY: How much of the other tissue is there, Dr. Clark, above the peduncle? None at all?

DR. CLARK: There is only a part of the peduncle left, and the amount that is left determines the rate of cooling. The pathway for shivering is more medial than the pathway for panting; part of the shivering fibres are in the peduncle. I am not saying they are part of the pyramidal tract; I am simply saying that there is something resembling shivering after this transection, and that these physiological observations are confirmed by subsequent studies of sections.

DR. STUART: If the animal is shivering, how does the body temperature fall?

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DR. CLARK: Well, it is not a strong shiver, and you have the problem of defining shivering. If you have your hand on the hind quarter of such a dog, you can feel a tremor which disappears when the animal is warm and shows up when he is cold. It is not enough to maintain normal temperature levels, but it is definitely there.

DR. STUART: Have you ever observed shivering following complete destruction of the preparation's cerebral peduncle?

DR. CLARK: Yes, but not as much as in the preparation with partial destruction. In the complete transection, if you lower his temperature to 29° C, quite frequently you can feel a tremor. Bard has found the same thing in his cats.

DR. FREEMAN: This phenomenon of an increased thermogenesis with some portions of the nervous system still intact would imply that there is some descending activity which potentiates shivering that is set up in the spinal cord, or that there are parts of the brain stem affected by the external cooling. Have you attempted to stimulate electrically in various portions of the brain anterior to the sections to see if you can increase this effect?

DR. CLARK: No, we have not. I would like to point out that we do not feel that these animals are truly poikilothermic. The fact that they still retain some indication of panting, some indication of shivering, indicates they are not poikilothermic. In addition, they show something in the way of vasomotor control. Thus, if you take a midbrain dog and lower his temperature into the cold and then bring it back into the warm, his skin temperature would jump up rather more rapidly than you would anticipate on the basis of simple rewarming. Consequently, we have fairly good evidence that, in the dog at least, there is some vasomotor control in the midbrain preparations.

DR. HEMINGWAY: Would you care, Dr. Clark, to comment on Dr. Keller's statement that the descending pathways for shivering are in the corticospinal tracts.

DR. CLARK: I think that this is one of his points which has been misinterpreted. He states that some of the fibers are in the

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corticospinal tract, not that the entire pathway is there. Some of the fibres are intermingled with corticospinal fibres.

DR. HEMINGWAY: Dr. Birzis destroyed the corticospinal tract in the medulla in acute experiments. She tested them two or three hours after the lesions were made and observed no shivering. Some lesions were large, some were small; but whenever the corticospinal tracts were destroyed, the animal did not shiver.

DR. CLARK: We do not know anything about the path below the midbrain, but it is quite definite that some of the fibres that mediate shivering are intermingled with corticospinal fibres in the midbrain.

DR. FREEMAN: Both she and I looked for unit activity in the cerebral peduncles in the midbrain but were not able to find any. However, this may be, as you point out, a statistical distribution problem.

DR. CLARK: With the number of fibres in this area, attempts to get unit activity from a particular type are like reaching into a bucket to pick out the one black marble.

DR. FREEMAN: Well, in that case, it would be the Mexican jumping bean in the marbles.

DR. HEMINGWAY: Dworkin observed shivering in decerebrate preparations, but others have failed to confirm this. Stuart and Bard have observed a tremor in decerebrate preparations, but this tremor is ineffective metabolically.

DR. CLARK: From the work we have on the way the temperature falls, I would say it is not very effective, although it is still shivering.

DR. STUART: Rather than shivering, I would say "intermittent muscular activity" that has no thermoregulatory function.

DR. CLARK: I would not say that because it appears and disappears according to the temperature.

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DR. STUART: In our experiments the method of cooling has been critical. The animal might display a generalized avoidance response to a stimulus that is nociceptive as well as cold.

DR. CLARK: That is hard to accept under the conditions of our experiment.

DR. STUART: It is easy to accept under the conditions of mine.

DR. HEMINGWAY: Is it possible that a small amount of tissue is left just above the cerebral peduncle?

DR. CLARK: What I am saying is that we found that these are usually cases where a complete transection was attempted, where the knife skipped a little bit over the bottom, so that only part of the peduncle is left and everything above it is gone.

MR. ADAMS: I believe there is support for Dr. Clark's remark in studies that were conducted a long time ago where it was shown that vasomotor changes were associated with environmental temperature changes.

DR. HEMINGWAY: But they are almost ineffective in preventing a fall in rectal temperature in the cold.

MR. ADAMS: In this type of preparation one should not argue that the vasomotor changes are completely ineffective.

DR. HEMINGWAY: There may be a tremor in a decerebrate preparation. Bard and Stuart have observed a tremor which appears in the cold and disappears with warmth, but this tremor is ineffective in temperature regulation.

DR. CLARK: I agree with you; it is not particularly useful because the animal's temperature falls markedly, but it is an indication, primarily, that the pathway is quite diffuse.

DR. HEMINGWAY: Yes, I would agree with that.

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DR. CLARK: Our preliminary, anatomical data, does not indicate that that is the case because in animals where we did a hemisection of the internal capsule, in a whole sagittal section, I find two or three little fibres in the degenerating pyramid. We don't know where they come from.

## REFERENCES

1. Abramson, D. I. Vascular responses in the extremities of man in health and disease. University of Chicago Press, 1944.
2. Akert, K. and F. Kesselring. Kaltzittern als zentralen Reiz-effect. *Helv. Physiol. Acta.* 9:290-295, 1951.
3. Andersson, B. Cold defense reactions elicited by electrical stimulation within the septal area of the brain in goats. *Acta. Physiol. Scand.* 41:90-100, 1957.
4. Bard, Philip and M. B. Macht. The behaviour of chronically decerebrate cats. *Neurological Basis of Behaviour. Ciba Symposium*, p. 55-75, 1958.
5. Bard, Philip and D. M. Rioch. A study of four cats deprived of neocortex and additional portions of the forebrain. *Bull. Johns Hopkins Hosp.* 60:73-147, 1937.
6. Bazett, H. C. and W. G. Penfield. A study of the Sherrington decerebrate animal in the chronic as well as the acute condition. *Brain.* 45:185-265, 1922.
7. Birzis, Lucy and Allan Hemingway. Descending brain stem connections controlling shivering in the cat. *J. Neurophysiol.* 19:37-43, 1956.
8. Birzis, Lucy and Allan Hemingway. Shivering as a result of brain stimulation. *J. Neurophysiol.* 20:91-99, 1957. a.
9. Birzis, Lucy and Allan Hemingway. Efferent brain discharge during shivering. *J. Neurophysiol.* 20:156-166, 1957. b.

HEMINGWAY, A.

10. Clark, George, H. W. Magoun, and S. W. Ranson. Hypothalamic regulation of body temperature. *J. Neurophysiol.* 2:61-80, 1939.
11. Clark, George, H. W. Magoun, and S. W. Ranson. Temperature regulation in cats with thalamic lesions. *J. Neurophysiol.* 2:202-207, 1939.
12. Dusser de Barenne, J. S. Recherches experimentelles sur les fonctions du systeme nerveux centrale, faites en particulier sur deux chats dont neopallium avait été enlevé. *Arch. neerl. de physiol. de l'homme et des animaux.* 4:31-123, 1919-20.
13. Dworkin, Simon. Observations on the central control of shivering and of heat regulation in the rabbit. *Am. J. Physiol.* 93:227-244, 1930.
14. Freeman, N. E. The effect of temperature on the rate of blood flow in the normal and in the sympathectomized hand. *Am. J. Physiol.* 113:384-398, 1935.
15. Freeman, W. J. and Allan Hemingway. Localization of unit potentials in brain stem associated with shivering. *Arctic Aeromed. Lab. Report 1959. a.*
16. Freeman, W. J. and Allan Hemingway. Manual for the construction, use and interpretation of records from stainless steel micro-electrodes. *Arctic Aeromed. Lab. Report 1959. b.*
17. Freeman, W. J., D. Stuart, and Allan Hemingway. Nervous control of shivering. IX. Role of the fields of Forel in shivering. *Arctic Aeromed. Lab. Report 1959.*
18. Hemingway, Allan, Paul Forgrave, and Lucy Birzis. Shivering suppression by hypothalamic stimulation. *J. Neurophysiol.* 17:375-386, 1954.
19. Hemingway, Allan and S. R. Hathaway. An investigation of chemical temperature regulation. *Am. J. Physiol.* 134:596-602, 1941.

## HISTORICAL REVIEW

20. Hertzman, A. B., W. C. Randall, and K. E. Jochim. The estimation of the cutaneous blood flow with the photoelectric plethysmograph. *Am. J. Physiol.* 145:716-726, 1946.
21. Iampietro, P. F., J. A. Vaughan, R. F. Goldman, M. B. Kreider, F. Masuci, and D. E. Bass. Heat production from shivering. *J. Applied Physiol.* 15 :632-33, 1960.
22. Isenschmid, R: and L. Krehl. Ueber den Einfluss des Gehirns auf die Warmeregulation. *Arch. f. Exptl. Path. u. Pharm.* 70:109-134, 1912.
23. Isenschmid, R. and W. Schnitzler. Beitrag zur Lokalisation des der Warmeregulation vorstehenden Zentralapparatus im Zwischenhirn. *Arch. f. Exptl. Path. u. Pharm.* 76:202-223, 1914.
24. Kaada, B. R. Somato-motor, autonomic and electrocorticographic response to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. *Acta. Physiol. Scand.* 23 (Suppl. 83): 105,1951.
25. Keller, A. D. Hypothermia in the unanesthetized poikilothermic dog. *Physiology of Induced Hypothermia.* Nat. Acad. Sci. Publ. No. 451, p. 61-79, 1956.
26. Keller, A. D. and Henry Batsel. The ambulatory and semi-poikilothermic dog (poikilothermic against cold). *Army Med. Res. Lab. Rept.* 84, Project 6-6-12-028, 10 June 1952. 1952.
27. Keller, A. D. and W. K. Hare. Heat regulation in medullary and midbrain preparations. *Proc. Soc. Exptl. Biol. Med.* 29:1067-68, 1931-32.
28. Lippold, O. C. J., J. W. T. Redfearn, and J. Vuco. The frequency spectrum of the muscular activity of shivering in the anesthetized cat. *J. Physiol.* 140 :49P, 1958.
29. Nyboer, Jan. The impedance plethysmograph, *Medical Physics.* 2:736, 1960.

HEMINGWAY, A.

30. Perkins, J. F. The role of the proprioceptors in shivering. *Am. J. Physiol.* 145:264-271, 1945.
31. Pinkston, J. O., Philip Bard, and D. M. Rioch. The response to changes in environmental temperature after removal of portions of the forebrain. *Am. J. Physiol.* 109:515-531, 1934.
32. Ranson, S. W. Regulation of body temperature. *Proc. Assoc. Research Nerv. and Mental Dis.* 20:342, 1940.
33. Ranson, S. W., C. Fisher, and W. R. Ingram. Hypothalamic regulation of temperature in the monkey. *Arch. Neurol. Psychiat. (Chicago)* 38:445-466, 1937.
34. Sherrington, C. S. Notes on temperature after spinal transection with some observations on shivering. *J. Physiol.* 58:405-424, 1923-24.
35. Teague, R. S. and S. W. Ranson. The role of the anterior hypothalamus in temperature regulation. *Am. J. Physiol.* 117:562-570, 1936.
36. Thauer, Rudolph and Georg Peters. Warmeregulation olive Hypothalamus. *Abhandl. Deutsch. Ges. f. inn. Med.* 49:188-190, 1937.a.
37. Thauer, Rudolph and Georg Peters. Warmeregulation nach operativer Ausschaltung der Warmezentrums. *Pfluegers Arch.* 239:483-514, 1937.b.

## RECENT ADVANCES IN THERMORECEPTOR PHYSIOLOGY

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I am going to discuss some recent problems of thermoreceptors which give the organism information about the temperature conditions of the surroundings. The previous concept of the electrophysiology of thermoreceptors was based merely on investigations of the afferent impulses in the cat's tongue. Figure 1 shows a record from a fine preparation of the lingual nerve of the cat during mechanical and thermal stimulation of the tongue. Mechanical stimulation alone will elicit a large discharge of impulses. During cooling we see a smaller single fiber discharge with a partial adaptation. When cooling the tongue and touching it at the same time, we get both types of discharges. Thus it is quite easy to discriminate in the cat's tongue between specific cold receptors which respond only to cooling and specific mechano-receptors which are not excited by cooling.

Unfortunately, we did not stop the experiment at this time, but started in Marburg two years ago with investigations of the afferent discharges from the cat's external skin. In connection with the problems of thermoregulation, it is important to record not only from the tongue, which is a rather specialized organ, but also to get information about the impulse traffic in the cutaneous nerves. We were very surprised to find practically no specific cold fibers in the external skin.

There is quite a number of A fibers showing very much the same behavior on cooling and warming as found in the lingual nerve, but the cold sensitive receptors in the cat's skin were also sensitive to mechanical stimulation, as shown in Figure 2. The discharge of this fiber during cooling and warming the skin is the same as has been found for the specific cold fibers in the tongue, but on touching the skin with a hair, a marked response can be seen. Neither could we record any A fiber potentials during warming the external skin of the cat.

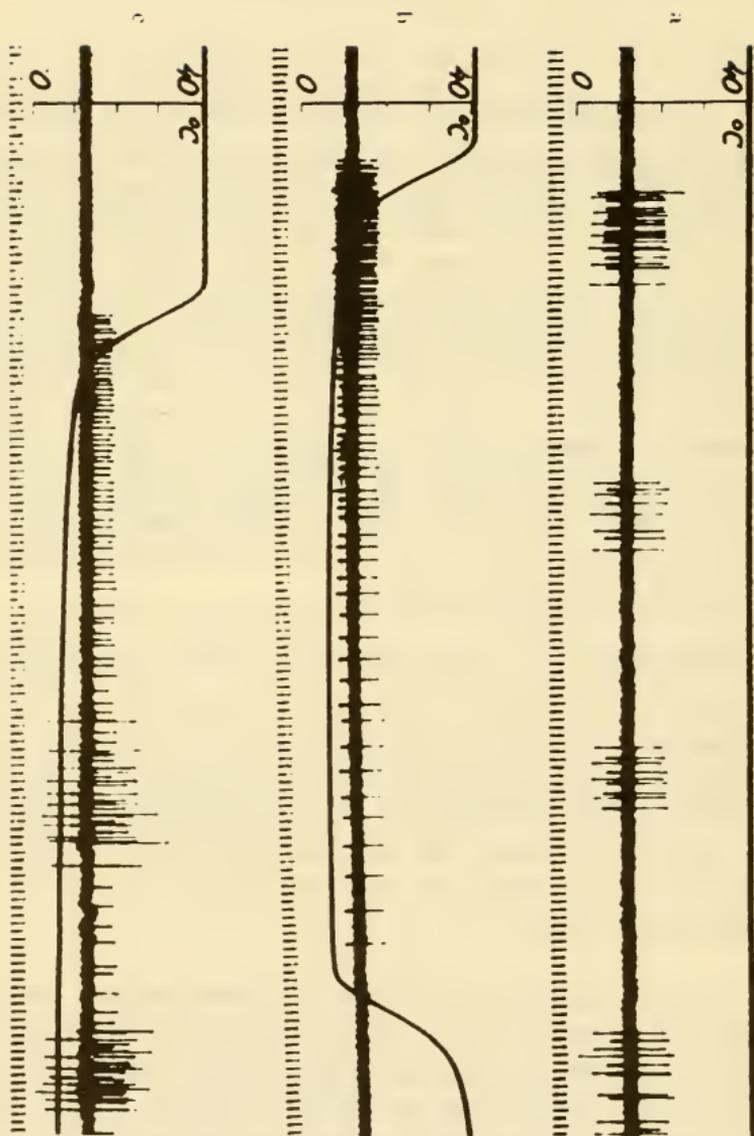


Figure 1. Afferent impulses in a thin strand of the cat's lingual nerve. a 4 x pressure on the tip of the tongue. b cooling. c cooling and 2 x pressure. Time marks 0.02 sec. (Hensel, 1952).

# THERMORECEPTOR PHYSIOLOGY

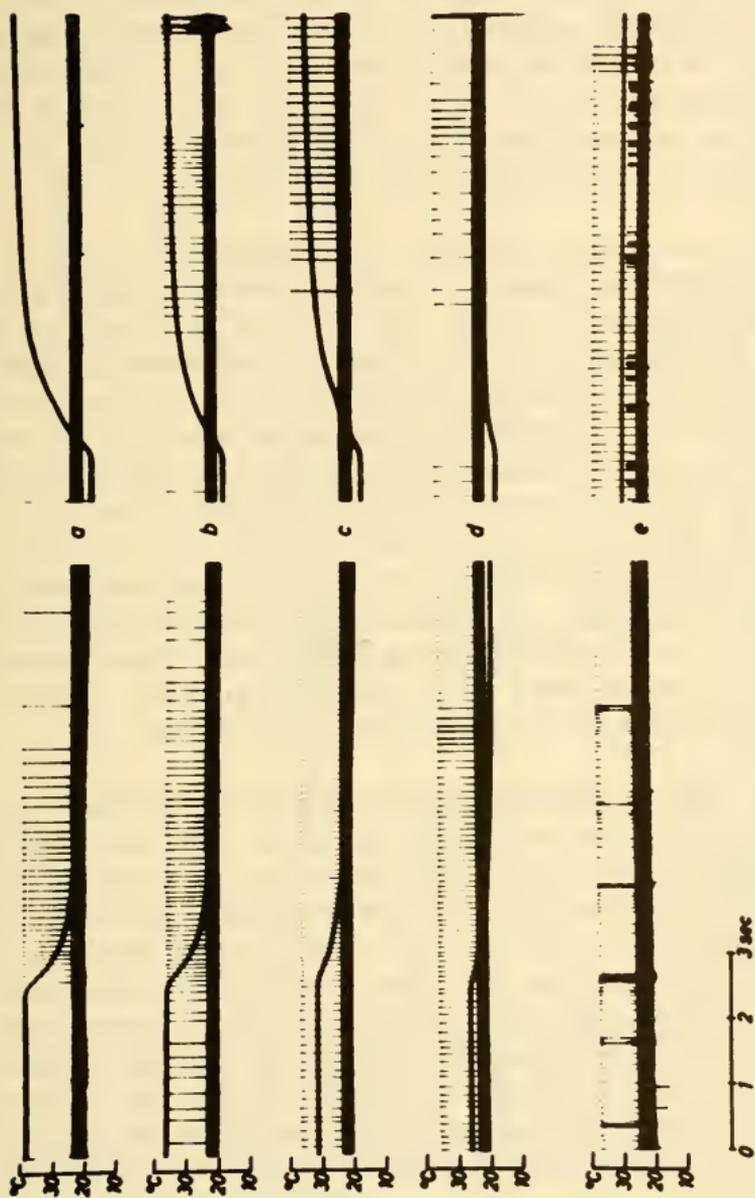


Figure 2. Afferent impulses in a non-specific single fiber from the cat's saphenous nerve. a - d cooling and re-warming the skin of the leg. e (left curve) touching the skin several times. (Witt and Hensel, 1959).

Now, the question remained open whether specific cold receptors might be connected with non-myelinated C fibers; about 80 per cent of the afferent fibers in the cutaneous nerves are C fibers. Recently, we had the opportunity of recording afferent impulses from single C fibers in the external skin of the cat. This work has been done together with Dr. Iggo, Edinburgh, and Dr. Witt in our laboratory, and we found that many cold receptors as well as warm receptors are connected with non-myelinated fibers.

Figure 3 illustrates the method. The saphenous nerve was dissected into very thin filaments in order to record impulses from single non-myelinated C fibers. The C fiber was identified by measuring its conduction velocity. This was accomplished by applying electrical stimuli to the nerve distally from the recording point. The impulses were recorded by means of two oscillographs; one oscillograph was used for normal recording of the spike, whereas the sweep of the second oscillograph was triggered by the electric stimulus. The conduction velocity could be found by measuring the distance between the stimulating and the recording point and by measuring the time between stimulus and the onset of the C fiber impulse at the recording electrode (Fig. 4). By means of this method, the conduction velocity of the non-myelinated temperature fibers of the skin turned out to be in a range of 0.5 to 1.5 m/sec.

Figure 5 shows the discharge of a single non-myelinated cold fiber when cooling the skin. After the onset of the discharge, a partial adaptation can be seen. Even cooling by several tenths of a degree centigrade is sufficient to cause a marked increase in the impulse frequency. The C fiber also shows a steady discharge at constant skin temperatures. The short inhibition of the discharge before the onset of cooling is due to a slight increase in temperature. Plotting the discharge frequency of a single C fiber against time, we get curves as shown in Figure 6. Sudden cooling causes a phasic increase in frequency. On rewarming, there is a transient inhibition and then the discharge reappears and finally reaches the initial level.

Figure 7 shows the discharge frequency of a specific non-myelinated warm fiber. The plots of the impulse frequency against time of this warm fiber show a phasic increase in frequency during warming (Fig. 8). Even warming by several tenths of a degree centigrade is sufficient to cause a marked increase in frequency.

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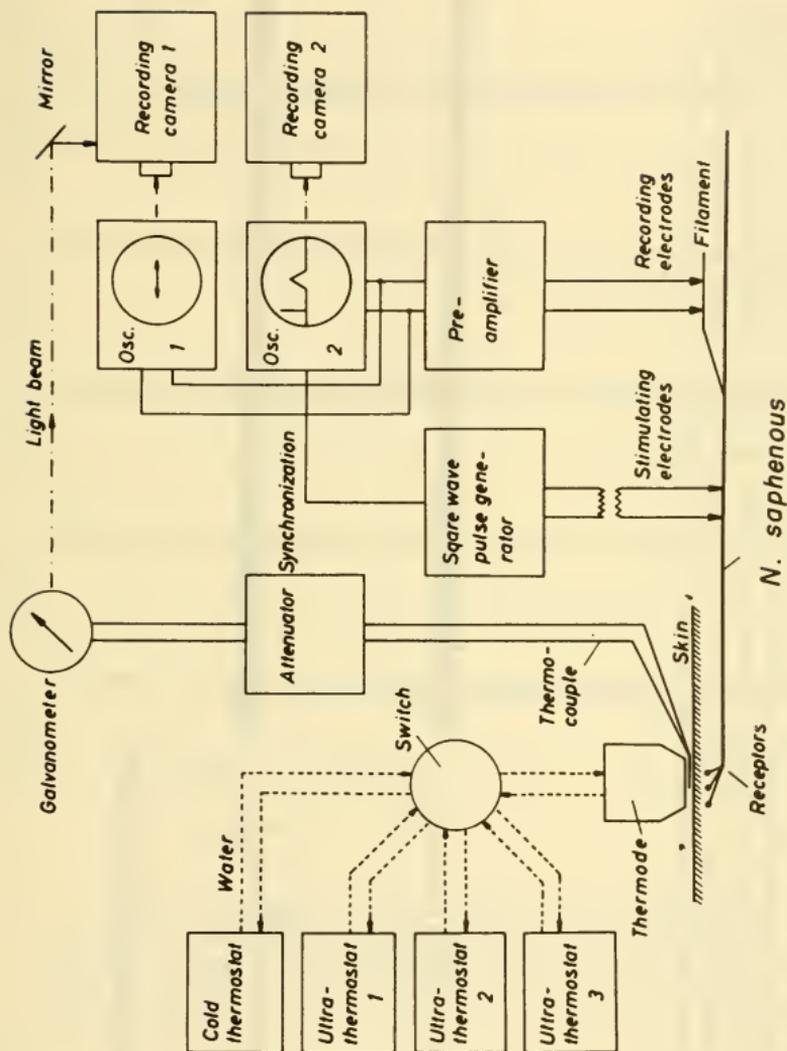


Figure 3. Method for recording single C fiber potentials during thermal stimulation and identification of the fiber by measuring its conduction velocity. (See text for further explanation.)

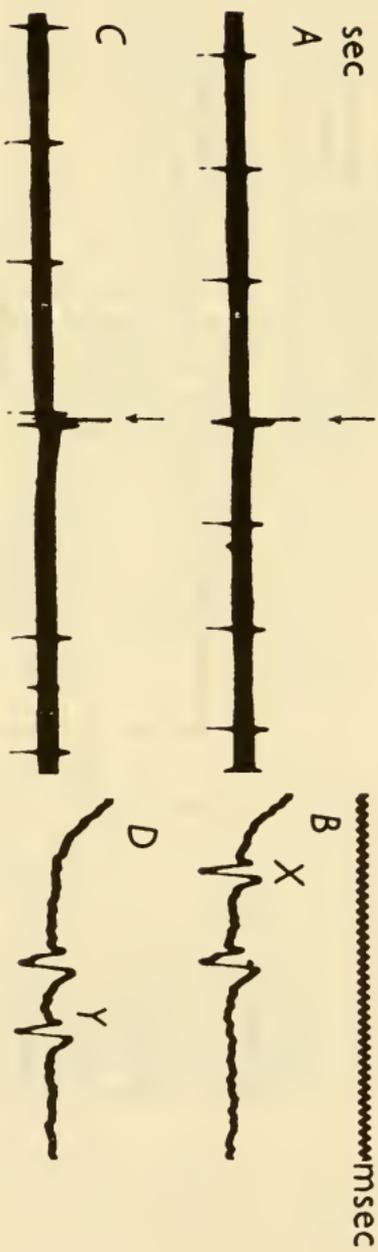


Figure 4. The identification of the active cold fiber in a multi-fiber strand of the saphenous nerve of the cat. A. Spontaneous discharge of a single C cold fiber and effects of electrical stimulation of the saphenous nerve (fiber No. 1). Arrows mark stimulus artifacts in A and C. B. Record with expanded sweep corresponding to that part of A marked by the arrow. The first impulse (marked X) is the spontaneous cold fiber discharge, the second is from another C fiber excited by electrical stimulation. C. The same discharge as in A, but with stronger electrical stimulation. There is now a gap in the series of impulses. D. Expanded sweep. Both impulses were caused by electrical stimulation. The first is identical with the second in the upper record, the second is in the cold fiber. The conduction velocity was 1.1 m/sec. (Hensel, Iggo, and Witt, 1960).

## THERMORECEPTOR PHYSIOLOGY

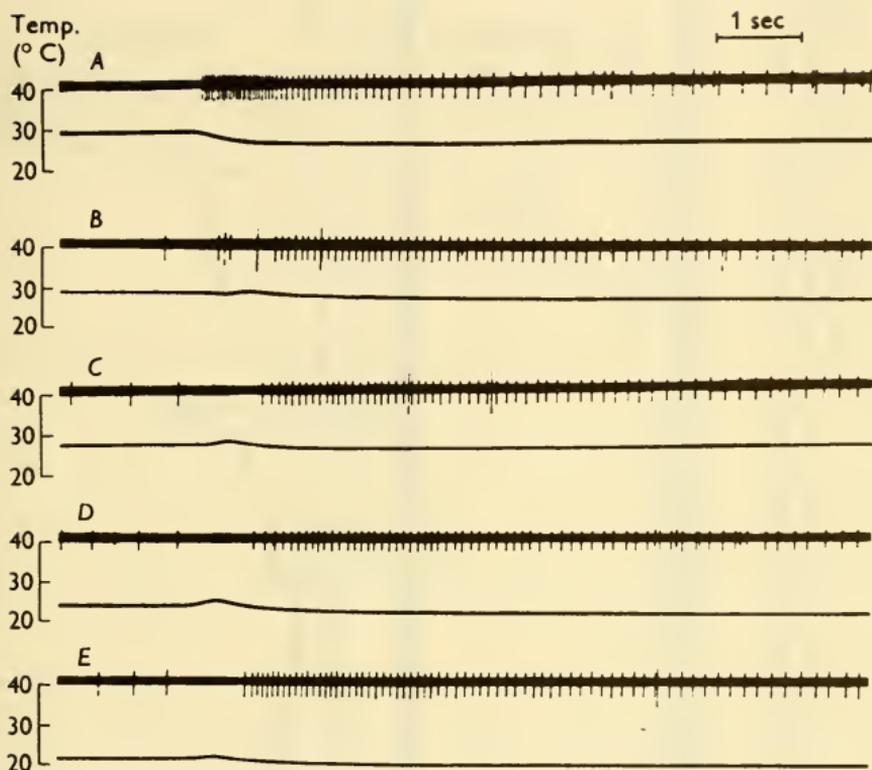


Figure 5. Afferent impulses of a single C fiber in the cat and skin temperature when cooling the skin (fiber No. 1). Conduction velocity 1.1 m/sec. A, Cooling from 29° C to 25.5° C; B, 29.3° C to 28° C; C, 28° C to 26.5° C; D, 24.5° C to 22.5° C. (Hensel, Iggo, and Witt, 1960).

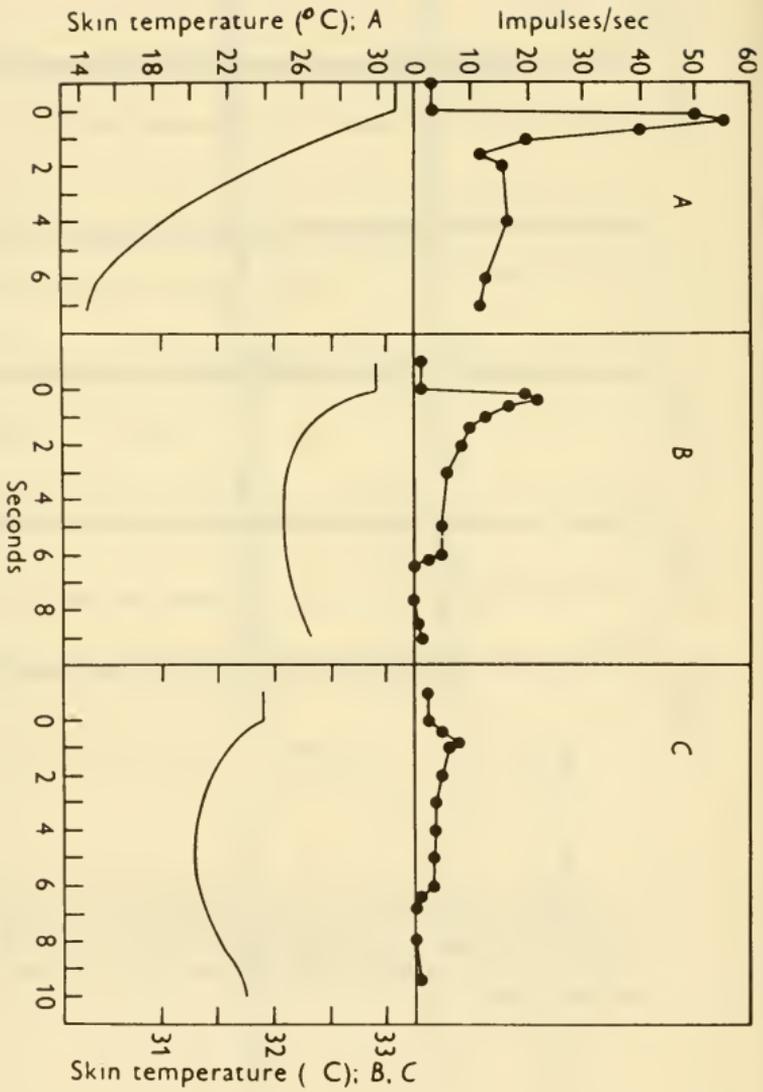


Figure 6. Impulse frequency of a single cold fiber in the cat when cooling and warming the skin (fiber No. 3). The conduction velocity of the fiber was 1.5 m/sec. The lefthand temperature scale refers to A, and the righthand scale to B and C. (Hensel, Iggo, and Witt, 1960).

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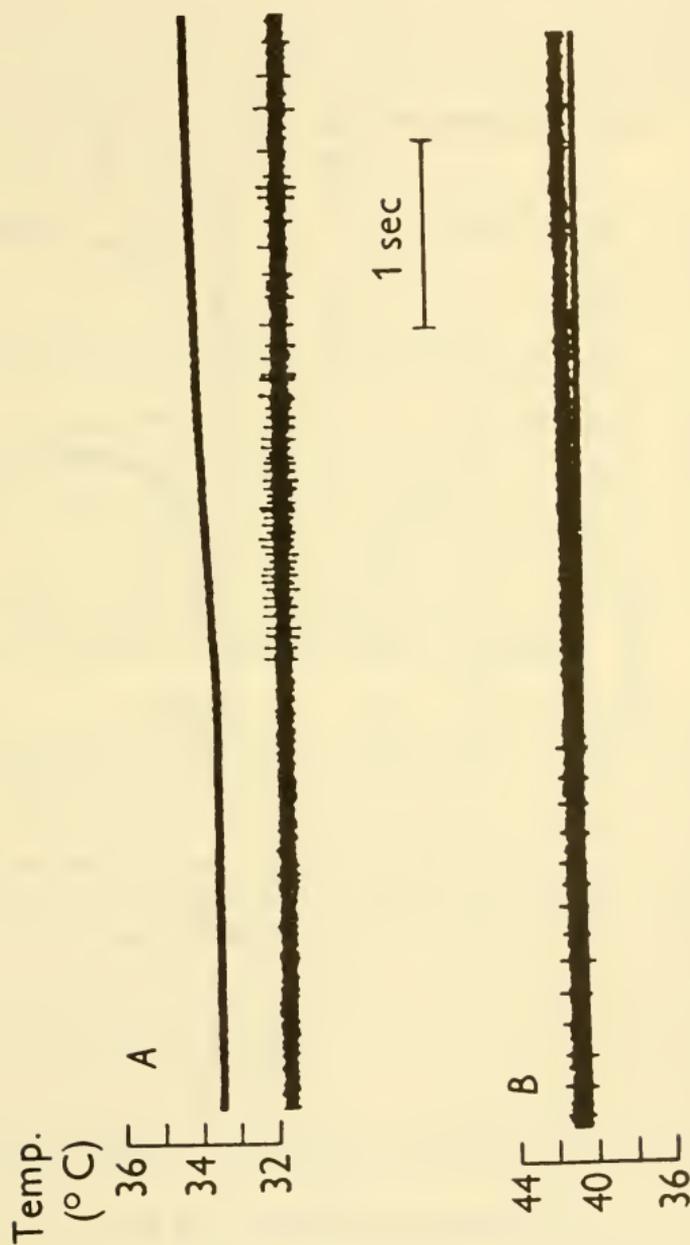


Figure 7. Afferent impulses recorded in a single warm fiber in the cat (fiber No. 7), from a warm receptor, during slight warming and cooling of the skin. (Hensel et al., 1960).

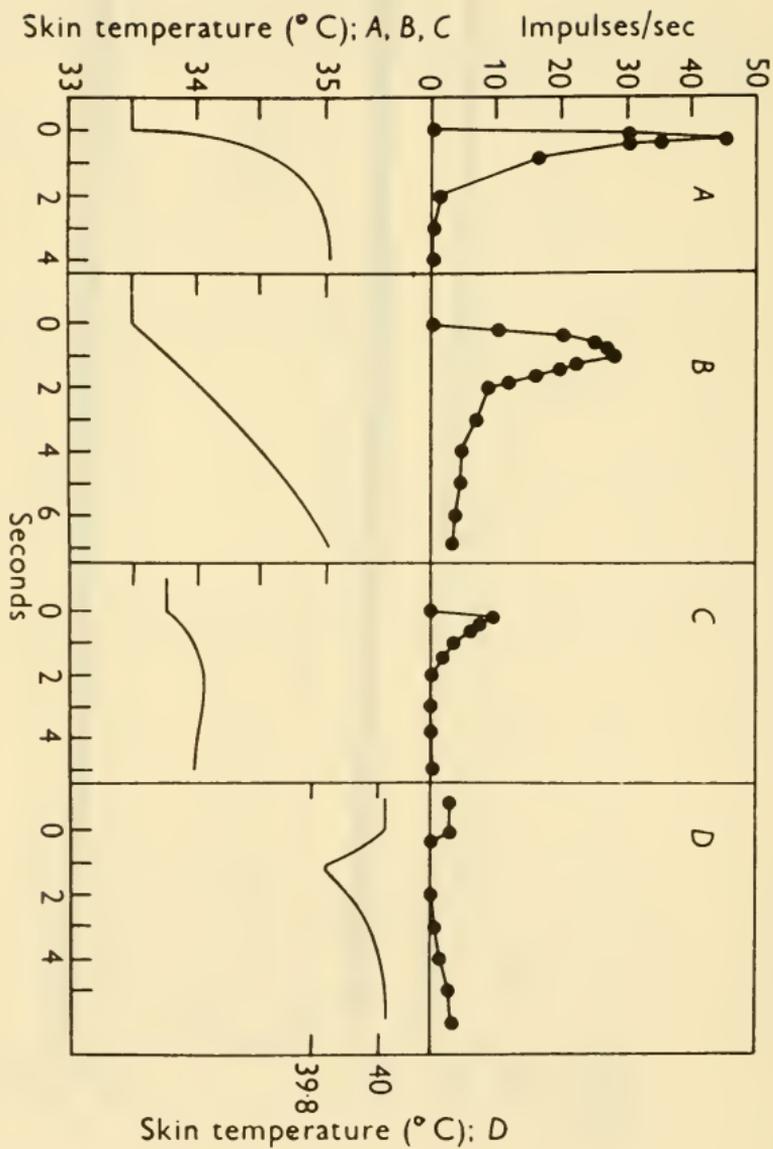


Figure 8. Frequency of the discharge of impulses in a single C fiber in the cat (fiber No. 7), from a warm receptor, during cutaneous temperature changes. The left hand temperature scale applies to A, B, and C, and the right hand scale to D. (Hensel, Iggo, and Witt, 1960).

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On cooling, there is a transient inhibition of the steady discharge, and on rewarming the discharge comes again.

As far as we know, all specific thermoreceptors in the cat's external skin are connected with C fibers. This is quite surprising because, according to the classic concept, the C fibers were supposed to be connected with pain. Later it was found that they were sensitive to mechanical stimulation. Now we know that the C fibers respond also to cooling and warming.

At constant temperatures the non-myelinated cold and warm fibers of the skin show a steady discharge, the frequency of which is dependent on the absolute temperature of the skin. Figure 9 shows an example for three different thermosensitive C fibers. The maximum of the warm fiber is above  $40^{\circ}$  C, whereas the cold fibers have maxima at lower temperatures. It is difficult to define from the steady discharge alone whether a receptor is a cold or a warm because the frequency curve has a positive and a negative temperature coefficient. But if we consider the discharge during temperature changes, a cold receptor will react in the whole temperature range, with an increase in frequency during cooling and a decrease during warming. The opposite is true for a warm receptor.

I think it is quite important to get some information not only about the impulse pattern in the cat, in the dog, or in other animals, but also in human subjects, because it is very difficult to draw any conclusion from animal experiments as to the behavior of human cutaneous receptors. First, the whole pattern of receptors might be quite different in human skin as compared with the cat's skin. The cat has a fur coat and probably a different distribution of receptors. Second, the cat would hardly tell you about its sensations. This problem becomes especially difficult in the case of non-specific receptors responding to cooling as well as to mechanical stimulation. Therefore, we have tried recently to record afferent impulses from human cutaneous nerve fibers. This work has been done in coordination with Dr. Boman during the last summer in our laboratory.

Figure 10 shows the first record from a single specific cold fiber in the human hand. The impulses were recorded from fibers running in the superficial branch of the radial nerve. The general behavior of this receptor is very similar to that of the cold receptors

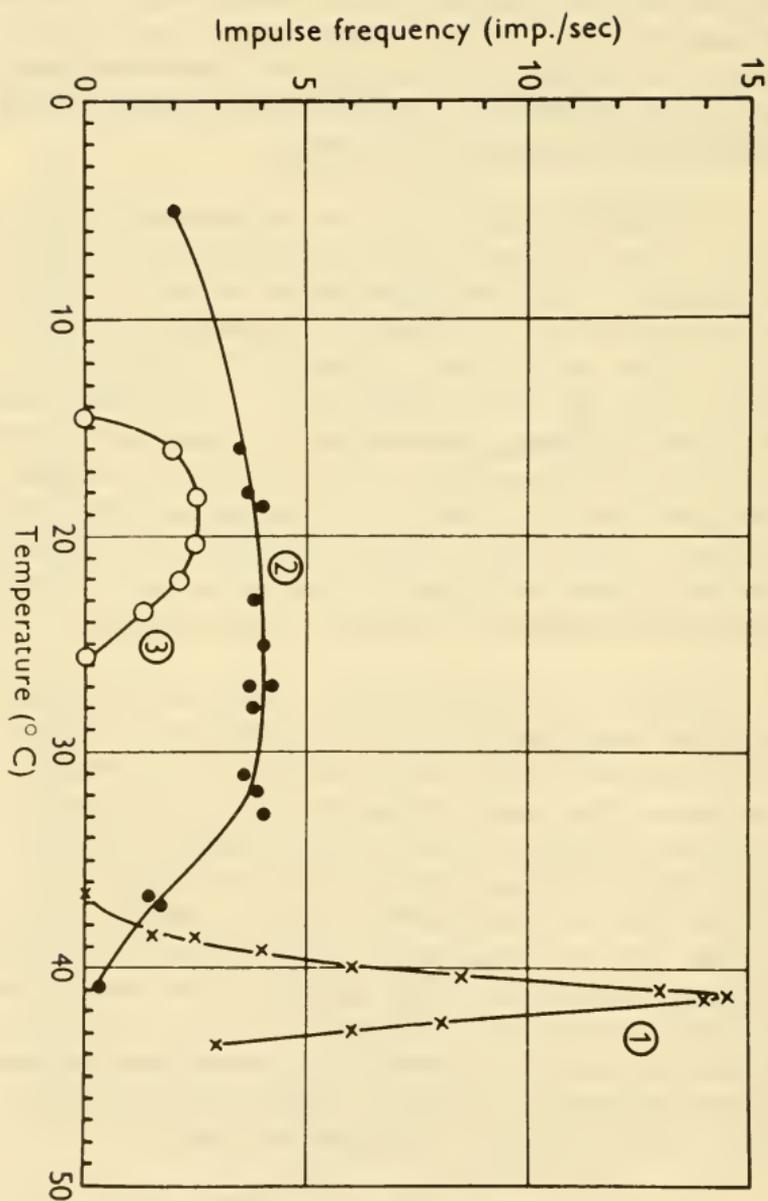


Figure 9. Steady discharge frequency of three different single C fibers in the cat as a function of constant skin temperature. 1, fiber excited by warming, fiber No. 8; 2, fiber excited by cooling, fiber No. 1; 3, fiber excited by cooling, fiber No. 3. (Hensel, Iggo, and Witt, 1960).

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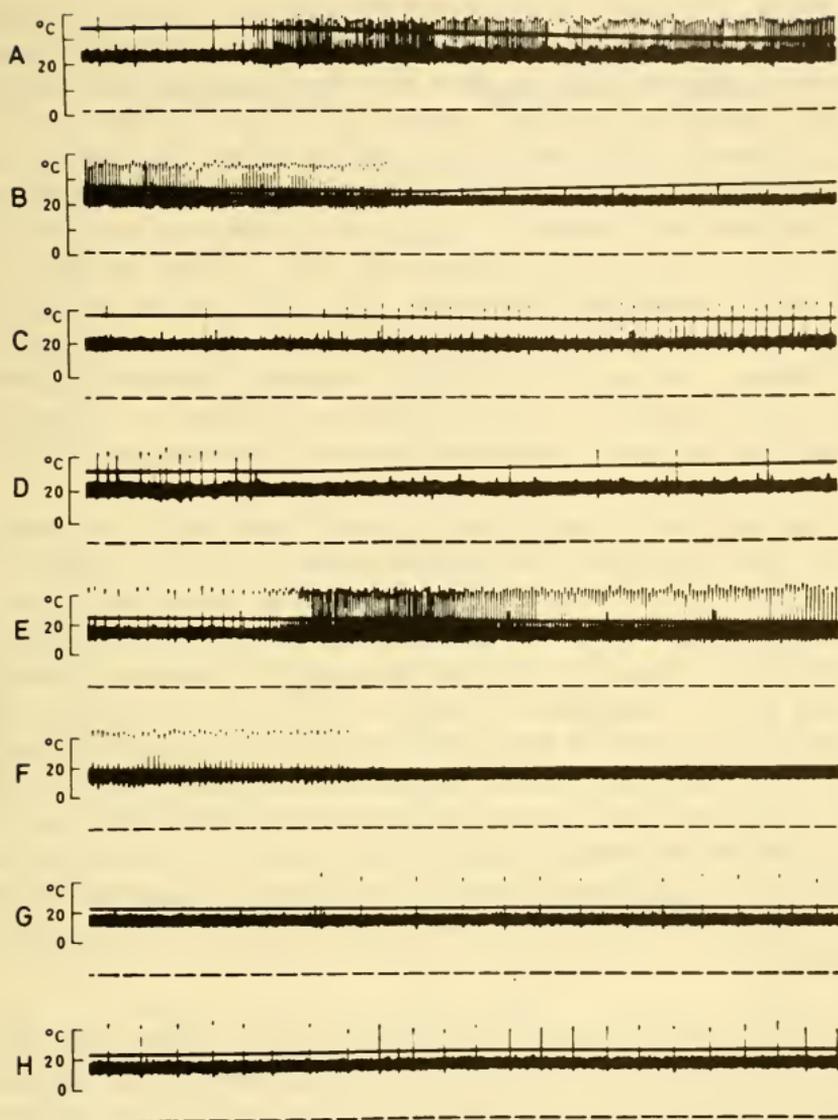


Figure 10. Afferent impulses in single "cold" fiber in a human subject (No. 18a) and temperature during cutaneous thermal stimulation. A, start of cooling from 34° C to 26° C. B, start of rewarming. C, start of cooling from 38° C to 35° C. D, start of rewarming. E, start of cooling from 24° C to 16° C. F, start of rewarming. G, 13 sec after rewarming has started. H, continued from record G. (Hensel and Boman, 1960).

in the cat. At constant skin temperature, we see a constant discharge of a certain frequency--on cooling, an increase in frequency, and on rewarming, an inhibition. The discharge frequency as a function of time during cooling and rewarming is shown in Figure 11. We were not able to study the steady discharge of this receptor at very low temperatures, but I think that the maximum is to be expected at a temperature of about  $15^{\circ}\text{C}$  (Fig. 12). During this work we also found some non-specific fibers which were excited by cooling as well as by mechanical stimulation (Fig. 13). A slight pressure of 13 grams causes a great increase in frequency and a partial adaptation. During cooling, the discharge frequency increases, whereas rewarming causes a transient inhibition. Mechanical stimulation causes a much higher increase in frequency than does rapid cooling.

The table shows some figures found in four single non-specific fibers from human skin. The maximum discharge during light pressure goes up to 125 impulses/sec, but on rapid cooling only a maximum frequency of 17 impulses/sec is reached. Now, what is the sensation connected with these non-specific cutaneous fibers? I believe it is a mechanical sensation. This can be concluded from an observation made by Ernst Heinrich Weber some hundred years ago, that weights put on the skin feel heavier when cold. This is a well established phenomenon and proved by several investigators. Any opposite experience, namely, that pressure will elicit a cold sensation, is not known. Thus the conclusion is justified that the functional significance of the non-specific receptors is a mechanical sensation.

As yet, we have not found any A warm fiber in human skin. Even when recording from multi-fiber nerve preparations, the total discharge frequency always increased during cooling and decreased during rewarming (Fig. 14). Of course, it is possible that specific warm impulses are travelling in the C fiber group. I think it is very probable, but as yet we were not able to record from single C fibers in human subjects.

The movie I am going to show now was made in connection with a television broadcast from our institute. The television company was kind enough to give us the whole film, from which we have cut a short film. It is concerned mostly with the method of recording afferent impulses from cutaneous nerve fibers in conscious human

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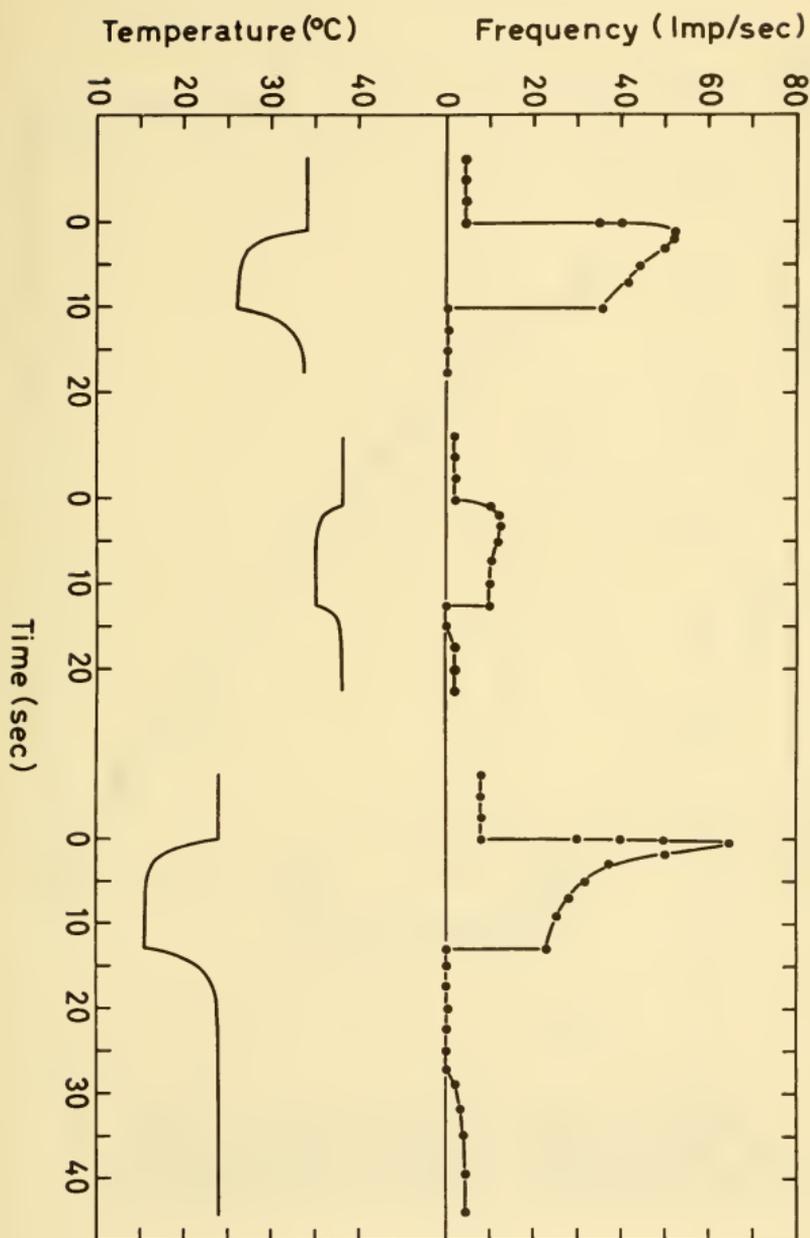


Figure 11. Impulse frequency of a single "cold" fiber in a human subject (No. 18a) during cutaneous temperature changes. (Hensel and Boman, 1960).

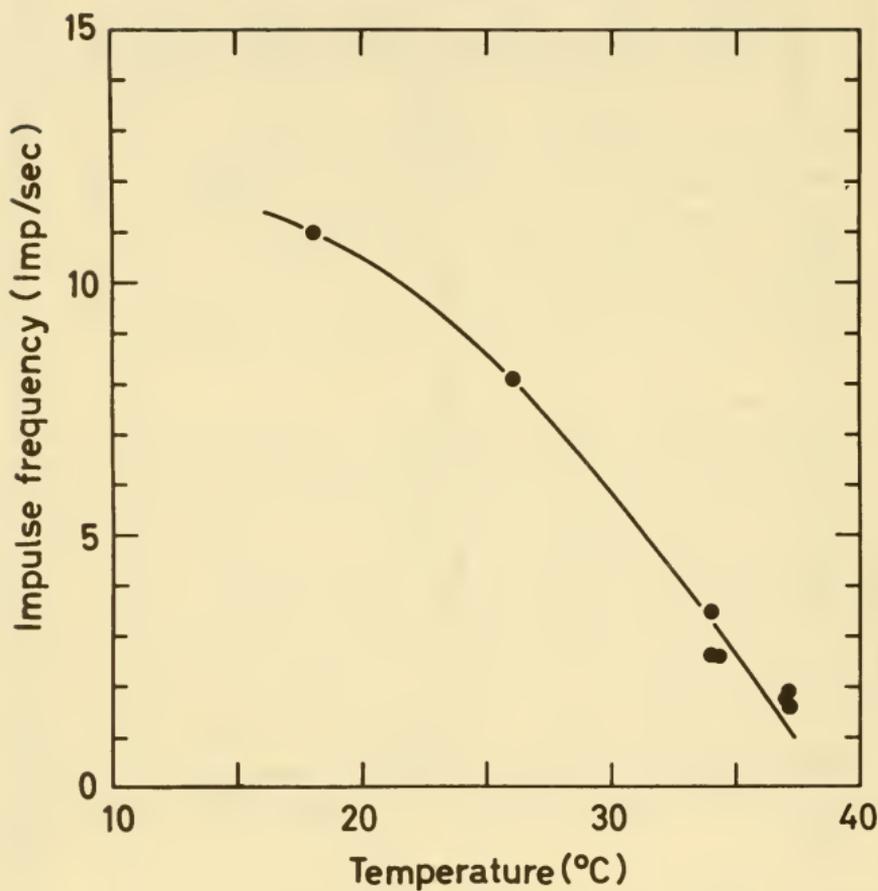


Figure 12. Frequency of steady discharge in a single "cold" fiber in a human subject (No. 18a) plotted against constant skin temperature. (Hensel and Boman, 1960).

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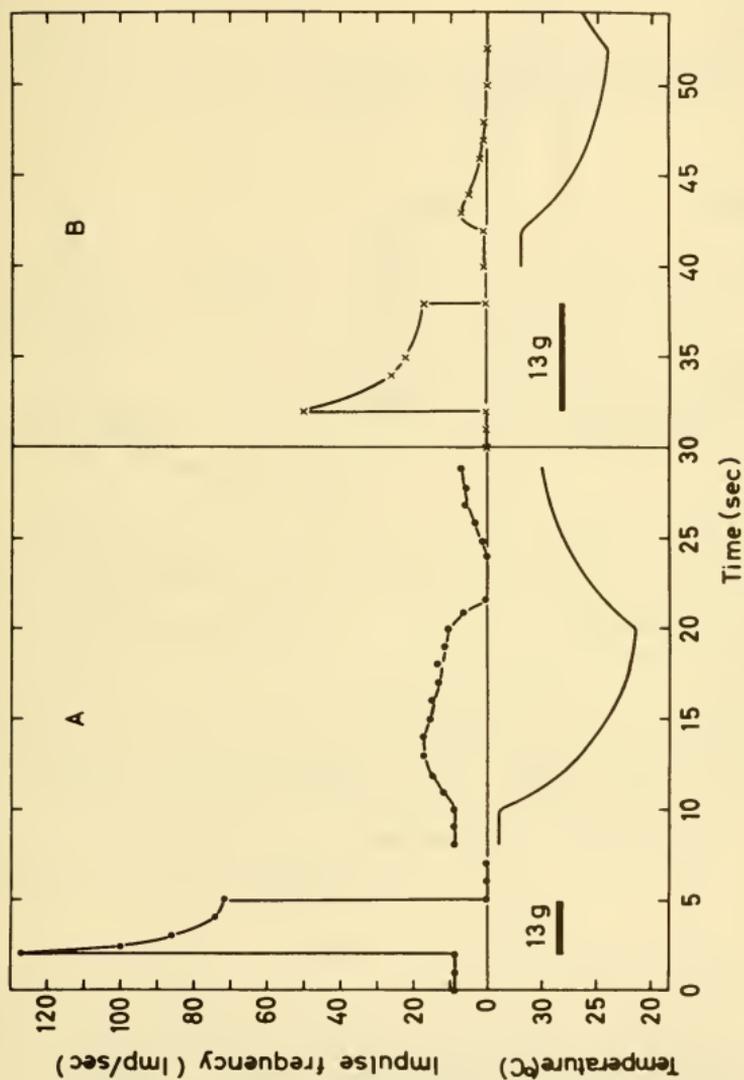


Figure 13. Impulse frequencies of two different single fibers in a human subject during cutaneous mechanical and thermal stimulation. A, fiber No. 12a, B, fiber No. 10. (Hensel and Boman, 1960).

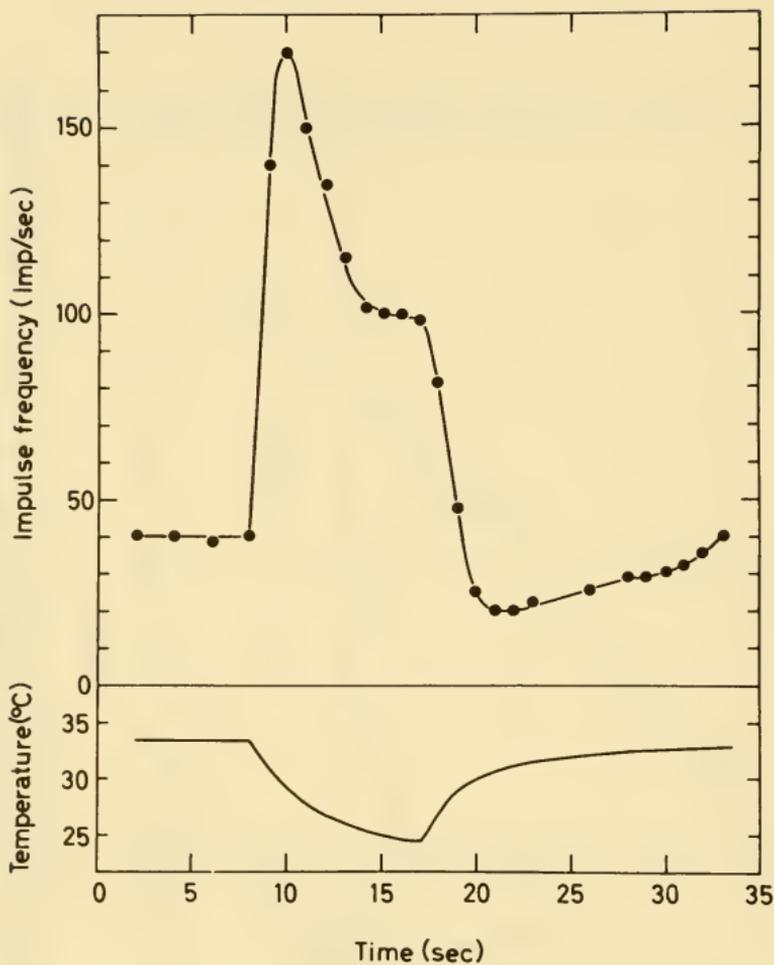


Figure 14. Total frequency of discharge in multi-fiber preparation in human subject containing at least six fibers (No. 12c) during cutaneous temperature changes. (Hensel and Boman, 1960).

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subjects. We are greatly indebted to our medical students for their cooperation as subjects in these experiments.

### MOVIE: CUTANEOUS AFFERENT NERVES IN HUMAN SUBJECTS

We use the superficial branch of the radial nerve which can be found easily by palpation. The course of the nerve is marked on the skin. Exposure of the nerve is made under a very short general anaesthesia lasting for about five minutes. The experiment proper is performed in the non-anesthetized subject. If the preparation is made carefully, the subject will feel quite comfortable.

The nerve preparation is made under a stereo-microscope. The superficial branch of the radial nerve is quite a thick nerve, about four or five millimeters in diameter, but we use only a very small part of the nerve, about one tenth. The nerve consists of several bundles connected with loose connective tissue. Before separating a bundle, the intact nerve is tested by means of weak electrical shocks in order to find the part with the most suitable receptive field. Then this bundle, which is about 0.5 mm in diameter, is separated from the remaining part of the nerve and cut proximally. At this moment, the subject feels a burning sensation in the receptive field which disappears after a few seconds.

The electrode is fixed in a micromanipulator and adjusted to the nerve strand. The nerve is put on a black plate for the final dissection into thin filaments. These filaments, of course, do not always contain single fibers in an anatomical sense, but they are thin enough to get mostly a single fiber discharge. The afferent impulses are recorded by a cathode ray oscillograph, whereas galvanometers are used for recording the skin temperatures. Heating and cooling the skin is brought about by water-circulated thermodes which rest on the skin in the same position for the whole time. Four thermostats set at various temperatures are connected alternatively with the thermode by means of a switch.

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Figure 15. Experimental arrangement for recording afferent impulses in cutaneous nerves in human subjects (before sterile covering).

1. Arm of the subject.
2. Metal holder for the arm.
3. Hand support for nerve preparation.
4. Adjusting screw for hand support.
5. Metal plate.
6. Skin marked for incision.
7. Lamp attached to microscope.
8. Stereo-microscope.
9. Support for stereo-microscope.
10. Magnification selector.
11. Black plate for nerve dissection.
12. Holder for electrode.
13. Electrode.
14. Micro-manipulator.
15. Shielding cage.
16. Leads from electrode to pre-amplifier.
17. Oscilloscope for observation.
18. Thermode.
19. Water inflow.
20. Water outflow.
21. Leads from thermocouple to galvanometer.
22. Small thermode for testing the receptive field.



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SUMMARY

In the external skin of the cat, no specific cold or warm fibers seem to exist within the group of myelinated A fibers but only non-specific receptors excited by pressure and cooling. However, numerous specific cold and warm receptors have been found with non-myelinated C fibers, the conduction velocity of which was between 0.5 and 1.5 m/sec. The quantitative sensitivity of these receptors corresponded well with the threshold for subjective temperature sensations in man.

In human subjects, only one specific cold fiber has been found as yet in the A group, whereas several A fibers responded to pressure as well as to cooling. The latter probably cause a mechanical sensation.

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### DISCUSSION

DR. FREEMAN: I am enormously impressed with your recording from the C fibers. This is a remarkable accomplishment. I notice that the wave form was initially upwards, then downwards again. What is its polarity?

DR. HENSEL: I do not know exactly how it was in this experiment. It is not always the case that you have waves in both directions.

DR. FREEMAN: Your technique for measuring time intervals will show your latency was at least as long as known latency. Is that correct?

DR. HENSEL: We are measuring the time between the onset of the stimulus and the onset of the impulses at a certain distance from the stimulated point.

DR. FREEMAN: Do you measure the degree of onset that accurately?

DR. HENSEL: No, the conduction velocity has been measured by applying well defined rectangular electric shocks. The distance between stimulating and recording point of the nerve was about 4 cm.

DR. FREEMAN: How do you figure the onset of your cold stimulus?

DR. HENSEL: This was measured by a thermocouple below the thermode.

DR. FREEMAN: But if your latency is a matter of milliseconds, what part of the onset of the cold do you take as your starting point for the stimulus threshold?

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DR. HENSEL: We did not measure conduction velocities of cold fibers using cold stimulation but only by electrical stimuli. We can be absolutely sure that the impulse set up by the electrical stimulus is identical with that caused by cold in the respective single fiber. The fiber can be identified by the characteristic shape of the impulse and by the collision technique shown in Figure 4.

DR. FREEMAN: How does the latency compare with A fibers in this technique?

DR. HENSEL: You mean the latency between the stimulus and the onset of the impulses?

DR. FREEMAN: No, using this technique for measuring the conduction velocity and the duration of the impulse and its height. How do your figures for these C fibers compare with your observations of A fibers under the same circumstances?

DR. HENSEL: Well, I would say that the latency of the A fibers is about 1/30 to 1/50 of that of the C fibers.

DR. STUART: Are the frequency spectra for pressure and temperature change in a single C fiber always different?

DR. HENSEL: I am not sure about that. Recently we found a non-specific fiber which was quite as sensitive to cooling as the specific cold fibers.

DR. CLARK: I think in one of your figures you said something about on and off potentials. Is that "off" due to the thermode change, or was it a real on and off effect?

DR. HENSEL: I think it is a real on and off effect. The overshoot in frequency during the onset of cooling is the mirror image of the false start during onset of rewarming. In some records, the whole course of the false start is not seen, as the impulse frequency cannot drop below zero.

DR. CLARK: That is on all your records except one?

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DR. HENSEL: Yes, that is right, but the general shape of the curve is the same in all experiments. This can be proved by applying standard cold stimuli during the transient stop of the discharge after rewarming. The longer the period of time after the cessation of the discharge, the more effective the cold stimulus. When plotting the effect of the standard cold stimulus against time, the resultant curve is the mirror image of the overshoot during cooling. But, of course, the impulse frequency cannot be less than zero.

DR. MINARD: Is there a rate of temperature change so slow that you do not observe the phasic discharge?

DR. HENSEL: Yes. I think it is not even necessary to make the change very slow because this partial adaptation occurs rather rapidly. A slow linear change of temperature with time through the whole temperature range will give very much the same frequency diagram as that for the steady discharge shown in Figures 9 and 13.

DR. MINARD: There have been some reports that individuals who have been exposed to gradual increase in cold, such as when they have been lying outside in a sleeping bag, have died, apparently without even waking up during the course of this cooling process; and the assumption was that the rate of change was so slow that this was not perceived as a cold stimulus.

DR. HENSEL: I think this concept contains some truth because the maximum frequency obtainable by rapid cooling is 15 times higher than that obtained during slow cooling or at constant temperature.

COL. QUASHNOCK: Dr. Hensel, would the subject report any residual changes in sensation either transient or permanent after recovery?

DR. HENSEL: Well, most of the subjects reported a decrease in sensitivity in an area about 2 cm in diameter. It was no complete anaesthesia but paraesthesia or hypaesthesia. In one subject there was no change at all because of the overlapping.

COL. QUASHNOCK: How many subjects have been done?

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DR. HENSEL: Eight as yet.

COL. QUASHNOCK: Did you suture the nerves after cutting them?

DR. HENSEL: No, because it was only a thin bundle 0.5 mm in diameter. We only cut this small part of the nerve, whereas the whole remaining part was undamaged.

DR. LIM: And you did not observe any warm receptors in all these subjects?

DR. HENSEL: No, we always saw an increase in frequency during cooling and a decrease during warming. But we have not studied the C fibers as yet. I am quite sure that warm receptors could be found in the C group.

DR. HEMINGWAY: Have you any idea what end organs are involved?

DR. HENSEL: I can say only that there are some areas in human skin which contain only so-called free nerve endings. From these areas, any kind of sensation can be elicited. This holds true also for the tip of the tongue in the cat. A thorough histological study of this area has been made by Dr. Kantner in Heidelberg (1957). He found only a network of free nerve endings in the tip of the tongue--except the taste buds, of course. As you can see in Figure 1, there are quite specific pressure and cold impulses, in spite of the absence of any encapsulated specialized nerve endings such as Krause's and Meissner's end organs.

DR. IRVING: I notice, sir, that the records from many of your cold stimulations cease at certain cold temperatures. Am I correct about this?

DR. HENSEL: Well, the lowest temperature for maximum firing that we have found so far in C fibers was about  $16^{\circ}$  C. Some C fibers were still firing at a temperature of  $5^{\circ}$  C, but at a very low rate.

DR. FREEMAN: How much vibration in the thermode do you get as a result of passage of water through it?

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DR. HENSEL: Oh, the vibration was quite small, but a few very sensitive mechanoreceptors could sometimes be excited by the vibration.

DR. LIM: During cooling, you have a curve coming down, but it never reached the zero line. At the end of the cooling period, what were the impulses per second?

DR. HENSEL: The maximum frequency of a cold fiber at constant temperature is about 10 impulses/sec.

DR. LIM: I noticed that your time scale is about a minute or so. If you prolong it for ten minutes, what is the effect?

DR. HENSEL: I would say that the final value is reached after about one minute. Thereafter the impulse frequency will remain constant as long as we are able to record from a single fiber, at least for several hours.

DR. LIM: But still above zero?

DR. HENSEL: Yes, for the whole time.

DR. FREEMAN: What was the relation between accommodation and sensitivity or the sensations of the subjects with regard to intensity?

DR. HENSEL: Generally, the impulse discharge is more sensitive than the conscious sensation. For example, a skin temperature of  $34^{\circ}\text{C}$  is absolutely indifferent for the subject, but there is a considerable discharge of the cold fibers.

DR. FREEMAN: Does the peak of sensitivity coincide with the peak of discharge?

DR. HENSEL: Yes, roughly. It is difficult to measure this very accurately in a subjective way.

DR. FREEMAN: Do you ever get a paradoxical sensitivity of warmth associated with this accommodation process?

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DR. HENSEL: No, we observed only a decrease of the cold sensation.

MR. ADAMS: What was the maximum impulse frequency?

DR. HENSEL: 150 impulses/sec in the cold fibers.

MR. ADAMS: Was this with cooling to  $13^{\circ}\text{C}$ ?

DR. HENSEL: We did not record the 150 impulses/sec in the human cold fiber I have shown. I think it was about 100 impulses/sec, but when cooling the most sensitive cold receptors from  $34^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ , the frequency will rise to about 150 impulses/sec. It depends on the rate of cooling. The higher the cooling rate, the higher the maximum frequency.

MR. EAGAN: There is an inference here that one would not feel cold if the receptors stayed below  $5^{\circ}\text{C}$ .

DR. HENSEL: Yes, I think so. The cold sensation will disappear at very low skin temperatures.

DR. RODDIE: Do you use any painful stimuli?

DR. HENSEL: Not yet, but this is part of our next program. We only used temperatures from  $15^{\circ}\text{C}$  to  $43^{\circ}\text{C}$ .

DR. HANNON: Could this decrease pain as the temperature goes below  $20^{\circ}\text{C}$ ? I believe you say there is a decrease in sensation.

DR. HENSEL: Yes.

DR. HANNON: How do you determine whether this is an accommodation or just a simple temperature effect?

DR. HENSEL: Well, accommodation means that a time factor is involved. If the temperature is lowered to  $5^{\circ}\text{C}$  and raised again, the discharge will reappear and after some time reach the initial level.

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DR. HANNON: Would you care to speculate how much of this is an Arrhenius effect, the temperature just slowing up the reaction?

DR. HENSEL: This is very difficult to say because the whole curve does not look like an Arrhenius diagram. I think this curve might perhaps be due to the difference between two processes, each of which follows the Arrhenius law.

DR. HANNON: Many rate reactions will show this phenomenon if the temperature range is wide enough. They usually describe these by two mathematical rate-processes.

DR. HENSEL: This is just a formal description. We do not know anything about the processes involved in the thermoreceptors. It would be very interesting to know more about the mechanisms for transforming the temperature into the impulse discharge of the receptor.

COL. QUASHNOCK: Is it possible to take the proximal portion of the nerve and stimulate it at the various frequencies to determine the threshold for sensation?

DR. HENSEL: We have not tried this, but it could be done very easily. We use electrical stimulation of the nerve before cutting it. The subject reports the site of the sensation.

DR. HEMINGWAY: You stated that slow cooling is not nearly as effective as fast cooling, and this brings up the point raised by Capt. Minard. During World War II we had some subjects who were cooled slowly, at the same time being very heavily clothed; I think they had clothing that built up to four clos. In these subjects we observed that rectal temperature would drop two or three degrees without the appearance of shivering.

DR. HENSEL: Yes, the same as observed in the measurement of  $\text{CO}_2$ . The rectal temperature will drop without any considerable sensation of cold. It might be a matter of the slow rate of cooling. The rate of cooling is much more important than the absolute temperature.

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DR. KAWAMURA: Does each single cold or warm fiber have its own temperature range?

DR. HENSEL: Yes, each fiber has its range of temperatures, but if you take the whole output of the nerve, then the maximum will be at a temperature of about 15° C. The whole output of the nerve is integrated as a whole spectrum of nerve fiber discharges. If you count the impulse traffic in a rather thick nerve preparation -- it cannot be done very accurately--it will have a maximum at about 15° C. And this corresponds quite well to the subjective cold sensation under constant skin temperature.

DR. STUART: What is the response to mechanical stimulus of the C fiber at the thirty-five impulse per second response?

DR. HENSEL: Excuse me, this was no C fiber. This was an A fiber, a non-specific A fiber.

DR. STUART: What was the discharge frequency during mechanical stimulation?

DR. HENSEL: It was higher than 35. I think 120 or 130. With strong pressure you will get even higher frequencies, up to 300 impulses/sec. I would like to emphasize that the temperature sensitivity of the non-specific fibers might be in the same range as that of the specific ones, but still the response to mechanical stimulation is much higher.

DR. STUART: This might suggest the central nervous system decodes diverse modalities by these diverse frequencies, even along the same fiber.

DR. HENSEL: Let us assume a non-specific fiber firing at 35 impulses/sec. How can you discriminate between light pressure or strong cooling, both of which cause the same impulse frequency? I think the sensation mediated by this fiber is a specific mechanical sensation. There are also some experiences in daily life; for example, when a very cold wind is blowing into your face. You feel not only cold but you also have a strange sensation of pressure. This might be due to the discharge of such non-specific fibers.

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DR. FREEMAN: In the light of your experience, would you have any suggestions as to how best to get into a cold swimming pool?

DR. HENSEL: You mean just jump in? It depends on what you like. If you come from a hot room, it is very pleasant to jump into the cold water. If the same cold jump starts from a very high temperature level, we get a lower discharge frequency than when starting from, say, 34<sup>o</sup> C.

DR. MINARD: I was wondering to what extent the static discharge is related to the spatial temperature gradient in the skin.

DR. HENSEL: This concept has been completely disproved. We are sure now that the spatial gradient does not play any role in the excitation of thermal receptors. We can cool the receptor layer from above or from below. There is no difference in the discharge. I think it is well established that the discharge is only dependent on temperature itself, not on the spatial pattern of temperature.

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REFERENCES

1. Hensel, H. Physiologie der Thermoreception. *Erg. Physiol.* 47: 166-368, 1952.
2. Hensel, H. and K. K. A. Boman. Afferent impulses in cutaneous sensory nerves in human subjects. *J. Neurophysiol.* 23:564-578, 1960.
3. Hensel, H., A. Iggo, and I. Witt. A quantitative study of sensitive cutaneous thermoreceptors with C afferent fibres. *J. Physiol.* 153:113-126, 1960.
4. Kantner, M. Die Sensibilität der Katzenszunge. *Acta. Neuroveg.* 15:223-234, 1957.
5. Witt, I. and H. Hensel. Afferent Impulse aus der Extremitätenhaut der Katze bei thermischer und mechanischer Reizung. *Pflügers Arch. ges. Physiol.* 268:582-596, 1959.

## THERMORECEPTOR PHYSIOLOGY

DR. HANNON: If there are no further questions, we can go on with Dr. Hensel, I believe; he has something possibly related to this.

DR. HENSEL: I appreciate very much this opportunity to discuss some data on metabolism of the non-anesthetized cat during hypothalamic cooling.

Figure 1 shows a device for the cooling. In most cases, two cooling units were implanted symmetrically into the anterior hypothalamus. The thermodes have an outer diameter of one millimeter. The right part or the left part of the anterior hypothalamus can be cooled separately, or both parts at the same time. The brain temperature at a certain distance apart from the thermode is measured by means of a thermistor. The cooling water comes in centrally and leaves the thermode through a lateral tube.

I must say I disagree a little with Dr. Hemingway, because we found that the cats are quite cooperative and can be trained to quite a high degree (Fig. 2).

A heated thermocouple unit was used for recording the cutaneous blood flow in the ear. For measuring the metabolism, the cat is put into a double-walled perspex box which can be circulated with water and set at any desired temperature by means of a thermostat. The measurement of  $O_2$  consumption and  $CO_2$  output is made in an open system. The chamber is perfused with a stream of air of constant velocity and the air coming out of the chamber is continuously analyzed for  $CO_2$  and  $O_2$ .

We studied quantitatively the heat production under various external temperatures, and at the same time, under the standardized hypothalamic cooling. We found the correlation shown in Figure 3. The lowest temperature in the chamber was about  $5^{\circ}C$  or  $6^{\circ}C$ , the highest  $40^{\circ}C$ . The lower the external temperature, the higher the metabolic increase during the same standardized hypothalamic cooling by about  $2^{\circ}C$ . I think this is another example of the correlation as shown by Dr. Lim between the external stimulus and the hypothalamic cooling in the unanesthetized and unrestrained cat.

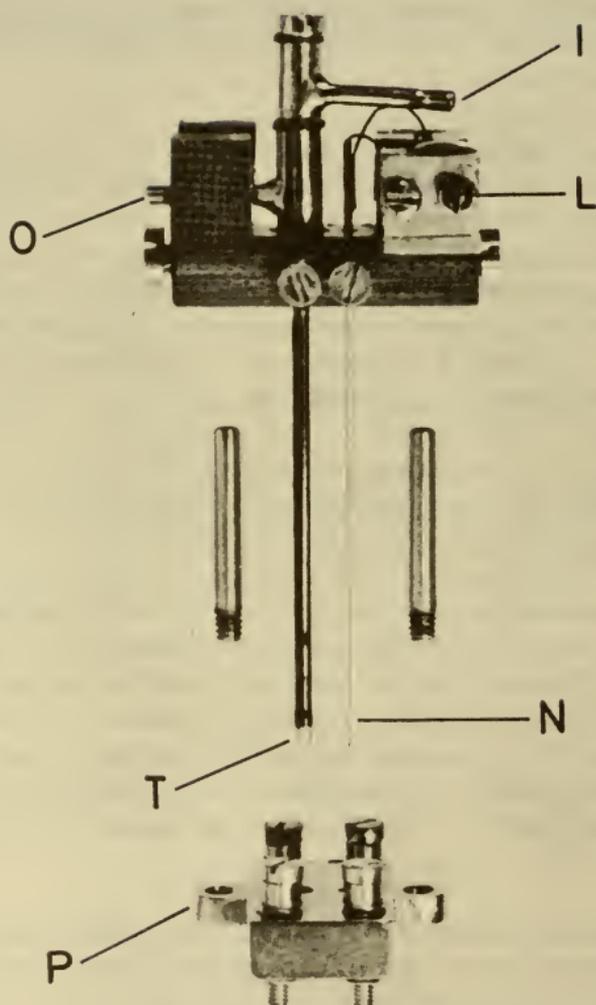


Figure 1. Device for cooling and heating the hypothalamus in the unanesthetized cat. T, thermode; I, inflow; O, outflow of water; P, metal plate with screws for the skull; N, needle with thermistor; L, leads to the thermistor.



Figure 2. Unanesthetized cat with cooling device for the hypothalamus; the polyethylene tubings for the water circulation and the leads to the thermistor can be seen. The heated thermocouple unit for measuring cutaneous blood flow is attached to the right ear.

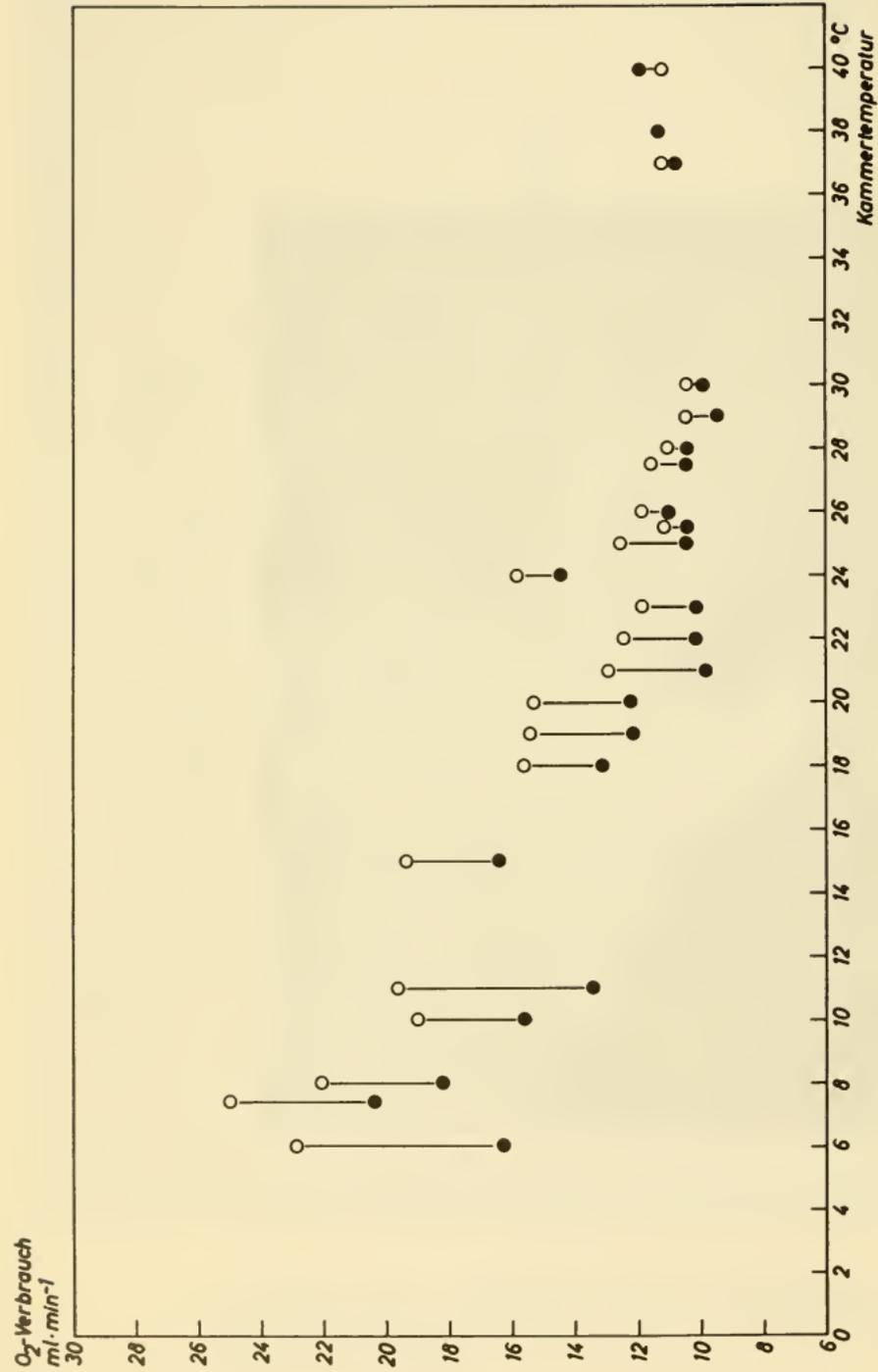


Figure 3. Metabolic rate of the unanesthetized cat as a function of external temperature and hypothalamic cooling. Filled circles, metabolic rate at various room temperatures. Open circles, metabolic rate when cooling the hypothalamus by about 2°C.

## THERMORECEPTOR PHYSIOLOGY

MR. ADAMS: Dr. Hensel, have you measured the temperature profile around the tip of the thermode?

DR. HENSEL: Yes, we did; the temperature is measured mostly at a distance of 1.5 millimeters apart from the thermode. It is quite a steep temperature gradient, and the end of the temperature field might be at a distance of about three or perhaps four millimeters, if you have a very slow cooling. But, normally, I would say about three millimeters around the thermode.

DR. HEMINGWAY: The increase in oxygen consumption rate was not very great, not nearly as much as you usually find in shivering. I think your maximum increase was about fifty percent.

DR. HENSEL: The cooling was actually not very deep, and we did not observe shivering in this experiment.

DR. HEMINGWAY: No shivering?

DR. HENSEL: No, I would not say it was shivering. Sometimes we observed some sort of behavioral regulation. The cats were curling up a little bit, but no strong shivering occurred in this experiment.

DR. HEMINGWAY: Would this increase be due to some motion, some voluntary activity on the part of the cat?

DR. HENSEL: Not in all cases.

DR. HEMINGWAY: If he is curling up and moving his muscles, it does not take much movement.

DR. HENSEL: No, some cats sat mostly quietly, and there was no visible external motion.

DR. HEMINGWAY: The cats were very kind to you then!

DR. HENSEL: Yes.

HENSEL, H.

DR. HEMINGWAY: It does not take much of a voluntary movement, just sitting up will increase the oxygen consumption rate twenty-five to fifty per cent, just a very slight movement and that is the difference. You were speaking about the difference between dogs and cats. A well-trained dog will lie quietly and will not leave the room.

DR. HENSEL: In many cases the cats were lying on the bottom of the chamber very quietly, just like a well-trained dog.

DR. STUART: These thermodes were implanted into the anterior hypothalamus. Have you ever implanted any into the posterior hypothalamus?

DR. HENSEL: Yes, we did, but we did not see any considerable effect. We saw it in the anterior hypothalamus, but I must say we did not make very many experiments as yet in the posterior hypothalamus. I would not draw a definite conclusion, but we failed in getting an effect as yet.

DR. LIM: In terms of oxygen consumption and differential cooling of the body, we found that there are two things we have to furnish. One is the onset of shivering; and in the onset of shivering, the peripheral mechanism is very important in the initiation of shivering, but in the maintenance of shivering, a central temperature is almost three times more important than the skin temperature in terms of oxygen consumption.

DR. HENSEL: Yes.

DR. CLARK: When you say "anterior hypothalamus", just how far anterior? Would it be over the optic chiasma?

DR. HENSEL: Yes, the position was above the optic chiasma. But you see, even if you have a very accurate position of the thermode, you have a temperature field around the thermode.

DR. CLARK: It would not get back to the tuberal region?

DR. HENSEL: No.

## THERMORECEPTOR PHYSIOLOGY

DR. FREEMAN: Dr. Hammel, when he places his thermode, merely has a plate which he attaches to the skull under anesthesia and allows the skin to grow over it.

DR. HENSEL: Yes.

DR. FREEMAN: Now, when he wants to do an experiment, he sterilizes the skin over this plate and forces the thermode down into the hypothalamus for the duration of the cooling and heating period, and when he is through with the animal for the day, he pulls it out and puts the animal away.

DR. HENSEL: Yes.

DR. FREEMAN: Now, he says that over a period of time there may be some damage to the hypothalamus.

DR. HENSEL: I would not agree with him. We had the thermode in the cat for half a year, and we have one cat in which we did the implantation five times, each time for half a year. It is now three years and the cat is quite as happy as in the beginning. So I do not think that there would be a serious damage.

DR. FREEMAN: You would leave yours in, though, for the full period of time? You do not take them out?

DR. HENSEL: No.

DR. FREEMAN: You leave it in once it is there?

DR. HENSEL: It remains for six months in the cat, and you can repeat this several times and go on without any disturbance.

DR. FREEMAN: One other technical question: how do you prevent over-heating with your device; that is, when you want to warm the animal, what level did you choose for your inflow temperature as an adequate stimulus?

DR. HENSEL: As yet, we studied only the cooling. We were just interested in this effect because the effects during heating are more

generally accepted than the effects during cooling, as you know.

DR. FREEMAN: You never over-cool?

DR. HENSEL: No.

DR. HEMINGWAY: You say you use a one-millimeter thermode and put that in the hypothalamus five times without damage?

DR. HENSEL: I would say, without any visible change in the cat's behavior.

DR. HEMINGWAY: Because the anterior hypothalamic region is not very many millimeters in extent.

DR. HENSEL: Of course, in other cats, we made a histological investigation of this region, but not in the cat where the implantation was made several times. This cat is still living.

DR. FREEMAN: That is humane, of course!

DR. HENSEL: But in the other cats where the implantation was made for only one time, there was very little damage and very little reaction.

DR. FREEMAN: How far laterally to the midline are these inserted?

DR. HENSEL: Three or four millimeters.

DR. FREEMAN: Any closer than that, we found that you either lacerate the choroid plexuses or you may obstruct the pyramidal row.

DR. STUART: Was this the same in the posterior hypothalamus, three or four millimeters from the midline?

DR. HENSEL: Yes, we tried various distances, but we did not see an effect as yet, nor with the vasomotor response.

## THERMORECEPTOR PHYSIOLOGY

DR. LIM: In this last slide you showed, is cooling the brain bilateral or unilateral?

DR. HENSEL: Bilateral. But we did not see a very considerable difference. It was a little bit more, but we got quite a high increase with unilateral cooling.



## CENTRAL AND PERIPHERAL MECHANISMS IN TEMPERATURE REGULATION

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One of the outstanding characteristics of the mammalian body is its chemical and physical control mechanisms by which a constancy of internal environment is maintained. The behaviors of hemodynamics, gas exchange, electrolyte balance, energy transfer, and hormonal interaction clearly indicate that their ultimate goals are in preserving an optimum intrinsic condition which allows harmonious and efficient performance of complex processes. The regulatory phenomena of body temperature are no exception from this general premise.

The understanding of temperature control has been greatly facilitated by the establishment of two cardinal neural mechanisms, namely, the major control elements located centrally in the hypothalamus which Dr. Hemingway described this morning, and the temperature sensing elements found peripherally in the skin, which Dr. Hensel described this afternoon. It is agreed that the central control mechanism may be subdivided into a motor unit which primarily governs heat dissipation and another which controls heat conservation. Furthermore, it is accepted that the peripheral thermoreceptors consist of two anatomical or electrophysiological units, that is, the receptors for cold and those for warmth, in the sense of functional anatomical units.

Although the existence of temperature-sensing elements in the hypothalamus has never been demonstrated, it may be assumed that such receptors exist in the vicinity of the motor units of heat dissipation and conservation. Therefore, an hypothesis is advanced allowing functional elements of temperature detection in the hypothalamus as they exist in the skin. Then, central control is believed to depend upon thermoreceptors located in the hypothalamus, so that the relevant "central temperature" is that of the hypothalamus

itself or of its perfusing blood. On the other hand, peripheral control is believed to depend upon efferent impulses arising in cutaneous thermoreceptors, so that the relevant "peripheral temperature" is that of the skin.

On the basis of this general premise, the relationships between the temperature control and detector mechanisms may be investigated, the principal aim of the study being to evaluate the relative roles of central and peripheral temperatures in the initiation of thermal panting in the warmth and shivering in the cold.

The roles of central and peripheral temperatures in the initiation of thermal panting or shivering have never been adequately defined. Some investigators stress the importance of central control, others of peripheral control, and some admit the possibility that perhaps both are involved. One fact which can be regarded as firmly established is that so called "pure central panting" can be produced by local heating of the hypothalamus in the anesthetized cat (Magoun et al., 1938). In addition, recent data indicate the existence of "pure central shivering" which can be produced by local cooling of the hypothalamus in the unanesthetized cat (Kundt, Bruck, and Hensel, 1957) and in unanesthetized dogs (Hammel and Hardy, 1959). Nevertheless, a great deal of uncertainty exists as to whether central and peripheral temperatures interact to initiate thermal panting or shivering. The reasons for such ambiguity are partly due to (1) the erroneous choice of rectal or colonic temperature as representing the central (brain) temperature, in particular, during transient states of induced hypothermia or hyperthermia, (2) the inherent difficulty of dissociating central and peripheral temperatures in the intact animal, and (3) the poorly defined criteria for the onset of thermal panting or shivering.

Thus it appears that the key for the successful answer to the problem is to overcome these three shortcomings revealed in the previous studies. In other words, (1) the brain temperature has to be measured directly in the vicinity of the hypothalamus instead of measuring rectal or colonic temperature, (2) the central and peripheral body temperatures have to be dissociated to allow a clear distinction between the action of two regional thermal stimuli and (3) the onsets of thermal panting and shivering must be defined.

## CENTRAL AND PERIPHERAL MECHANISMS

### METHODS

To meet the necessary requirements which are described above, it was necessary to use the anesthetized preparation. The mongrel dogs were anesthetized with barbital sodium with or without morphine sulfate. In some series chloralose was also used. The use of anesthesia has its advantages and also its disadvantages. On the side of advantages, it eliminates one of the sources of ambiguity, namely, the panting or shivering responses due to so-called conditioned reflexes. Barbital sodium is one of the long-acting barbituates and our preliminary study indicates that a stable background of normal blood pressure and respiration can be maintained for more than 8 to 10 hours following a single dose of this reagent. On the side of disadvantages, of course, it is well known that the barbiturates depress the thermoregulatory mechanisms. However, this disadvantage is minimized by using the minimum amount of anesthesia necessary for the surgery.

Body temperature was measured by means of copper-constantan thermocouples soldered into hypodermic needles. In the study of thermal panting, the hypothalamic thermocouple was inserted through a trephine opening in the parietal bone. The angle and depth of insertion required to reach the desired area were determined previously by measurements on the brains of dogs of similar size. We used the medium size of dogs. The position was checked at post-mortem in each experiment, and was found to be within the thermosensitive area described by Magoun and his co-workers (1938). This technique of parietal approach, however, is rather time consuming. Therefore, a simple method of orbital approach was used in the study of shivering. The latter technique consists of implanting a thermocouple through an orbital fissure or optic foramen, into the hypothalamic region. In dogs these cranial openings are relatively large and straight. The hypothalamic, esophageal, gastric, and rectal thermocouples served as core temperature sensing elements. Four other thermocouples were inserted subcutaneously in front and hind legs and in the anterior and lateral abdominal walls.

In the experiments in which head and trunk temperatures were independently regulated, head temperature was controlled by warming or cooling the carotid arterial blood. This was accomplished by inserting a glass coil in the course of arterial blood and then the glass coils were immersed in the water bath (Fig. 1). Figure 2 shows the glass coils (length = 1.5 m, i.d. = 4 mm, o. d. = 6 mm): the proximal end of a carotid artery is connected to the inlet B and blood temperature is monitored by the thermocouple D. The three-way stopcock E served as a tap through which air bubbles or clots may be removed. The temperature of warmed or cooled arterial blood is recorded by the thermocouple C and the blood returns to the head of the animal through the outlet A which was cannulated to the distal end of a common carotid artery.

In the study of thermal panting, the temperature of the animal's trunk was controlled by heating or cooling the trunk alone in a temperature cabinet which had heating and cooling units. On the other hand, in the studies of shivering, the regional cooling or warming of the trunk was accomplished by means of ice or warm water contained in a plastic sheet which covered the animals from the neck down to the thigh and extremities.

The onset of thermal panting was defined arbitrarily when the respiratory rate reached 100/min. To define the initiation of shivering, the electromyogram was monitored from four muscle groups at the regions of neck, thigh, lower, and upper legs. For this purpose the Gilson's electromyograph and integrator were used. The tracing A in Figure 3 indicates the muscle potentials for 10-second duration. When any one of the afore-mentioned muscles begins to show a deflection of 3 mm (i.e., 6 to 9 mV in terms of the integrated potential) it is designated as the onset of shivering.

# CENTRAL AND PERIPHERAL MECHANISMS

## CAROTID HEAT EXCHANGE SYSTEM

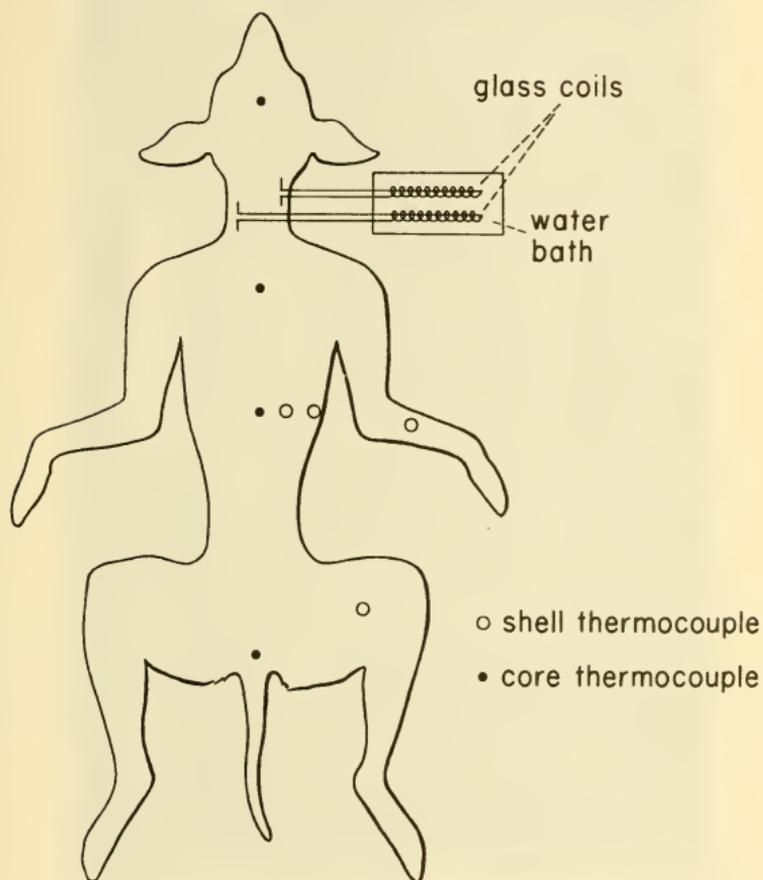


Figure 1: The method of regulating head temperatures by warming or cooling the carotid arterial blood.

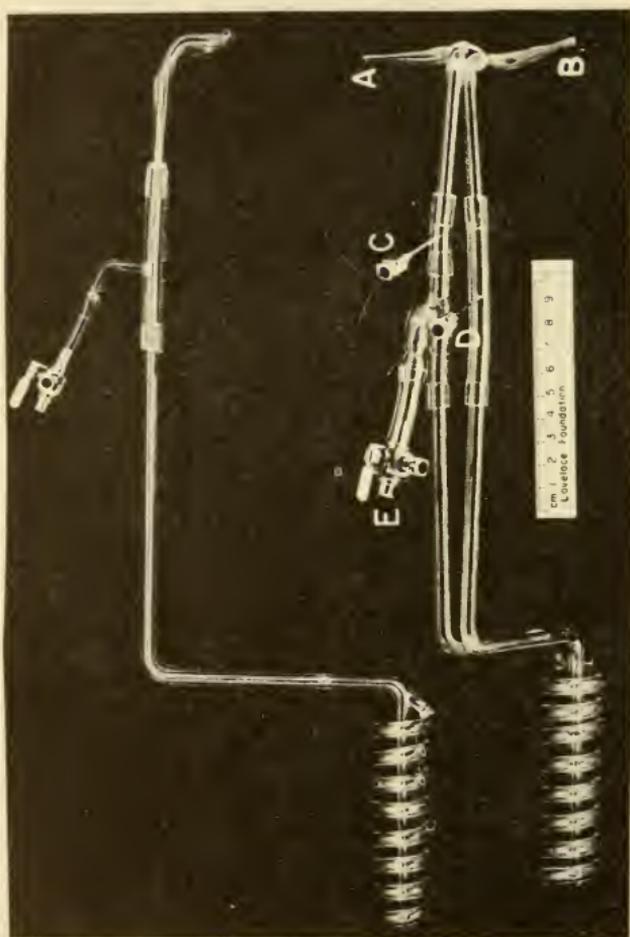


Figure 2. The glass coils (length - 1.5 m, i. d. - 4 mm, o. d. - 6 mm) which were immersed in a water bath.

# CENTRAL AND PERIPHERAL MECHANISMS

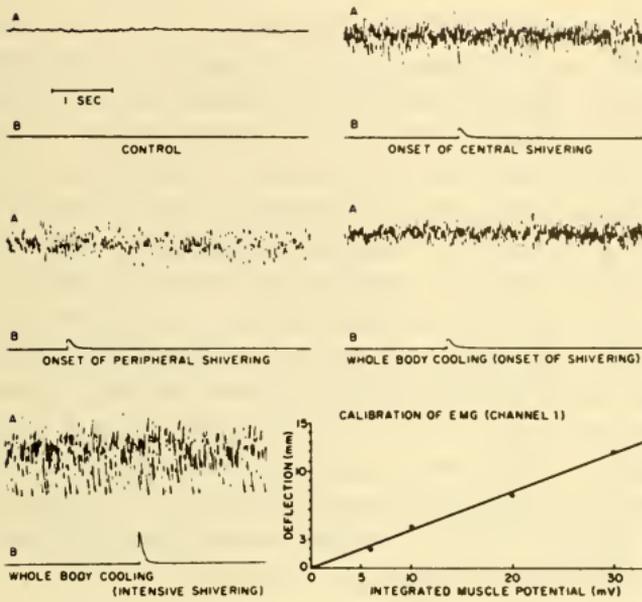


Figure 3. Tracings from Gilson's electromyograph and integrator.

Series I - Whole Body Heating

I shall describe the heat experiment first and then the cold experiments. In the first series, 10 animals were heated in the cabinet for an average period of 3 hours, and, as we anticipated, all 10 animals panted. The average hypothalamic, subcutaneous, and rectal temperatures at the onset of panting are presented in line 1 of Table I. The mean preheating control temperatures were  $37.2^{\circ}\text{C}$ ,  $36.1^{\circ}\text{C}$  and  $37.0^{\circ}\text{C}$  for the hypothalamus, the subcutaneous tissues and the rectum, respectively. Since both central and peripheral temperatures rose significantly, it is impossible to decide whether one or the other or both were responsible for the initiation of panting. Since individual animals were heated at different rates (cabinet temperatures of  $31^{\circ}\text{C}$ ,  $34^{\circ}\text{C}$ ,  $37^{\circ}\text{C}$ ,  $41^{\circ}\text{C}$ ) and control temperatures varied over a considerable range ( $34^{\circ}\text{C}$  to  $40^{\circ}\text{C}$ ), the data were analyzed to determine whether the temperature thresholds for panting varied with the control temperature or heating rate. No significant correlations were found.

Thus, when the whole body of the barbitalized dog is heated, panting occurs when both central and peripheral temperatures are in the neighborhood of  $41^{\circ}\text{C}$ . These temperature thresholds are independent of both control temperature and rate of heating within the range studied.

Series II - Peripheral Heating

In the next series we wished to determine whether "pure peripheral panting" could be produced or not. Therefore, the trunks of four anesthetized dogs were heated in the cabinet at temperatures between  $45^{\circ}\text{C}$  to  $50^{\circ}\text{C}$  for 3 hours, while their hypothalamic temperatures were kept between  $36^{\circ}\text{C}$  to  $38^{\circ}\text{C}$  by carotid cooling. Panting did not occur in any of the animals, the respiratory rate increasing from a mean control value of 24/min to only 46/min at the end of the heating period. The average maximum temperatures reached at the end of the heating period are summarized in line 2

## CENTRAL AND PERIPHERAL MECHANISMS

 TEMPERATURE THRESHOLDS FOR PANTING, OR MAXIMUM  
 TEMPERATURES REACHED WITHOUT PANTING. MEAN VALUES

Procedure	No. of Animals	No. Panting	Temp., °C. $\bar{X} \pm S\bar{x}$		
			Hypothal.	Subcut.	Rectal
Series I—whole body heating†	10	10	41.3 ± 0.1	40.7 ± 0.2	41.1 ± 0.1
Series II—peripheral heating—barbital	4	0	36.3 ± 0.6	45.1 ± 0.6	41.1 ± 0.4
Series II—peripheral heating—chloralose	4	0	38.0 ± 0.4	44.3 ± 0.5	41.2 ± 0.4
Series III—central heating	6	4	42.8 ± 0.4	34.8 ± 0.4	37.9 ± 0.4
Series IV—repetitive cooling—initial panting	7	7	46.0 ± 2.7	38.5 ± 2.3	37.5 ± 2.0
			41.1 ± 0.4	43.2 ± 0.9	39.2 ± 0.7

† Mean control temperatures were  $37.2 \pm 0.4$ ,  $36.1 \pm 0.6$ , and  $37.0 \pm 0.4$  for hypothal., subcut., and rectal respectively.

Table I. Temperature thresholds for panting, or maximum temperatures reached without panting. Mean values.

of Table I. Note that the average hypothalamic temperature was kept at the low value of  $36.3^{\circ}\text{C}$ , whereas the subcutaneous temperature of the thigh reached the high value of  $45.1^{\circ}\text{C}$ . The latter is  $4.4^{\circ}\text{C}$  above the level of this temperature at the time panting began in whole body heating. The mean rectal temperatures were identical in the two series.

A second group of four dogs anesthetized with chloralose was subjected to the same procedure with essentially identical results. None of these four animals panted, the respiratory rate increasing from the mean control value of 18/min to only 47/min at the end of the heating period. The maximum temperatures reached at this time are summarized in line 3 of Table I. The mean hypothalamic temperature was somewhat higher, and the subcutaneous temperature somewhat lower than in the barbital group, but the latter temperature was still  $3.6^{\circ}\text{C}$  above the threshold for panting in whole body heating.

From this series we conclude that if hypothalamic temperature is kept between  $36^{\circ}\text{C}$  to  $38^{\circ}\text{C}$ , panting cannot be produced in the anesthetized dog by peripheral thermal stimuli alone within the temperature range studied. It is considered unlikely that these results would have differed if the head skin had been included in the heating. The results thus imply that panting in whole body heating cannot depend upon peripheral stimuli alone. Such stimuli do, however, produce some increase in respiratory rate, and this may be called "pre-panting hyperpnea."

### Series III - Central Heating

In the next series, we wished to determine whether "central panting" could be produced or not. Therefore, the hypothalamic temperature was gradually raised by heating the carotid arterial blood over a period of 40 to 60 minutes. Of six animals so treated, four panted while the other two showed only pre-panting hyperpnea. The hypothalamic, subcutaneous, and rectal temperatures at the onset of panting (or the maximum levels attained without panting) are summarized in lines 4 and 5 of Table I. Note that

## CENTRAL AND PERIPHERAL MECHANISMS

subcutaneous and rectal temperatures remained at low levels whereas hypothalamic temperature was considerably elevated. Comparing the mean temperature thresholds for panting in the present series with those of Series I, we note that the hypothalamic threshold is  $1.5^{\circ}$  C higher in the former, and this difference is statistically significant ( $p < 0.01$ ). Two animals of the present series failed to pant even though their hypothalamic temperatures exceeded  $43^{\circ}$  C.

From these results, we infer that "central panting" can be produced in the anesthetized dog, but that the hypothalamic temperature threshold is higher in central heating than in whole body heating. This implies, then, that both central and peripheral temperatures contribute to the initiation of panting in whole body heating. It is considered likely that hypothalamic rather than head skin receptors played the major role in the "central panting" of this series, although some contribution from the latter is probable.

### Series IV - Termination of Panting by Central or Peripheral Cooling.

If it is true that both central and peripheral temperatures contribute to the initiation of panting in whole body heating, then panting established by simultaneously raising both temperatures should disappear whenever either one alone is lowered to a lower level while the other is kept at its "whole body threshold." In the next series, panting was established in seven anesthetized dogs by simultaneously heating the head (by carotid warming) and trunk (in the cabinet). In four of the animals, hypothalamic temperature was then lowered to  $37^{\circ}$  C and re-elevated to  $41^{\circ}$  C repeatedly while trunk temperatures were kept nearly constant at high levels. In all four animals, panting stopped whenever hypothalamic temperature fell to approximately  $38^{\circ}$  C to  $39^{\circ}$  C and reappeared when the latter was re-elevated to  $41^{\circ}$  C. The average behavior of the temperatures and respiratory rate of these four dogs during the heating and cooling cycles is shown in Figure 4.

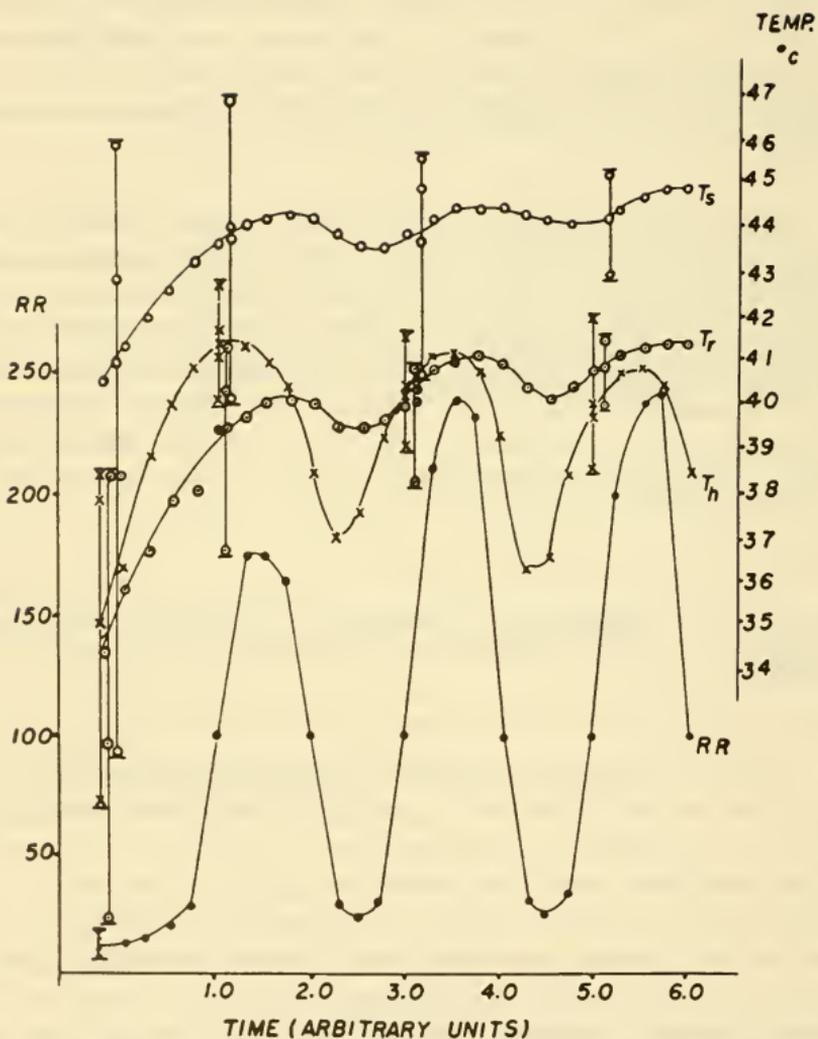


Figure 4. The behavior of temperature and respiratory rate during repetitive central cooling.

## CENTRAL AND PERIPHERAL MECHANISMS

As a next step after panting had been established in the remaining three animals, the trunk was cooled until its subcutaneous temperature fell to  $37^{\circ}\text{C}$  and then reheated while hypothalamic temperature was kept constant at  $41^{\circ}\text{C}$ . In all three of these dogs, panting disappeared whenever the subcutaneous temperature fell to approximately  $38^{\circ}\text{C}$  and reappeared when it was re-elevated to  $41^{\circ}\text{C}$ . The average behavior of the temperatures and respiratory rate during the heating and cooling cycles is shown in Figure 5.

Therefore it appears that both central and peripheral temperatures contribute to the initiation of panting in whole body heating. Furthermore the difference we observed in hypothalamic thresholds between the series of whole body heating and of central heating was actually due to the absence of peripheral thermal stimuli in the latter.

From these data of four Series, we are justified to conclude that both central and peripheral temperatures contribute to the initiation of thermal panting in the anesthetized dog, although the central mechanism is distinctly more potent than the peripheral mechanism.

Subsequent questions are, then, whether such a dual mechanism operates also at the onset of shivering under similar experimental conditions during hypothermia; and if so, does it differ in shivering from thermal panting.

### Series V - Whole Body Cooling

In the next series, systemic hypothermia was induced at a mean reduction rate of  $4^{\circ}\text{C}$  (core temperature) per hour in 13 anesthetized animals. All the animals shivered and the average body temperatures at the initiation of shivering are shown in Table II. The hypothalamic, visceral and subcutaneous temperatures existing at the onset of shivering in 13 anesthetized animals were  $37.3^{\circ}\text{C}$ ,  $37.5^{\circ}\text{C}$ , and  $30.0^{\circ}\text{C}$ , respectively, and these were considerably

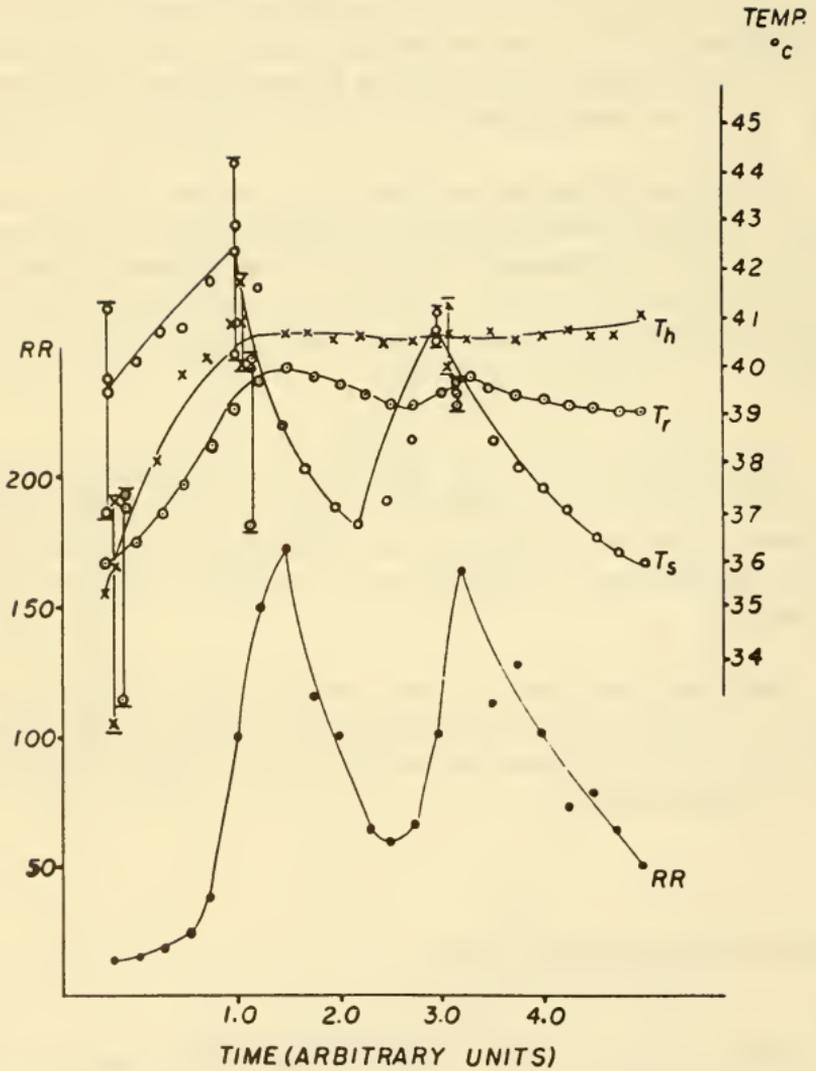


Figure 5. The behavior of temperature and respiratory rate during repetitive peripheral cooling.

CENTRAL AND PERIPHERAL MECHANISMS

TEMPERATURE THRESHOLDS FOR SHIVERING

Procedures	Number of Animals		Temperature (°C) ± S.D.		
			Hypothalamic	Visceral	Subcutaneous
I. Whole Body Cooling	13	c.	37.9±0.5	38.1±0.6	33.2±1.3
		e.	<b>37.3±0.8</b>	<b>37.5±0.8</b>	<b>30.0±2.2</b>
II. Central Cooling	7	c.	38.0±1.2	37.7±0.9	33.7±1.3
		e.	<b>36.2±1.3</b>	37.7±0.8	33.8±1.2
III. Peripheral Cooling	10	c.	38.3±0.8	37.9±1.2	33.3±1.3
		e.	38.3±0.6	37.7±1.1	<b>29.7±2.0</b>

c = pre-cooling control

e = onset of shivering

Table II. Temperature thresholds for shivering.

lower than those of the precooling control period, which were  $37.9^{\circ}\text{C}$ ,  $38.1^{\circ}\text{C}$  and  $33.2^{\circ}\text{C}$ , respectively. Since both central and peripheral temperatures were reduced significantly, it is impossible to differentiate whether one or the other or both were responsible for the production of shivering.

#### Series VI - Central Cooling

In the next series, we wished to determine whether central shivering could be produced. Therefore, the brain temperature alone was gradually lowered in seven animals by cooling the carotid blood over an average duration of 35 minutes (range: 15 to 55 min). All animals began to shiver on the average within 15 minutes (range: 5 to 30 min) at a brain temperature of  $36.2^{\circ}\text{C}$  (Table II). Note that on the average the cerebral temperature was reduced from  $38.0^{\circ}\text{C}$  to  $36.2^{\circ}\text{C}$ , while the visceral and surface temperatures were maintained at practically the same levels as in the control period. A comparison of the hypothalamic temperature thresholds for shivering in whole body cooling and those of the central cooling indicates a significant difference ( $p < 0.05$ ), the latter being markedly lower than the former. From this series it is concluded that central shivering can be produced in the anesthetized dog, but that the hypothalamic temperature threshold is lower in central than in whole body cooling.

In the genesis of central shivering in our preparation, one might suspect that peripheral thermoreceptors in the head, such as are known to exist in large number in the facial region supplied by the trigeminal nerve, particularly might have contributed some peripheral stimuli for shivering. This is one of the criticisms against this type of cooling or heating experiment. To explore the role of these receptors, a thermocouple was implanted in a nostril and an electrical heating tape was wound around the mouth and the nose. Central shivering was produced by lowering the brain temperature and the tape was warmed until the nostril thermocouple registered an average of  $44^{\circ}\text{C}$ , the mean heating duration above  $40^{\circ}\text{C}$  being 6 minutes. None of three animals so treated ceased to shiver, nor did the muscle potentials of shivering diminish. Thus it is most

## CENTRAL AND PERIPHERAL MECHANISMS

likely that hypothalamic rather than skin receptors played the major role in central shivering.

### Series VII - Peripheral Cooling

In the next series, we wished to determine whether peripheral shivering could be initiated. The trunks of 10 animals were cooled for an average period of 19 minutes (range: 5 to 34 min), while their brain temperatures were kept between  $37.6^{\circ}\text{C}$  and  $40.2^{\circ}\text{C}$  by carotid warming. All animals began to shiver within nine minutes (range: 0.5 to 20 min) at the mean surface temperature of  $29^{\circ}\text{C}$  to  $30^{\circ}\text{C}$ , although the average visceral temperature was not altered or only slightly reduced (Table II). Interestingly enough, a comparison of the surface temperature thresholds between whole body cooling and peripheral cooling Series disclosed no statistical difference ( $p>0.5$ ) which implies that the shivering observed in whole body cooling is primarily of reflex origin. From these results it is concluded that shivering can be produced in anesthetized dogs by peripheral thermal stimulus alone when the hypothalamic temperature is maintained at the range of  $38.0^{\circ}\text{C}$  to  $40.0^{\circ}\text{C}$ .

### Series VIII - Repetitive Cooling and Termination of Shivering by Central and Peripheral Warming.

The data acquired in the above three Series in the cold (Table II) indicate that both central and peripheral shivering exist and that shivering observed in whole body cooling is predominantly of peripheral origin. To supplement these findings, four animals were repeatedly cooled and rewarmed centrally as well as peripherally. All animals responded to such a repetitive procedure.

To explore further the interrelationship between central and peripheral temperatures during shivering, central shivering was

produced in three animals (Table III), the hypothalamic temperature being maintained between  $34^{\circ}\text{C}$  to  $37^{\circ}\text{C}$ . This was followed by warming the animal's trunk (water temperature =  $40^{\circ}\text{C}$  to  $45^{\circ}\text{C}$ ) to examine whether such a thermal counteraction on the part of the periphery could suppress central shivering. All three animals ceased to shiver within 1 to 2 minutes of peripheral warming at a mean surface temperature of  $34.9^{\circ}\text{C}$ . Utilizing the same preparation the procedure was reversed. This time, peripheral shivering was produced by surface cooling and then central warming was initiated to test whether the opposing temperature on the part of brain center could arrest peripheral shivering. All three animals ceased to shiver after 10 to 28 minutes of central heating at an average brain temperature of  $41.5^{\circ}\text{C}$ .

From the results of these cooling experiments (Tables II and III), it is inferred that shivering can be produced by differential cooling of the head or the trunk alone as well as by whole body cooling, but the peripheral mechanism of shivering is very potent.

In the studies of thermal panting, peripheral heating up to  $45^{\circ}\text{C}$  (brain temperature,  $36^{\circ}\text{C}$  to  $38^{\circ}\text{C}$ ) did not produce panting in dogs under either barbital sodium or chloralose anesthesia. In the studies on shivering, however, the reduction of skin temperature from  $33^{\circ}\text{C}$  to  $30^{\circ}\text{C}$  while maintaining a brain temperature of  $38^{\circ}\text{C}$  invariably produced a shivering response. This distinctive difference in the roles of peripheral stimuli in shivering and thermal panting leads us to conclude that, in general, the thermal influx from the periphery in the cold plays a more dominant role than in a warm environment. To elucidate further, the relative importance of central and peripheral thermal stimuli in the initiation of thermal panting and shivering, the hypothalamic and subcutaneous temperature thresholds for panting and shivering are plotted in Figure 6. The open circles indicate temperature thresholds for panting and the closed circles those for shivering in whole body as well as regional heating and cooling experiments. The trend of the two curves is shown by the freehand drawings (Fig. 7) which are designated as the iso-panting and the iso-shivering line, respectively. It appears that the slope of the iso-shivering line is much steeper than that of the iso-panting line, which suggests that at a fixed level of brain temperature, the alterations in the skin temperature play a more significant role at the onset of shivering than thermal panting. Conversely at a fixed skin

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TERMINATION OF SHIVERING BY  
CENTRAL AND PERIPHERAL WARMING (n = 3)

	Average Temperature (°C) and Range	
	Hypothalamic	Subcutaneous
A.		
Control (pre-cooling)	38.5 (37.8~39.2)	34.2 (33.8~34.8)
Central Shivering	35.7 (34.4~37.3)	34.1 (34.0~34.2)
Cessation of Shivering	35.0 (34.3~36.3)	<b>34.9</b> (34.5~35.2)
B.		
Control (pre-cooling)	38.5 (38.3~38.9)	33.9 (33.6~34.2)
Peripheral Shivering	38.8 (37.2~40.0)	31.5 (30.3~32.7)
Cessation of Shivering	<b>41.5</b> (40.3~42.6)	28.5 (25.0~31.6)

Table III. Termination of shivering by central and peripheral warming.

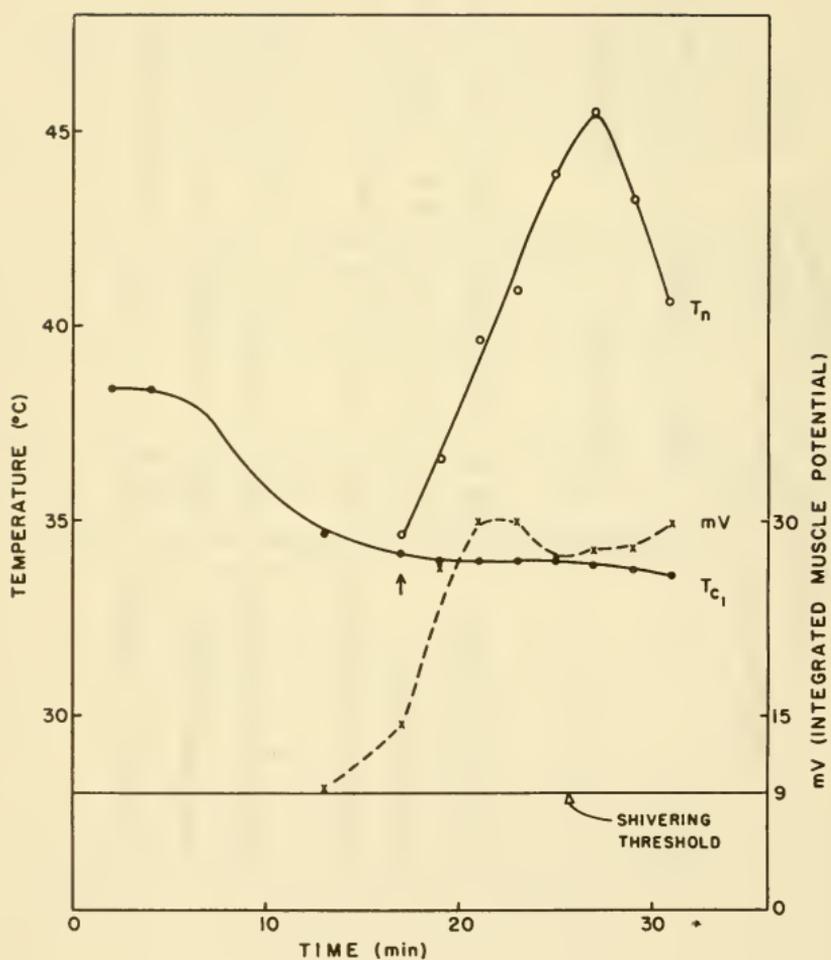


Figure 6. Integrated muscle potential during cooling.

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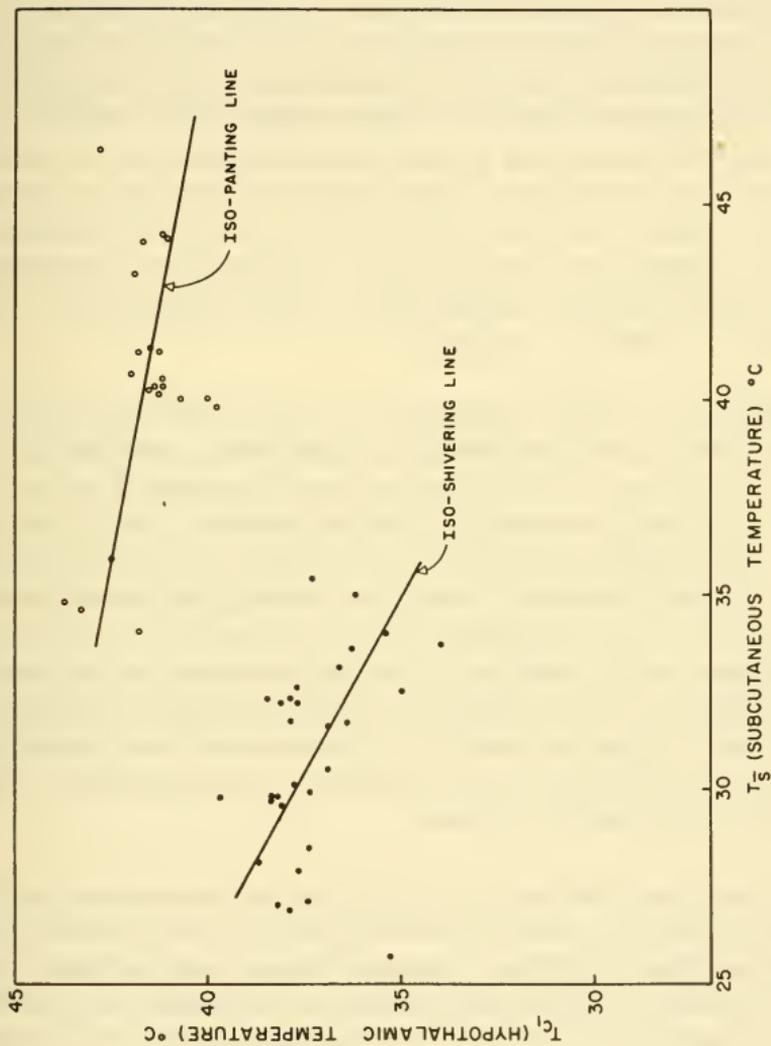


Figure 7. Hypothalamic and subcutaneous temperature thresholds for panting and shivering.

temperature the variations in the brain temperature have a greater influence in the initiation of panting than shivering.

The relative roles and interactions of central and peripheral mechanisms at the onset of panting and shivering, as revealed in our study, are certainly established in the animals under anesthesia. However, it is not certain whether such relationships between central and peripheral mechanisms also exist in the unanesthetized animal. The elucidation of control mechanisms of body temperature in the unanesthetized animal is quite difficult since shivering or panting may be produced by a conditioned reflex, and also a regional or steady state dissociation of body temperature is almost impossible in the intact animal. In addition to this, due to the current uncertainty, particularly advocated by Dr. Benzinger, a careful study concerning the control mechanisms of body temperature in the unanesthetized animal is needed.

Although our data are generally in accord with the duality hypotheses, that is, that both central and peripheral mechanisms are involved in the control of body temperature, the mode of interaction of the two cardinal mechanisms remains unknown. And in addition, despite the classical works by Dr. Ranson and his associates, which provided a valuable evidence for locating the central control mechanisms of body temperature in the hypothalamus, the necessity for additional work concerning the neuroanatomy of the central thermoregulatory area is apparent. Employing modern neurophysiological tools, it may be possible to demonstrate more clearly the locations and functions of heat dissipation and conservation in the forebrain as well as the midbrain.

In conclusion then, peripheral and central mechanisms for the initiation of thermal panting and shivering have been studied in the anesthetized dog employing a thermal dissociation technique. Our first conclusion is that thermal panting can be produced by central but not by peripheral heating alone. The hypothalamic temperature threshold for panting is higher in central heating alone than in whole body heating. Thermal panting established by whole body heating disappears whenever either central or peripheral temperature alone is lowered. Thus, it is concluded that both central and peripheral temperatures contribute to the initiation of panting, although the central temperature is more important.

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Our second conclusion is that shivering can be produced during differential cooling of the head or the trunk alone as well as in the course of whole body cooling. Either "peripheral" or "central" shivering can be produced repeatedly and also inhibited by elevation of skin temperature in "central shivering" or brain temperature in "peripheral shivering". From these data, it is inferred that the onset of shivering in the anesthetized animals depends upon both central and peripheral temperatures; the peripheral temperature in shivering in this case is more potent than the central temperature.

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## DISCUSSION

DR. HENSEL: May I make a general suggestion not to use the word "receptor" for the central mechanism. I think it is better to use "receptor" only for a defined mechanism. Of course, the central mechanism can be sensitive to temperature. It can be changed in the activity of some neural unit, but it must not be a receptor in the sense of receptor.

DR. LIM: Not in the anatomical sense.

DR. HENSEL: May I ask another question? I think it is very important to discriminate between the natural conditions and the artificial conditions in the experiments because if you cool an animal from outside, under natural conditions, you would get at the same time an increase in hypothalamic temperature. I think under natural conditions it very seldom occurs that hypothalamic temperature actually drops during external cooling. The drop in hypothalamic temperature can be brought about by artificial cooling, of course, but it does not occur when cooling a cat in a cold chamber.

DR. LIM: Yes, we knew this. That was the one reason we added this rather artificial situation. The main purpose was to dissociate two areas, by means of which we can maintain any level of steady state.

DR. HENSEL: Yes, of course, the discrimination of the mechanism is very important.

DR. CLARK: May I also make a comment: First of all, I think in all probability your conclusions are fine. I am not willing to accept

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that your experiments prove them. I would be much happier if you had sectioned the fifth nerve bilaterally, for one thing. Another thing, I am not willing to accept a respiratory rate of one hundred as equal to panting. Much more important than rate as far as panting is concerned is amplitude, and I would be much more happy to accept a small amplitude respiration.

DR. LIM: Then, what is your definition of panting?

DR. CLARK: If I am defining panting, I do not use rate at all. The cat and the dog have to open their mouth, retract the angle of the mouth, and move the tongue. That is a matter of semantics.

Then, you said skin and brain are essential elements. Dr. Blatteis of our group has evidence that there are possibly some temperature sensing elements in the iliac vessels, and I do not know of any work myself that rules out the possibility of temperature sensing elements in several other places. I doubt if they are there, but I think that the data are not in.

As for your hypothalamic temperatures, Magoun, in his diagrams, has only indicated a position with reference to a sagittal plane, but gives no data on whether it is medial or lateral. Again, however, I think you are probably right.

DR. LIM: Our areas were within three to four millimeters of the center line which is very close to the medial line. Our definitions of panting and shivering are arbitrary, depending on our different workers. I do not know whether we have a clear-cut definition to make everybody happy on this, but I doubt it very much.

DR. IRVING: Should you not have some indication of the function of the panting, namely, that it was dissipating heat in an additional degree? I think that is implicit in what Dr. Clark is saying.

DR. LIM: Usually the tongue is protruded and, of course, the surface of the tongue is very important in the dissipation of heat. In most of the animals we studied their tongues were protruding. And we think this definition of respiration rate of 100/min is adequate for our purpose.

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DR. CLARK: Well, the chief thing is, of course, that with an increase in amplitude you are primarily getting a ventilation of the dead space, which is implied in the term "panting". Actually, I have seen cats panting at temperatures below 38° C.

DR. HEMINGWAY: I have studied panting in both anesthetized and unanesthetized dogs and I agree with Dr. Clark; there is an abrupt change in the respiratory pattern when an animal pants. It is quite different from the hyperventilation that you get, say, with the decerebrate animal. It is possible just by raising the temperature of a cold-blooded animal and warm blooded animals that have been made poikilothermic by decerebration to get this hyperpnea or hyperventilation, but the normal animal without anesthesia has a distinct change in pattern. There is a drop in tidal volume which is very striking. I do not think you can really tell with an anesthetized animal whether he is panting or not; it is so different from that of the unanesthetized animal. In the former you can have hyperventilation or hyperpnea, but it is difficult to say when you have panting. With an unanesthetized dog, it is very easy.

DR. JOHANSEN: Is it conceivable that the vascular changes in the brain produced by your cooling of the carotid blood could bring in another stimulus that could interfere with the temperature, per se?

DR. LIM: I did not mention it in detail, but we did obtain some data on the threshold levels with whole body heating in intact animals, without any insertion of coils into the brain circulation. In other experiments with repetitive heating or cooling, we produced panting by simultaneous heating of the brain and the skin. There was no statistical difference between the results of these experiments as far as thresholds are concerned. This would indicate that the disturbance of the cerebral circulation by insertion of the coil may not be a major problem.

DR. JOHANSEN: To the best of my knowledge, the internal carotid is the main supply to the tongue of the dog. So, although you warm the nostrils and the skin of the face, you might also have an input from the tongue.

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DR. LIM: That is very possible.

DR. HENSEL: There is practically nothing.

DR. MINARD: Dr. Lim mentioned Dr. Benzinger's work, and I would like to point out that Dr. Benzinger found it possible in the human subject to bring about this dissociation between skin and deep temperature. He also felt, as Dr. Lim does, that this is important in determining the regulatory responses in the conscious unanesthetized human subject. It is possible to bring about such dissociation by having the man either at rest or working, in a hot or cold environment. By selecting various environmental conditions and work rates, it is possible to obtain a wide variety of core and skin temperatures.

DR. LIM: In that connection, I was very happy to learn recently of Dr. Benzinger's finding, that the skin temperature plays a very important role in the cold. This was exactly what I found.

DR. MINARD: I would say, from what I know of Dr. Benzinger's work, that there is no disagreement whatever in your results and his regarding cold conditions. I think he has come to some interpretation of a mechanism acting centrally, but as far as the experimental findings go, there is absolutely no disagreement between his findings and yours.

DR. HENSEL: I think it is necessary to emphasize that Dr. Benzinger's concept is applied only to sweating in human subjects, not to vasomotor responses, nor to any kind of cold responses. It is a concept that should be restricted to mechanisms. I think he would completely agree with your findings, and I must say that I am very happy about them too. They agree very well with our results in the unanesthetized cat, where we made the local hypothalamic temperature change by means of a chronically implanted thermode.

DR. LIM: In some of our experiments we studied the contribution of the vertebral arteries to the cerebral circulation. Of course, the brain circulation is mainly through the carotid arteries. Ligation of the vertebral arteries did not make much difference in our experimental results, so we think, at least in dogs, that the blood going to the brain through the vertebral arteries is rather small.

DR. HEMINGWAY: It is possible, though, to tie out both common carotids. I have seen this done in a dog, and the dog is perfectly happy for a while, except for some atrophy of the facial musculature. He will live for a few days without showing any effect, thus indicating the vertebral circulation is extensive enough to substitute for the carotid circulation.

MR. ADAMS: I wonder if Drs. Clark and Hemingway would be willing to accept an index of panting based on respiratory, evaporative heat losses, rather than on respiratory volume or pattern?

DR. HEMINGWAY: Like your water loss, it goes up very abruptly. If you will notice, when a dog starts to pant, he first takes a few deep breaths; then all of a sudden there is an abrupt rise in respiratory rate and a drop in tidal volume at the same time. If you measure the water output that goes up abruptly, too. It should also be noted that it is also possible to stop shivering without any change in skin temperature by just warming the anterior hypothalamus. A number of people have done this. No change at all in skin temperature is observed.

MR. EAGAN: Is it possible that there is a sufficient association of the heat loss center and the heat conservation center, that you could get, with a suitable choice of conditions, a pre-panting hyperpnea at the same time as shivering?

DR. LIM: I do not know, but I accept it for the sake of the discussion. I do not know how clearly the two centers are defined.

DR. CLARK: I would say that the center for heat conservation is fairly well defined and that the center for heat dissipation is much less clearly defined than we would be led to believe from reading the literature.

MR. EAGAN: I was thinking of the functional association.

DR. CLARK: I would not expect simultaneous shivering and panting because where you have opposing centers, you are going to have interconnecting inhibitory and excitatory fibres.

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DR. LIM: The only experiment I have that would suggest such a phenomenon is one where we studied exercise in the unanesthetized dog. We put the animal on a treadmill which was immersed in a water tank, so that he could be cooled during exercise. It appeared that such animals shivered as well as panted. Here again this was observed in the unanesthetized dog and there may be a conditioned reflex involved.

DR. HENSEL: I think one must be careful with the studies during work because there is evidence that work will set the thermostat to another level. It is not just a rise in the core temperature.

DR. HEMINGWAY: Anesthetics such as morphine really disturb temperature regulation. For example it is possible to get shivering and what appeared to be panting at the same time with morphine anesthesia. This is such a disturbance caused by the anesthetic. I have always felt that temperature threshold values for skin temperature and rectal temperature and brain temperature under anesthesia are quite variable. You can get almost anything you want, depending upon the depth of the anesthesia. After giving phenobarbital anesthesia, all these thresholds are depressed, then they come back. Shivering comes back first and the thermocutaneous vasomotor response comes back later. However, you are never sure just what the anesthetic level is or how much depression has been caused by the anesthesia.

DR. LIM: That is certainly true in short-acting anesthesia, particularly amytal, but barbital-sodium is long acting. We have based several studies on how the latter affects the blood pressure, respiration, and body temperatures. They all stay fairly constant, and within normal range for eight hours or more after a single dose. Thus, we thought barbital-sodium was the best preparation for our studies because it maintains a steady background.

DR. HENSEL: Concerning the vasoconstriction during hypothalamic cooling, there is quite a high impairment in the anesthetized as compared to the non-anesthetized cat. It can abolish the whole mechanism even during the light anesthesia. I do not know how it is with studies of shivering, but this is a difficult problem in circulatory studies.

DR. HEMINGWAY: Anesthetics cause the skin temperature to go up very quickly, and it stays at certain elevated levels for a long period of time. Thus, it would seem that the cutaneous vasomotor response is so sensitive to anesthetics that they would seriously interfere with skin temperature measurements.

DR. FREEMAN: There is one thing about your work that bothers me a great deal and makes me wonder about its relevance to normal processes. This is the high temperatures that you have to use to activate whatever you are stimulating. This has been my experience also. In order to get panting, or, for that matter, vasodilation in an anesthetized cat, you have to heat above the level which we ordinarily consider to be harmful to the brain. That is, above  $42^{\circ}\text{C}$ , which is so high that the response will decay if you maintain it for any length of time. Furthermore, if you try to get it twice or three times, you may get it the second time, never the third. This is associated with a marked disturbance of the animal. His pulse rate will usually go way down, his blood pressure will go down, his nociceptive reflexes will disappear, and his muscle tone disappears completely; he is completely placid, and there is a very slow recovery period thereafter. I think what this thing represents is some form of brain damage which may be related to manifestations you see in sunstroke.

DR. LIM: With our dosage of anesthesia, as shown in the first figure, the temperature threshold in both central and peripheral areas is somewhere around forty-one. I would think of forty-two or forty-three degrees as being high, but we were using forty-one degrees centigrade in the panting studies.

DR. FREEMAN: There is an interesting history of this so-called central response. In the first clear distinction of central versus peripheral heating by Roché, somewhere back around 1898, he defined central panting more in terms of its overwhelming durability in the face of anoxia. He set  $40.7^{\circ}\text{C}$  as a specific level of an emergency reaction. When panting did occur at this level, it would persist in the face of anoxia or asphyxia for a period of two, three, or even four minutes, whereas panting induced by external heating in an intact animal would be interrupted in a matter of thirty seconds or so. Now, most people that have tried to get this central phenomenon find that it is dependent upon the type of anesthesia being used. For example, Magoun published a short statement some two years after

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his original paper saying that they had only been able to get it in animals under urethane or under ether. This was our experience also. We did not get it under phenobarbital except in one instance. The people in Sweden have also found it only under chloralose and urethane anesthesia. Hess reported that he only saw it in cases where he was making lesions by local heating, but never in the course of minimal diathermy. Dr. Hemingway, what is your experience in conscious animals? How high do you have to heat to get this response?

DR. HEMINGWAY: We were not able to produce panting by heating the anterior hypothalamus with diathermy, but we were able to stop shivering and cause cutaneous vasodilation. During such experiments we could not measure the hypothalamic temperature except very roughly -- perhaps to one-half or one degree. This was due to the diathermy current interfering with the temperature measurements. All of our measurements, therefore, had to be determined after the diathermy current had been turned off, during which time the temperature was falling quite quickly. Typically, heating of the anterior hypothalamus cause a cutaneous vasodilation, a cessation of shivering, but no panting.

DR. LIM: Was there any increase in respiratory rate, say, in terms of so-called pre-panting hyperpnea?

DR. HEMINGWAY: No indication at all.

DR. HENSEL: We saw the onset of panting in the unanesthetized cat, during local hypothalamic rewarming.

DR. HEMINGWAY: Where were you heating it?

DR. HENSEL: In the anterior hypothalamus.

DR. LIM: Dr. Hammond, in Dr. Hardy's group, produced it in the unanesthetized dog.

DR. HEMINGWAY: Dr. Magoun reported it in the anesthetized cat, but he was heating the anterior hypothalamus. I was using dogs, unanesthetized dogs.

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DR. MINARD: I want to clarify one point. When I spoke of Dr. Benzinger's work being in no disagreement with Dr. Lim's, I was referring to his recent work on the cold side; but with reference to what he has observed in the control of sweating on the warm side, there is this difference: he regards the central temperature as the only controlling factor in that sweat rate is independent of skin temperature.

DR. HENSEL: This is quite possible, but in the unanesthetized condition, the peripheral mechanism may be quite different.

DR. RODDIE: I think that we have quite good evidence that there is a peripheral element looking after both heat and cold. People like Kirschlich and Cooper have shown radiant heat on one extremity will cause a vasodilation in the opposite extremity within several seconds; and this was abolished if they cut the sympathetic nerves which were supplying the radiated area. With respect to cooling, I think most people, if they cool a subject rapidly, find that the shivering commences very soon, and at a time when esophageal temperature, which is about as close to a hypothalamic as one can get in man, is actually elevated.

DR. LIM: Can you get a peripheral mechanism?

DR. RODDIE: The peripheral mechanism is quite strong.

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REFERENCES

1. Benzinger, T. H. On physical heat regulation and the sense of temperature in man. *Proc. Nat. Acad. Sc.* 45:645, 1949.
2. Birzis, L. and A. Hemingway. Efferent brain discharge during shivering. *J. Neurophysiol.* 20:156, 1957.
3. Hammel, H. T., J. D. Hardy, and M. M. Fusco. Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. *Am. J. Physiol.* 198:481, 1960.
4. Kundt, H. W., K. Bruck, and H. Hensel. Das Verhalten der Hautdurchblutung bei Kuhlung des vorderen Hypothalamus. *Naturwissenschaften* 44:496, 1957.
5. Lim, P. K. and F. S. Grodins. Control of thermal panting. *Am. J. Physiol.* 180:445, 1955.
6. Lim, T. P. K. Central and peripheral control mechanisms of shivering and its effect on respiration. *J. Appl. Physiol.* 15: 567, 1960.
7. Magoun, H. W., F. Harrison, J. R. Brobeck, and S. W. Ranson. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* 1:101, 1938.
8. Perkins, J. F. The role of the proprioceptors in shivering. *Am. J. Physiol.* 145:264, 1945.



# THE ROLE OF VASOCONSTRICTOR AND VASODILATOR NERVES IN THE CONTROL OF THE PERIPHERAL CIRCULATION

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Over the last few years, there has been a gradual development in our notions of the nervous control of peripheral blood vessels in man. Today I want to review the pattern which seems to be emerging. As you know, blood flow in the limbs is mainly distributed to skin and muscle and both these tissues appear to have a rich vasomotor innervation. All these fibres are not actively concerned in temperature regulation but an understanding of their various functions is very helpful in the design and interpretation of experiments on the peripheral vascular responses to heat and cold. First of all, therefore, I will deal with the vasomotor control of muscle vessels and then with that of skin vessels.

## VASOMOTOR NERVES TO MUSCLE

### Vasoconstrictor Fibres

Until 1943 the available evidence suggested that muscle blood vessels had little or no vasoconstrictor innervation. When measured as soon as one week following cervical sympathectomy, forearm blood flow was not found to be increased (Stein, Harpuder, and Byer, 1948). Blocking the deep nerves to the muscles did not increase the temperature of the overlying skin (Woollard and Phillips, 1932; Grant and Pearson, 1938). Stimuli which caused large changes in vasoconstrictor tone in the hands and feet produced little or no change in flow in the muscular parts of the limbs (Abramson, 1944). The inference that muscle had a negligible vasoconstrictor innervation

seemed justified. However, appropriate experiments showed that this was not the case. Using venous occlusion plethysmography to measure forearm blood flow, Barcroft, Bonnar, Edholm and Effron (1943) found that blocking the motor nerves to the forearm with local anaesthetic increased flow two to three fold. This increase did not seem to be in skin since it was seen even when the cutaneous circulation was suppressed by iontophoresis of epinephrine into the skin. Blocking only the cutaneous nerves to the forearm did not increase flow. From these and other control observations it was concluded that skeletal muscle is normally subjected to appreciable vasoconstrictor tone and that the fibres concerned were distributed to the muscle in the motor nerves.

It was not clear at that time what role these fibres played in the normal regulation of the circulation. Reflex changes in forearm blood flow were known to occur during body heating (Wilkins and Eichna, 1941). Barcroft, Bonnar and Edholm (1947) found that attempted suppression of the cutaneous circulation in the forearm by the epinephrine iontophoresis technique failed to prevent the reflex vasodilatation during body heating. They concluded that release of vasoconstrictor tone in muscle contributed to this vasodilatation.

However, in 1952, McGirr found that the rate of clearance of  $\text{Na}^{24}$  from human muscle did not increase during body heating. This result could not be reconciled with those of the plethysmographic experiments unless it were postulated that vasodilatation occurred in 'non-metabolic' vessels. This was not a very satisfactory state of affairs and further work on the subject became necessary. Barcroft, Bock, Hensel, and Kitchin (1955) used heated thermocouples to estimate muscle blood flow. They found that forearm flow did not increase during body heating; a fall was the usual finding. Roddie, Shepherd and Whelan (1956) used changes in the oxygen saturation of effluent venous blood from skin and muscle to estimate simultaneously the contribution of these tissues to the vasodilatation. Though the oxygen saturation of skin blood rose to almost full saturation, there was no significant rise in that from muscle (Fig.1). Improvement in the technique for iontophoresis of epinephrine into forearm skin allowed Edholm, Fox, and Macpherson (1956) to produce more effective suppression of the skin circulation than had been obtained in earlier experiments (Barcroft, Bonnar, Edholm, and

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Effron, 1943). With this degree of suppression forearm flow did not increase during body heating. It was clear, therefore that vasoconstrictor fibres to muscle were not involved in the peripheral vasodilatation during body heating. Blair, Glover, and Roddie (1960) found that the fall in forearm blood flow during body cooling could be prevented by blocking the cutaneous nerves in the forearm, providing further evidence that vasoconstrictor fibres to muscle do not take part in thermoregulatory reflexes. The normal function of these fibres remained obscure.

Over the last few years, the reflex effects of passively raising the legs of a recumbent subject on peripheral blood vessels have been studied in considerable detail (Roddie and Shepherd, 1956; Roddie, Shepherd, and Whelan, 1957). This stimulus caused reflex vasodilatation in the forearm but there was no comparable change in the hand (Fig. 2). The oxygen saturation of muscle venous blood was increased but that of skin was not affected. These findings suggested that muscle rather than skin vessels were responsible for the vasodilatation. The changes were mediated through sympathetic vasomotor nerves since they were abolished by acute nerve-block or by cervical sympathectomy. Release of vasoconstrictor tone rather than vasodilator fibre activity was never greater than could be accounted for by full release of vasoconstrictor tone; it was not reduced by atropinizing the forearm but was abolished by intra arterial infusion of the sympatholytic agent bretylium tosylate. It was concluded that alterations in vasoconstrictor tone in muscle were responsible for the changes in forearm blood flow with change in posture.

A wide variety of stimuli are now thought to affect the level of vasoconstrictor tone in muscle. Negative pressure breathing (Blair, Glover, and Kidd, 1959), squatting (Sharpey-Shafer, 1956) and intrathoracic pressure transients (Sharpey-Shafer, 1953; Roddie, Shepherd, and Whelan, 1958) are thought to cause reflex vasodilatation. Tilting a subject into the vertical position (Bridgen, Howarth, and Sharpey-Shafer, 1950), positive pressure breathing (Blair, Glover, and Kidd, 1959), the Valsalva manoeuvre (Roddie, Shepherd, and Whelan, 1958; Sharpey-Shafer, 1955), exercise (Blair, Glover, and Roddie, 1961), radial acceleration (Howard and Garrow, 1958), and hypercapnia (McArdle, Roddie, Shepherd, and Whelan, 1957) are

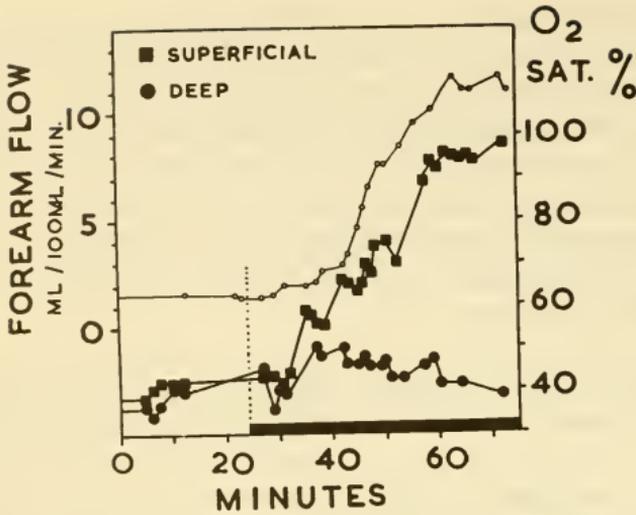


Figure 1. The effect of body heating on the oxygen saturation of deep and superficial venous blood and forearm blood flow. The black rectangle represents the period of body heating. Left forearm blood flow,  $\circ$ ; oxygen saturation of superficial venous blood (right forearm)  $\bullet$ ; oxygen saturation of deep venous blood (right forearm)  $\blacksquare$ . (After Roddie, Shepherd, and Whelan, *J. Physiol. (Lond.)*, 134: 444, 1956).

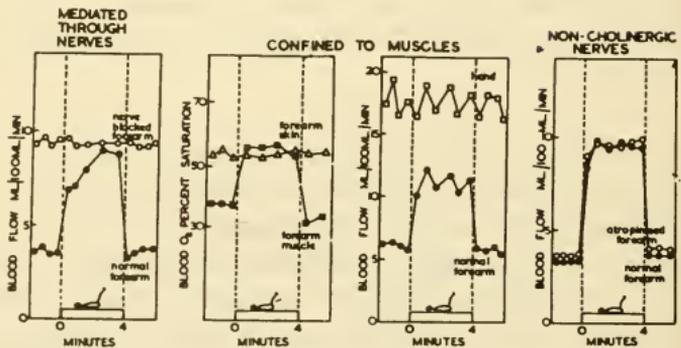


Figure 2. Changes in forearm blood flow with change in body posture. The open rectangles represent the periods during which the subjects' legs were raised from the horizontal to the vertical position.

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thought to cause reflex vasoconstriction. There is evidence that alterations in the activity of stretch or baroreceptors in the low pressure area of the intrathoracic vascular bed may be responsible for some of the changes in the vasoconstrictor tone (Roddie and Shepherd, 1958), but this part of the problem is quite complex and there is not time to discuss it today.

### Vasodilator Fibres

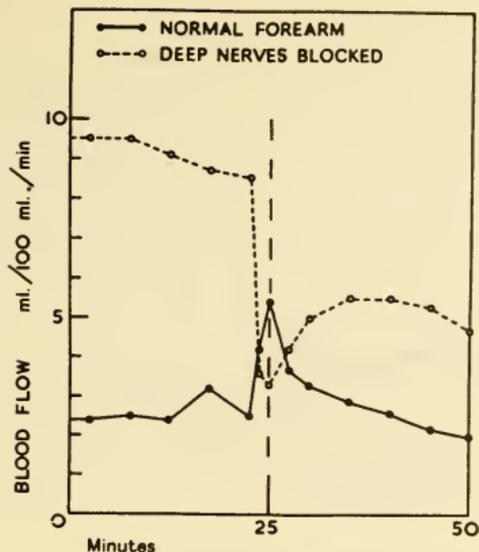
The first evidence that human skeletal muscle had a vasodilator innervation was provided by Barcroft and Edholm (1945). They found that vasodilatation occurred in the forearm during fainting (Fig.3). The conclusion that the vasodilation in the normal forearm was actively excited was based on a comparison of the average levels of flow in normal and nerve-blocked forearms during the faint; the flow in the normal arm rose to a higher level than that in the nerve-blocked arm. Though this evidence is highly suggestive, it is not absolutely conclusive since the observations on the normal and nerve-blocked forearms were not made simultaneously in the same subject. However, evidence has since been found that vasodilation in muscle is a constant feature of the vasovagal syndrome (Anderson, Allen, Barcroft, Edholm, and Manning, 1946).

It seemed unlikely that a potent vasodilator system should exist just to facilitate fainting so a vigorous search was made to find a stimulus which would excite these fibres under more normal physiological conditions. As mentioned before we could find no evidence that these fibres were involved in baroreceptor reflexes. Another incentive to search for a stimulus was the abundant evidence for these fibres supplying muscle in other experimental animals. In the cat and dog, cholinergic vasodilator innervation of skeletal muscle is well established and the central connections and efferent distributions of these fibres has been extensively studied (Uvnas, 1954). It was found that they played no part in either chemoreceptor or baroreceptor reflexes but the exact nature of the physiological reflex stimulus was not obtained. Abrahams and Hilton (1957) have recently shown that stimulation by electrodes implanted in those

places in the brain stem which discharge these fibres in anesthetized cats provoke the 'fight or flight' reaction in conscious cats. It seemed possible, therefore, that emotional stress might be the effective physiological stimulus.

It has been known for a long time that stimuli such as mental arithmetic frequently cause an increase in forearm blood flow (Abramson and Ferris, 1940; Grant and Pearson, 1938). Gollehoffen and Hildebrandt (1957), using Hensel's heated thermocouples to measure skin and muscle blood flow, found that the vasodilatation occurred mainly in muscle, but this response was usually attributed to epinephrine. Evidence that cholinergic vasodilator fibres contributed to vasodilatation in muscle during emotional stress was obtained in some experiments where we tried to provoke a 'fight or flight' reaction in our subjects (Blair, Glover, Greenfield, and Roddie, 1959). Medical students were frightened, worried, or embarrassed by means judged likely to be most effective for each individual (Figs. 4 and 5). In most experiments the subject had an indwelling needle in the brachial artery. The operators, by their whispered conversation and demeanour, led the subject to believe that they were alarmed because of blood loss at the arterial puncture site and the precarious state of the subject's health. About half of the subjects complained of pain in the arm and throbbing in the head. After a few minutes the real purpose of the hoax was explained and anxiety was promptly relieved. Figure 6 shows the result of one such experiment. During the period of stress forearm blood flow rose to about 50 ml/100 ml/min, a level similar to that found immediately after severe exercise of the forearm muscles and much greater than that usually achieved by full release of vasoconstrictor tone. The size and rate of recovery of the vasodilation were greater than that usually seen during epinephrine infusions. The changes in hand blood flow and arterial pressure also were not typical of those seen with epinephrine infusions. It seemed unlikely that release of epinephrine from the suprarenal glands in response to stress could fully explain the response. The fact that forearm but not hand blood flow increased during stress suggested that muscle vessels might be responsible for the vasodilatation. This was supported by the finding that the oxygen saturation of muscle but not skin venous blood increased during stress (Fig. 7). Sympathetic vasomotor fibres to muscle contributed to the vasodilatation since it was reduced by blocking the motor nerves to the forearm and by

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### FAINTING, 9 NORMAL 6 BLOCKED

Figure 3. Changes in blood flow in the normal and nerve-blocked forearm during fainting. Fainting occurred at the time indicated by the vertical dashed line. (After Barcroft and Edholm, *J. Physiol. (Lond.)*, 104:161, 1945).

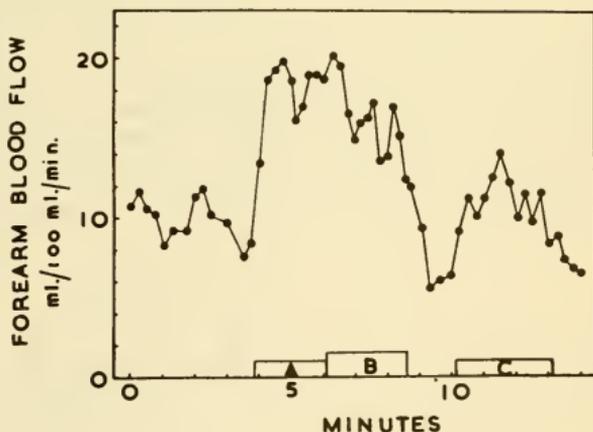


Figure 4. Changes in forearm blood flow during emotional stress. At the beginning of rectangle A, the subject, who was a medical student, was told that he would be given an oral examination in physiology within a few minutes. During rectangle B, he was given an oral examination. During rectangle C, personal remarks were made about an acquaintance of the subject. Though he showed no outward signs of emotion, forearm blood flow increased considerably.

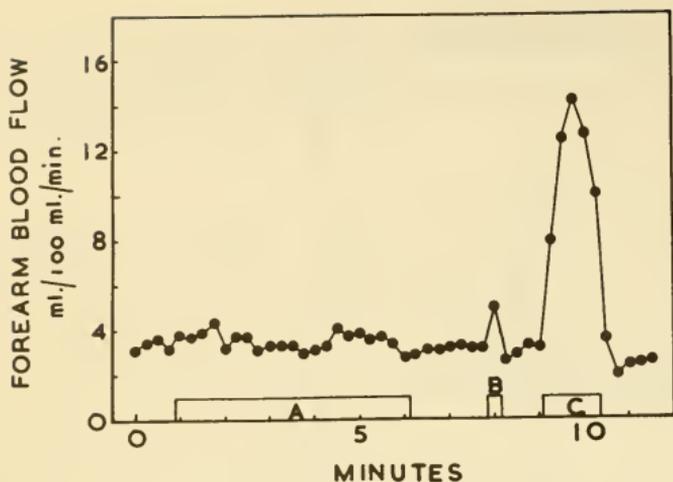


Figure 5. Forearm blood flow during emotional stress. During rectangle A, the subject, a departmental head, was given mental arithmetic to do. During B, he was led to believe that boiling water was being poured on his hand, and during C, he was told that a fire had broken out in his office.

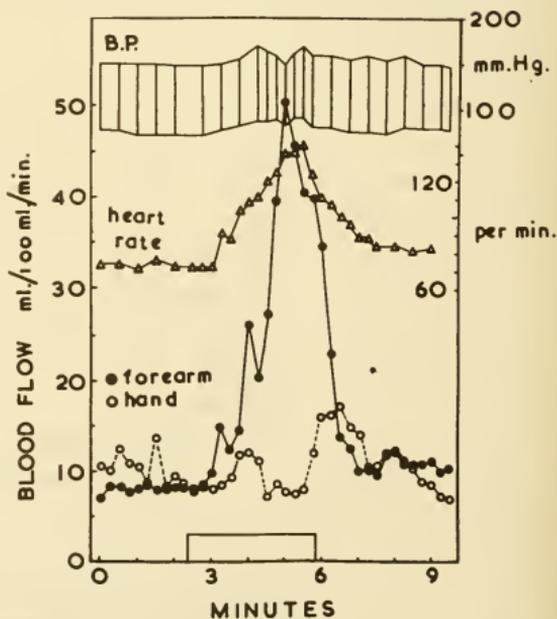


Figure 6. Effect of severe emotional stress on arterial pressure, heart rate, forearm blood flow, and hand blood flow. During the time represented by the rectangle, it was suggested to the subject that he was suffering from severe blood loss (After Blair et al., *J. Physiol. (Lond.)*, 148:633, 1959).

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cervical sympathectomy (Fig. 8). It was not affected by blocking only the cutaneous nerves to the forearm. The following observations suggested that the vasomotor contribution was mediated through activity of cholinergic vasodilator fibres rather than release of vasoconstrictor tone. In some cases emotional stress produced a greater vasodilation in the normal forearm than in the contralateral nerve-blocked forearm. The vasodilation was reduced and occasionally abolished by atropinizing the test forearm (Fig. 9). Bretylium tosylate, in doses which abolished reflex vascular reactions usually attributed to alterations in vasoconstrictor tone in muscle, did not affect the vasodilation during stress. It was concluded that cholinergic vasodilator fibres are distributed to human skeletal muscle and that they are activated during emotional stress.

It has been suggested that generalized vasodilator activity at the beginning of exercise might help to adapt the circulation to the circulatory needs of exercise rapidly (Uvnas, 1954). In an attempt to determine the part played by vasomotor fibres in the limbs in the general circulatory response to exercise, blood flow was measured in the hands and forearms of recumbent subjects during leg exercise on a bicycle ergometer (Blair, Glover, and Roddie, 1961). Exercise resulted in a considerable increase in vasoconstrictor tone in muscle but there was no evidence that discharge of vasodilator fibres was an integral part of the general vasomotor response to exercise. In inexperienced subjects vasodilator discharge was occasionally seen during exercise but it is likely that this discharge was due to associated emotional stress. Emotional stress may also contribute to the muscle vasodilation described during fainting (Barcroft and Edholm, 1945).

### Vasomotor Nerves to Skin

Because of the relative ease with which estimation of blood flow can be made in the hand or foot, the vascular innervation of the extremities has been extensively studied. However, it should be stressed that the vasculature of the hand and foot are very highly specialized and adapted to serve temperature regulation. Many false

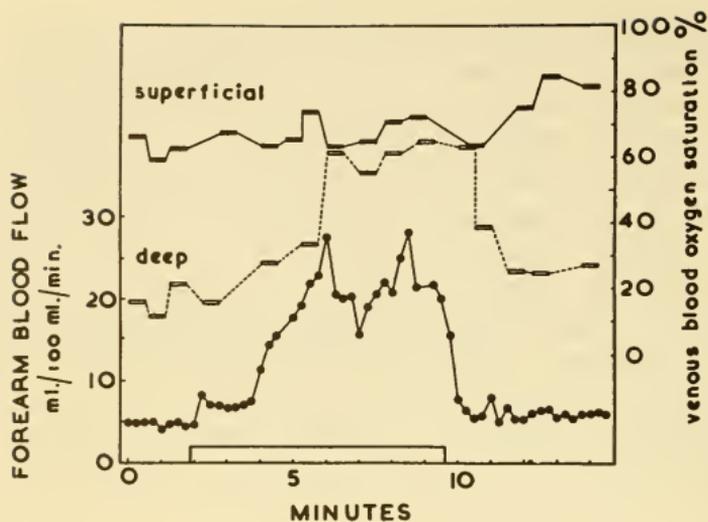


Figure 7. Oxygen saturation of blood from superficial forearm veins  $\blacksquare$  and deep forearm veins  $\square$ ; forearm blood flow in the opposite forearm  $\bullet$ . During the time represented by the rectangle, it was suggested to the subject that he was suffering from severe blood loss. (After Blair et al., *J. Physiol. (Lond.)* 148:633, 1959).

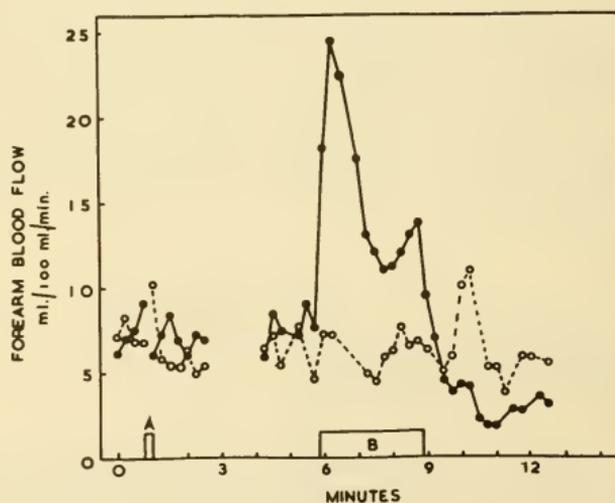


Figure 8. Effect of stress on bloodflow through a normal  $\bullet$  and a sympathectomized  $\circ$  forearm. At A, the subject performed a Valsalva manoeuvre, and during B, a mental arithmetic problem was given. (After Blair et al., *J. Physiol. (Lond.)* 148:633, 1959).

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impressions of vasomotor regulation in the body have been gained by considering vasomotor responses in the hand to be representative of those occurring in other tissues. It is now quite clear that the conclusions from experiments on hand skin cannot be extrapolated to forearm skin, let alone to the other tissues of the body. For this reason it is convenient to consider the innervation of different skin areas separately from that of hand skin.

Forearm skin. Vasomotor innervation of forearm skin can be conveniently demonstrated by the type of experiment illustrated in Figure 10. Blood flow was measured by venous occlusion plethysmography in both forearms of a comfortably warm subject. At the beginning of the experiment the level of blood flow was similar on the two sides. When the cutaneous nerves to one forearm were blocked, there was little change in the level of flow on that side relative to that on the control side. This indicated that the cutaneous vessels are not subjected to any appreciable vasoconstrictor or vasodilator tone when the subject is comfortably warm (Edholm, Fox and Macpherson, 1957). When the subject was then cooled, by directing a fine spray of cold water over his chest and abdomen, the blood flow on the innervated side fell to a lower level than that on the nerve-blocked side. This result indicated that cutaneous vessels are innervated with vasoconstrictor fibres which are active in temperature regulation (Roddie, Shepherd, and Whelan, 1957a). It has recently been shown (Blair, Glover, Kidd, and Roddie, 1960) that these fibres are adrenergic, since the vasoconstriction of forearm skin on cooling the body can be prevented by intra arterial infusion of bretylium tosylate.

When a recumbent subject is comfortably warm, the rate of blood flow through the forearm is about 4-5 ml/100ml/min. Cooling the body causes flow to fall to about 1.5 to 2.5 ml/100ml/min, and as indicated above, this reduction is due to activity of vasoconstrictor fibres. A reduction of the same order is produced by suppression of the skin circulation by iontophoresis of epinephrine into the skin (Cooper, Edholm, and Mottram, 1955). It is likely, therefore, that vasoconstrictor nerves to the forearm skin, like those to the hand skin, can stop the flow of blood through the skin tissue completely.

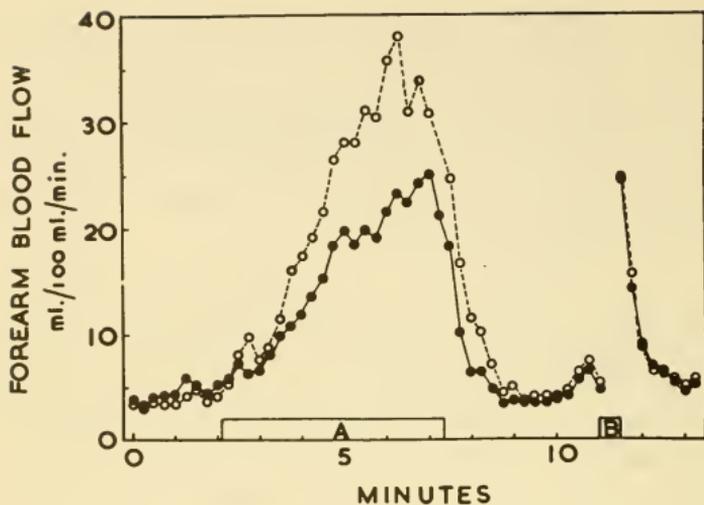


Figure 9. The effect of atropine on the increase in forearm blood flow during stress. The rectangle A represents the period of stress; at B, the circulation to both forearms was arrested for two min. o, normal forearm; ●, atropinized forearm. (After Blair et al., *J. Physiol. (Lond.)*. 148:633, 1959).

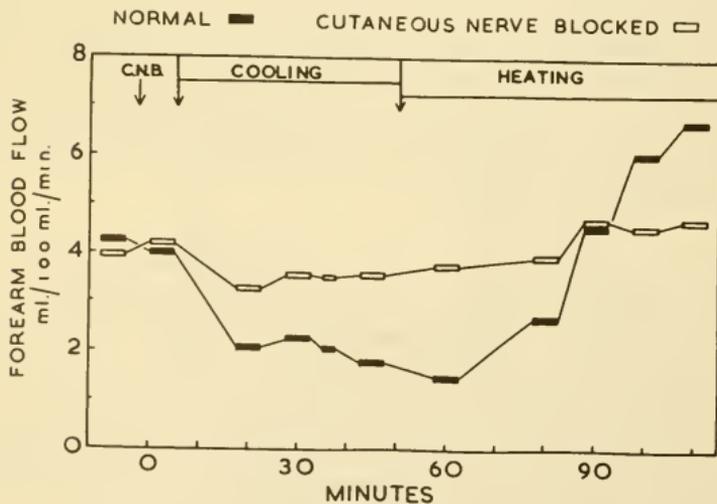


Figure 10. The effects of body cooling and heating on blood flow in the normal and the cutaneous nerve-blocked forearm. C. N. B.; cutaneous nerves on left side blocked with local anaesthetic. (After Blair, Glover, and Roddie, *J. Physiol. (Lond.)*. 153:232, 1960).

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When the subjects were heated, the bloodflow on the innervated forearm rose substantially above that in the forearm where cutaneous nerves were blocked. This increase could not be explained by release of vasoconstrictor tone and indicated that forearm skin vessels had a vasodilator nerve supply. A clue to the way these vasoconstrictor and vasodilator fibres work together was obtained by experiments of the type illustrated in Figure 11. Forearm and hand blood flow were simultaneously measured and at the beginning of the experiment the subject was cold. When the subject was heated, the pattern of vasodilation in the forearm differed from that in the hand (Roddie, Shepherd, and Whelan, 1957b). The increase in forearm flow occurred in two phases. The first increase, a very small fraction of that attainable by heating, occurred synchronously with the precipitous increase in hand blood flow. This increase, like that in the hand, was not affected by atropinization of tissues (Fig. 12) and it is possibly due to release of vasoconstrictor tone. The second phase of the forearm vasodilation, which comprises the major part of that attainable by heating, occurred at a time when the hand blood flow had reached its maximum and when sweating in the forearm had commenced. Atropinization of the forearm delayed and reduced this phase, suggesting that the mechanism responsible was at least in part cholinergic.

This close association of the second phase with the onset of sweating suggested that the vasodilation might be linked in some way with sweat gland activity, a situation analogous to that seen in the functional vasodilation in the submandibular salivary gland (Hilton and Lewis, 1955). There is now evidence that the vasodilation in forearm skin during body heating may be due to products released during sweat gland excitation rather than to the excitation of specific vasodilator nerve fibres. Fox and Hilton (1956, 1958) found that sweat collected from the hand and forearm contained bradykinin-forming enzyme. They also found that the amount of bradykinin in the subcutaneous tissue spaces increased during body heating (Figs. 13 and 14). They suggested that bradykinin-forming enzyme was a normal product of sweat gland activity, and that it could escape from the gland to act on the protein in the subcutaneous tissue space to form bradykinin. They considered that the bradykinin thus formed might contribute to the cutaneous vasodilation. Be that as it may, it does not affect the general conclusion that the

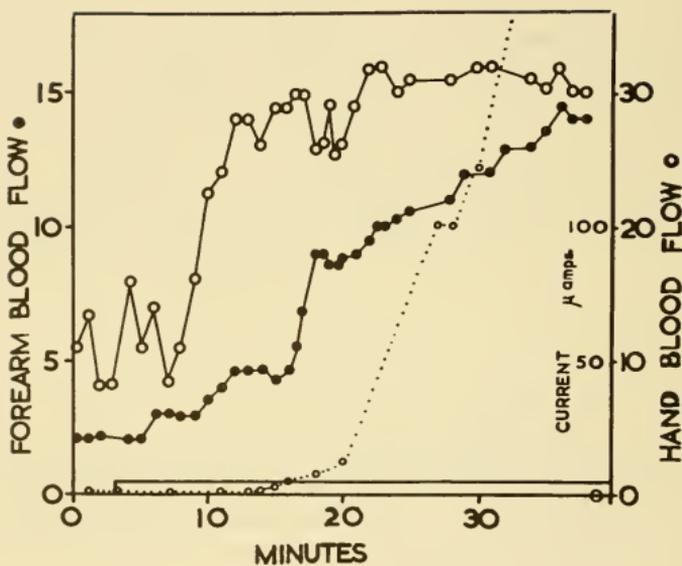


Figure 11. Forearm and hand blood flow before and during body heating. The rectangle represents the period of body heating. Forearm flow, ●; hand flow in ml/100 ml/min, ○; current ( $\mu A$ ) flowing through the forearm skin as an index of sweat gland activity, ○. (After Roddie, Shepherd, and Whelan, *J. Physiol. (Lond.)*, 136: 489, 1957).

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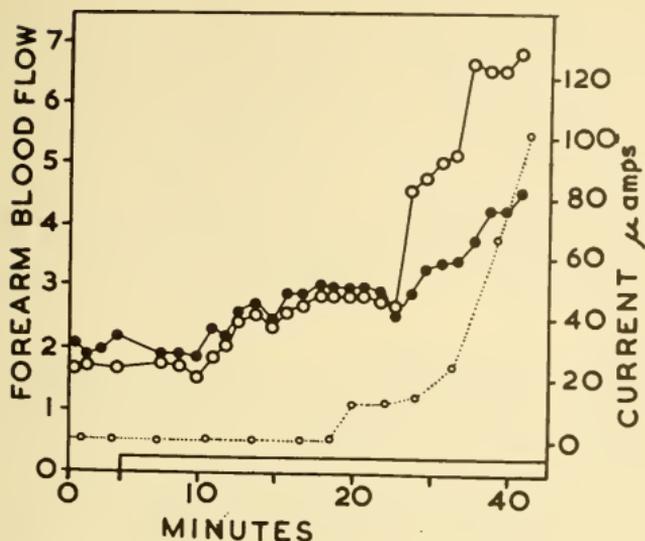


Figure 12. Forearm blood flow before and during body heating. Control forearm, O ; atropinized forearm, ● ; current as in Figure 11, o . Immediately before observations commenced 0.3 mg atropine sulphate was given. The open rectangle represents the period of heating. (After Roddie, Shepherd, and Whelan, *J. Physiol. (Lond.)*. 136:489, 1957).

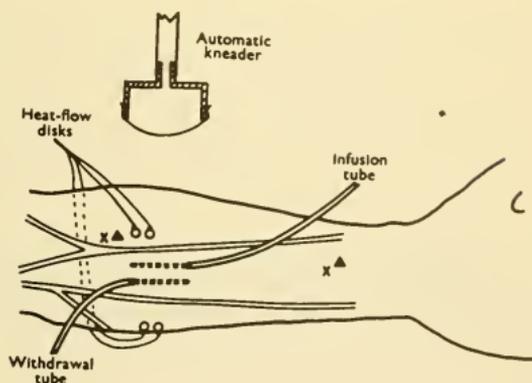


Figure 13. Experimental setup used to sample tissue fluid from the subcutaneous tissue space in the forearm. (After Fox and Hilton, *J. Physiol. (Lond.)*. 142:219, 1958).

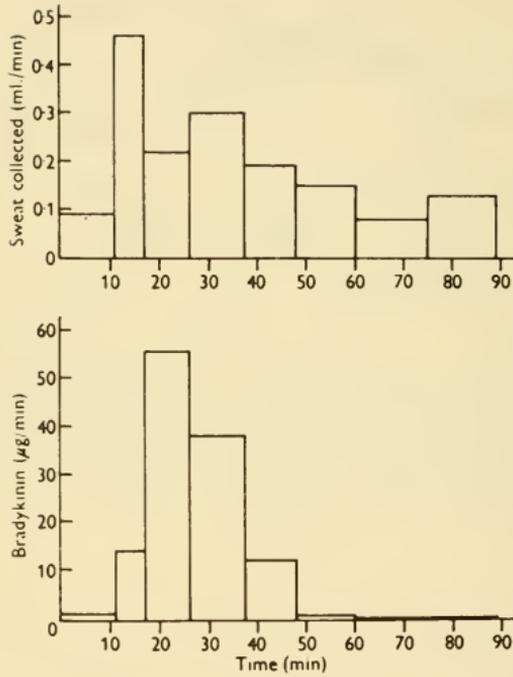


Figure 14. Histograms of the amounts of sweat collected from a human forearm during a period of body heating and of the corresponding bradykinin-forming activity of each sample. (After Fox and Hilton, *J. Physiol. (Lond.)*, 142:219, 1958).

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cutaneous vasodilation in the forearm during body heating, unlike that in the hand, is not due to release of vasoconstrictor tone, but rather to an active vasodilator mechanism, mediated through fibres running with the cutaneous nerves. It has recently been shown that the vasomotor innervation of upper arm, calf, and thigh skin is qualitatively similar to that in the forearm (Blair, Glover, and Roddie, 1960), but there is no evidence that the vasomotor fibres to these areas are involved in any but temperature regulatory reflexes.

Hand skin. The blood vessels in the hand are normally subjected to a high degree of vasoconstrictor tone. Blocking the nerves to the hand with local anesthetic normally increases the blood flow through the hand from its normal range of about 3 to 10 ml to about 30 to 40 ml/100ml/min (Fig. 15). Body heating causes a large reflex vasodilation in the hand, but this increase can be explained entirely by release of vasoconstrictor tone. Despite the evidence for vasodilator innervation to the hands of patients with Raynaud's disease (Lewis and Pickering, 1931), careful investigation has failed to provide any evidence that such fibres are activated during body heating in normal individuals. During heating the blood flow in a normal hand does not exceed that in a nerve-blocked hand (Arnott and Macfie, 1948; Gaskell, 1956; Roddie, Shepherd, and Whelan, 1957c) and atropinization of the hand does not reduce the vasodilation (Gaskell, 1956; Roddie, Shepherd, and Whelan, 1957b).

It seemed possible that the body of the hand might show an intermediate stage between the fingers, with predominantly vasoconstrictor innervation, and the forearm skin, with predominantly vasodilator innervation. Experiments of the type described above were therefore carried out, in which blood flow through the body of the hand was measured by venous occlusion plethysmography, the circulation being arrested by rubber bands at the base of each digit (Fig. 16). However, the body of the hand behaved as did the whole hand (Roddie, Shepherd, and Whelan, 1957b). The skin of the hand seems to function as a distinct unit in regard to vasomotor innervation and there is an abrupt transition to a different type of vasomotor control somewhere about the wrist.

However, acetylcholine has been obtained from extracts of human digital arteries and cholinesterase has been identified in

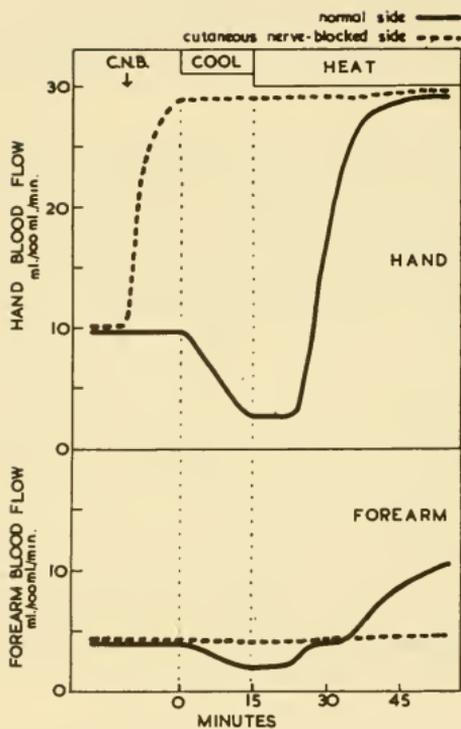


Figure 15. Schematic representation of the changes in blood flow in the normal and nerve-blocked hand and forearm during body cooling and heating. At C. N. B., the vasomotor nerves to the hand and to the forearm skin were blocked with local anesthetic solution.

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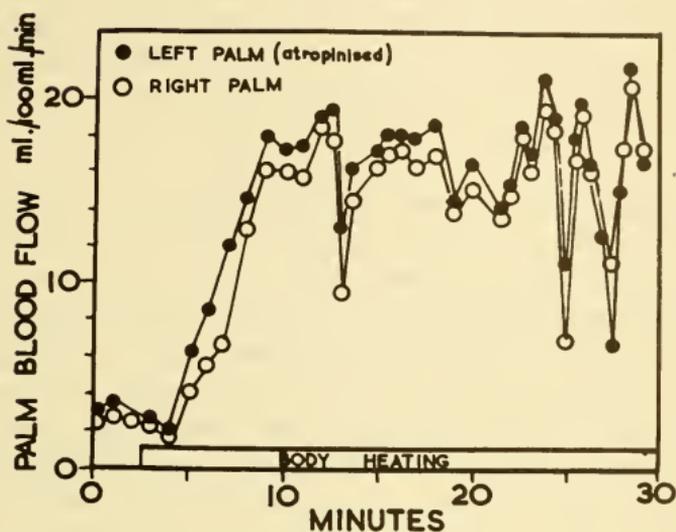


Figure 16. Blood flow through the bodies of the hands, before and during indirect heating. The circulation to the digits was arrested throughout by rubber bands applied around the base of each digit. Control hand, o ; experimental hand, • . Atropine sulphate (0.3 mg) was infused into the brachial artery on the experimental side immediately before observations commenced. (After Roddie, Shepherd, and Whelan, *J. Physiol. (Lond.)*. 136:489, 1957).

sections of digital skin (Hurley and Mescon, 1956; Armin et al, 1953). Recently, Allwood et al (1960) have found an increase in hand blood flow in subjects exposed to a mental arithmetic test. Quite large vasodilations were seen in some patients who suffered from hyperhydrosis. Emotional stress is known to cause sweating in the hand, and it is possible that sweat gland activity, by leading to the formation of bradykinin-forming enzyme, may contribute to this type of vasodilation. It does not seem however, that cholinergic vasodilator fibres play an important part in the reflex changes in hand blood flow seen in normal individuals.

Though vasoconstrictor fibres to the hand obviously play a large part in temperature regulatory reflexes, their activity is greatly influenced by trivial and often inappropriate stimuli. The high degree of reactivity which hand blood vessels normally exhibit has made the study of vascular reflexes very difficult. If a subject sees the door of the laboratory being opened, his hand blood flow frequently falls to zero. Inflating a pneumatic cuff on one arm (Roddie, 1951) or taking a deep breath (Bolton, Carmichael, and Sturup, 1936) causes a highly significant vasoconstriction in the hand. This is especially true in the untrained subject. It is therefore practically impossible to tell whether the vasoconstriction which often occurs in the hand during, say, carbon dioxide inhalation (Gellhorn and Steck, 1938), exercise (Blair et al, 1961a; Muth et al, 1958), or positive pressure breathing (Fenn and Chadwick, 1947) is a specific response to a particular stimulus, or merely the normal sequence of the psychic disturbance which the stimulus unavoidably causes. Nevertheless, careful studies would suggest that these fibres are not involved in postural reflexes (Beaconsfield and Ginsburg, 1955) nor those associated with intra thoracic pressure changes (Roddie et al, 1958).

To summarize, the blood vessels of the extremities of the limbs are normally subjected to a high degree of vasoconstrictor tone even though the subject is comfortably warm. The very large increase in hand blood flow during body heating seems due entirely to release of vasoconstrictor tone, and there is no evidence that vasodilator fibres contribute to this increase. In the forearm skin the cutaneous vessels are not subjected to appreciable vasomotor influence when the subject is comfortably warm. Cooling the subject causes flow to fall due to vasoconstrictor fibre activity.

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Head and trunk skin. There is little information about the innervation of skin in the head and trunk, mainly because of the great technical difficulty of estimating cutaneous blood flow in these areas with precision. An attempt has been made, however, to study the vasomotor innervation of these parts using skin temperature changes to estimate blood flow changes in the skin (Blair, Glover, and Roddie, 1961a). The use of skin temperature as measure of skin blood flow has well known limitations. The relationship between the two quantities is not linear, and at high skin temperatures large increases in blood flow can occur without increases in skin temperature. Where the skin overlies a large mass of tissue, the skin temperature may reflect the temperature of the tissue mass more than the circulation through the skin. In addition, changes in skin temperature may reflect changes in the circulation distal to the site of measurement except when the measurement is made at the extremities. Nevertheless the method has the merit of simplicity, so that observed differences in skin temperature are unlikely to be due to instrumental or technical difficulties. This facilitates comparison of circulatory changes in symmetrical skin areas on both sides of the body.

It was found that nose skin behaved rather like finger skin; cooling the body caused a much larger fall in the nose and finger skin temperature than in body temperature, indicating active vasoconstriction in these areas. In the ear, cheek, chest, and forehead there was no evidence for vasoconstriction during cooling. When the body was heated, however, evidence of vasodilation was found in all these skin areas. When the vasomotor nerves to the ear were blocked, there was a large increase in skin temperature, and the increase in ear temperature during body heating did not exceed this level (Fig. 17). It was concluded that the changes in ear blood flow subserving temperature regulation are mainly due to alterations in vasoconstrictor tone. In the cheek and chest, cutaneous nerve-block did not alter skin temperature yet reduced the rise in skin temperature normally seen during body heating (Fig. 18). It was concluded that the vasodilation in these areas is not due to release of vasoconstrictor tone, but rather to an active vasodilator mechanism mediated through fibres running with the cutaneous nerves.

This work is still incomplete and is unsatisfactory in many respects. Most of the skin in the body is still uncharted as regards

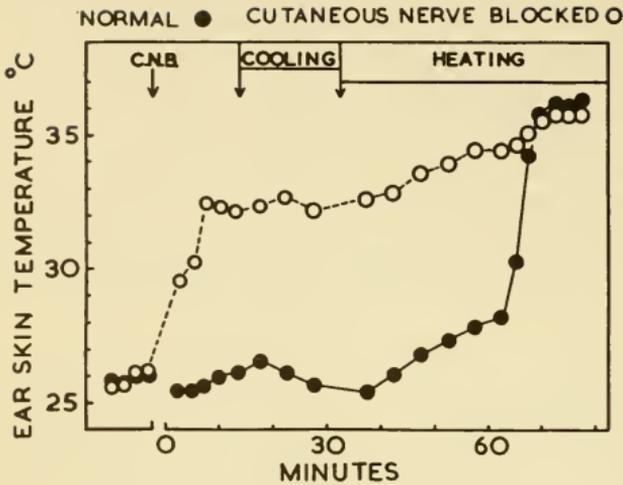


Figure 17. Changes in the skin temperature of the normal and nerve-blocked ear during body cooling and heating. At C. N. B., the great auricular nerve to one side was blocked as it appeared behind the posterior border of the sternomastoid muscle. (After Blair, Glover, and Roddie, *J. Appl. Physiol.*, 16:119, 1961).

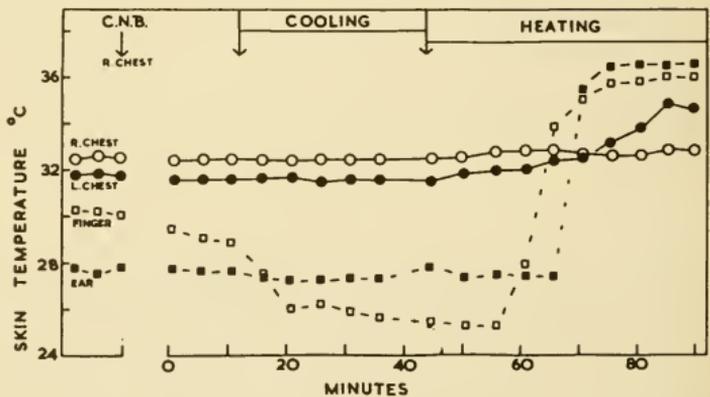


Figure 18. Changes in the skin temperature of the normal and nerve-blocked chest during body cooling and heating. At C. N. B., the supraclavicular nerves supplying the skin of the right chest were blocked with local anaesthetic. (After Blair, Glover, and Roddie, *J. Appl. Physiol.*, 16:119, 1961).

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vasomotor innervation and it will not be possible to explore these areas adequately until a technique is devised which permits precise and quantitative measurement of skin blood flow over large tissue masses.

### SUMMARY

Recent experiments suggest that human skeletal muscle has both an adrenergic vasoconstrictor and a cholinergic vasodilator innervation. The former take part in certain baroreceptor and chemoreceptor reflexes, whereas the latter take part in the circulatory adaptations during emotional stress. Both sets of fibres can be activated independently of each other, and also independently of those supplying skin blood vessels. The chief vasomotor innervation of the extremities is vasoconstrictor. Here the vessels are normally subjected to a high degree of vasoconstrictor tone, and the reflex changes in blood flow which occur during temperature regulation can be explained by alterations in vasoconstrictor tone. The skin of the proximal parts of the limbs is not subjected to any appreciable vasoconstrictor or vasodilator tone when the subject is comfortably warm. However, during body cooling, the vessels constrict, due to vasoconstrictor fibre activity, and during body heating, they dilate, due to an active vasodilator mechanism mediated through fibres running with the cutaneous nerves.

DISCUSSION

DR. HENSEL: I have a question concerning the method of monitoring the skin temperature. You have just stressed the drawbacks of skin temperature measurement as a measure of blood flow; in your last figure, you showed three different increases, the highest increase in the finger and medium in the ear and then in the chest; and you started with three different initial temperatures. As I saw, the finger was about  $25^{\circ}\text{C}$ , the ear was  $28^{\circ}\text{C}$ , and the chest  $22^{\circ}\text{C}$ . So, the increase in skin temperature is a function of the initial temperature. If you have the same increase in blood flow, you get a higher increase in skin temperature, the lower the initial temperature. It is extremely difficult to draw any quantitative conclusions. The skin temperature cannot rise more than to  $36^{\circ}\text{C}$  or something like that.

DR. RODDIE: I would agree with this. I think that this can only be a first approach.

DR. HENSEL: Yes, and I would suggest trying this again with the heated thermocouple technique which can be used for quantitative evaluation of the skin.

DR. RODDIE: Actually, we have tried that and we were not completely happy. The reason for this was that the heat elimination which they record depends so much on the actual positioning of the heated thermocouple on the skin, that we felt it was difficult to compare absolute values on two sides of the body. If we found a slight difference in flow after heating, couldn't this be due to slight movement of the thermocouple?

DR. HENSEL: What type of heated thermocouple did you use, the type with a wire or with a plate?

DR. RODDIE: We used the type with the plate.

DR. HENSEL: I think it should work if properly applied.

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DR. RODDIE: Yes, but, as you know, some places when you apply it to the skin, you seem to get a greater sensitivity than in other places on the skin. And this does make it difficult to compare the absolute levels after a period of heating.

DR. HENSEL: Did you measure the zero value?

DR. RODDIE: No. You cannot really do that on the chest.

DR. HENSEL: Yes, you can do that. A balloon works very well. You get a zero flow and then you can check it quantitatively. I think you should try that.

DR. RODDIE: Well, I think so, this definitely needs a better method of measuring skin blood flow.

DR. HENSEL: May I add a second question? I had some difficulties in understanding your conclusion concerning the inhibition of vasoconstrictor tone during raising the legs. You have drawn this conclusion by the failure of atropine.

DR. RODDIE: Yes. We have.

DR. HENSEL: And afterwards, you showed that there might be some evidence for a non-cholinergic dilator mechanism. So, I would think your first conclusion is not correct.

DR. RODDIE: When the legs were raised, a vasodilation occurred in the muscle.

DR. HENSEL: Yes. It did.

DR. RODDIE: No matter how high the legs were raised, the blood flow on the normal side did not rise above that on the opposite nerve-blocked side.

DR. HENSEL: And you did not get any higher level as found in nerve blocking?

DR. RODDIE: No. We did not.

RODDIE, I. C.

DR. HENSEL: Yes. I think that in the experiment with mental arithmetic there is quite strong evidence for a non-cholinergic vasodilator mechanism. Gollenhofen found in many cases by giving very high doses of atropine the effect is only very slightly decreased if at all. So I think the amount of non-cholinergic vasodilator fibres might be quite considerable.

DR. RODDIE: Yes, I think this varies quite a lot from stimulus to stimulus because we found an enormous variation in the reduction in the vasodilatation during emotional stress that we could obtain by atropine. Sometimes it was negligible with the lesser degrees of fright, but usually when we had genuine fear it was larger.

DR. HENSEL: It is difficult with your method; you can only call the ambulance car one time!

DR. MINARD: I would like to ask what the effect of norepinephrine is on blood vessels to muscle.

DR. RODDIE: If you give norepinephrine intra-arterially to one forearm, after a transient increase in flow in the forearm, vasoconstriction occurs, and this persists as long as the infusion lasts.

DR. MINARD: I am interested then in how this blocking agent acts. You say you block the vasodilator effect by means of this blocking agent?

DR. RODDIE: Yes, bretylium tosylate is now being used for hypertension. It is taken up specifically by the noradrenergic nerve fibres where it acts as a local anaesthetic. With sufficient dosage, it apparently will block practically all fibres but with the right critical dosage, it blocks mainly the adrenergic fibres. It is quite a useful tool and is the best sympathetic adrenergic block that we have used. It does not block the effect of circulating epinephrine or norepinephrine, just the nerve fibres.

DR. HEMINGWAY: The evidence for vasodilator fibres goes way back to the time of Thomas Hood. In a blocked nerve, in an area where the nerve is blocked, the blood flow is less than as a result of local heating.

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DR. RODDIE: Yes, that is correct. That was seen on the fingers of patients with Raynaud's disease, but they were never able to demonstrate this on normal people. This question has been pursued quite hotly ever since because it seemed unreasonable that this type of fibre should be confined to these patients.

DR. HEMINGWAY: Well, my point is, will the release of bradykinin, which has been used as evidence for the existence of vasodilator nerves, explain that?

DR. RODDIE: I suppose it is possible, if these patients with Raynaud's disease were rather anxious people and were upset by the procedures that Sir Thomas first subjected them to. This could account for a vasodilatation on the normal side and the absence of a vasodilatation on the nerve blocked side.

DR. HEMINGWAY: Well, the other thing I am trying to get at is this; is it necessary to postulate the existence of vasodilator fibres if you have the bradykinin mechanism?

DR. RODDIE: No, but there has been this difficulty of what to call these fibres. A fibre is a vasodilator if you think that there is only one intermediary. Now, it is very difficult to prove that there is only one intermediary. I, personally, think it would be better not to call these fibres to skin "vasodilator", but it is hard to think of a concise alternative.

DR. HEMINGWAY: It is an old, old argument, you know. All the evidence is rather indirect for the existence of the vasodilator.

DR. RODDIE: I think so. Of course, this criticism applies to the muscle vasodilators, too. One thinks that the acetylcholine released at the nerve ending acts directly on the blood vessels and it is possible that acetylcholine acts on some cell, which in turn produces an agent which acts on blood vessels.

MR. EAGAN: I believe the term you used was vasodilator mechanism.

DR. RODDIE: Yes, but that sometimes confuses people, too.

RODDIE, I. C.

DR. FREEMAN: How do you account for the absence of this mechanism in the palm of the hand?

DR. RODDIE: This is difficult. Fox and Hilton believe that in the hand, release of vasoconstrictor tone permits such a large increase in flow that the effect of bradykinin cannot be picked up by present techniques.

DR. FREEMAN: Have they also considered the possibility that local metabolites of the same sort as are produced in other active tissues might be responsible for vasodilatation in the skin?  $\text{CO}_2$  is probably the best example produced in the brain.

DR. RODDIE: That will not quite fit since increase in the blood flow which this substance or this mechanism produces is very much greater than is necessary for the demands of the metabolic needs of the tissues. When the body is heated, the oxygen saturation of the efferent venous blood from the skin rises to practically full saturation.

DR. HANNON: These two areas are normally exposed, whereas the skin of the forearm is covered. Is there a possibility that you might get some different response in a native living in the tropics who had his forearm skin exposed?

DR. RODDIE: I do not know of any evidence that would support this. We have looked at a very narrow group of people, Irish medical students, and ourselves, but have not really extended it beyond that.

MR. EAGAN: I believe that Edholm, Fox, and McPherson, in their first experiments had concluded that there was no vasoconstrictor control to forearm skin. Now, was this because they just did not start with cooled subjects so that they were at the neutral zone in the beginning?

DR. RODDIE: Yes, that is it. In Belfast, where we are used to rather colder conditions than in London, when we blocked the nerves, our subjects were usually sufficiently cold to show some release of vasoconstrictor tone.

DR. FREEMAN: Perhaps to change the subject a little bit, Dr. Hannon's question brings up the general notion of how great a role

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conditioning process plays in these vasomotor reactions. Have you ever had any experience along those lines? I realize your patients are oftentimes one-shot deals, so they do not have much time for learning.

DR. RODDIE: Well, we find that the more we train the subjects, the more stable are their blood flows. We have difficulty with people who are brought to us for the first time. However, you can condition people. Certainly you can condition the vasodilation of the forearm muscle during stress quite easily. However, when an experiment is done which involves repeated infusion of a certain drug, you can often see this increase in flow as the clock comes around to the time when the infusion should start. Whether this is conditioning or apprehension I am not sure.

DR. FREEMAN: Maybe they are the same, basically?

DR. RODDIE: Yes.

DR. FREEMAN: What is your interpretation of blushing?

DR. RODDIE: Blushing is not understood. I think it means that there is a vasodilator nerve supply to the face and ears. We have looked at this a little bit during the experiments in emotional stress. During blushing, the vessels in the skin of the face and the ear dilate whereas in the skin of the fingers they will constrict. But it is very hard to devise a stimulus which will produce a blush repetitively, and we find that when we are trying to devise these things that we blush more than the subject.

DR. HANNON: One other point here, you stated correctly that the skin is concerned with cold exposure with control of heat loss. There is also, in prolonged cold exposure, the possibility that the muscles can affect, not heat loss, but heat production, and there is some evidence of an increase in circulation of muscle that is not tied to heat production. I believe that Canadian workers have worked on this.

DR. RODDIE: Yes.

DR. FREEMAN: Dr. Stuart and I were wondering the other day just how much thermo-responsiveness these vasomotor areas have in the spinal animal.

DR. RODDIE: I have really no information about that at all.

DR. FREEMAN: One of the old-fashioned neurological reflexes that can be elicited in a spinal man is erection of pilomotor, that is, goose flesh. If nociceptive stimulus is applied to the foot, let us say, and one can evoke goose flesh all over the lateral extremity, this would imply that there are some mass reflex type activities which may not be specifically related to goose flesh. Those mechanisms are still there, but they are not tied into the right stimulus. There is obvious vasomotor activity of some sort, but is it related to temperature changes? Have you had any experience on this, Dr. Hensel?

DR. HENSEL: No. Another question. How did you test the effectiveness of your atropine infusion?

DR. RODDIE: By giving an infusion of acetylcholine before and afterwards. The effect of acetylcholine will be abolished after infusion. In addition, in the heating experiment, we could tell how long the atropine was effective by the length of time we were able to abolish sweating.

DR. HENSEL: Did you test with acetylcholine in the heating experiments?

DR. RODDIE: Yes, the vasodilation which occurs in the skin is depressed and delayed by atropine. However, it is not abolished. Rather, as in the sub-mandibular salivary gland, it is still detectable. However, even at a time when the blood flow in the forearm is rapidly rising, we still find that the effect of injected acetylcholine is still abolished. The situation in the skin, therefore, seems to be analogous to that seen in the sub-mandibular salivary gland.

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### REFERENCES

1. Abrahams, V. C. and S. M. Hilton. Active muscle vasodilatation and its relationship to the 'fight or flight' reactions in the conscious animal. *J. Physiol. (Lond)*, 140:16P, 1957.
2. Abramson, D. I. Vascular responses in the extremities of man in health and disease. Chicago, Univ. of Chicago Press, 1944.
3. Abramson, D. I. and F. B. Ferris. Responses of blood vessels in the resting hand and forearm to various stimuli. *Am. Heart J.*, 19:541, 1940.
4. Allwood, M. J., H. Barcroft, J. P. L. A. Hayes, and E. A. Hirsjarvi. The effect of mental arithmetic on the blood flow through normal, sympathectomized and hyperhydrotic hands. *J. Physiol. (Lond.)*, 148:108, 1960.
5. Anderson, D. P., W. J. Allen, H. Barcroft, O. G. Edholm, and G. W. Manning. Circulatory changes during fainting and coma caused by oxygen lack. *J. Physiol. (Lond.)*, 104:426, 1946.
6. Armin, J., R. T. Grant, R. H. S. Thompson, and A. Tickner. An explanation for the heightened vascular reactivity of the denervated rabbit's ear. *J. Physiol. (Lond.)*, 121:603, 1953.
7. Arnott, W. M. and J. M. Macfie. The effect of ulnar nerve block on the blood flow in the reflexly vasodilated digit. *J. Physiol. (Lond.)*, 107:233, 1948.
8. Barcroft, H., K. D. Bock, H. Hensel and A. H. Kitchin. Die Muskeldurchblutung des Menschen bei indirekter Erwärmung und Abkühlung. *Pflüger's Arch. ges Physiol.*, 261:199, 1955.
9. Barcroft, H., W. McK. Bonnar and O. G. Edholm. Reflex vasodilatation in human skeletal muscle in response to heating the body. *J. Physiol. (Lond.)*, 106:271, 1947.

10. Barcroft, H., W. McK. Bonnar, O. G. Edholm, and A. S. Effron. On sympathetic vasoconstrictor tone in human skeletal muscle. *J. Physiol. (Lond.)*, 102:21, 1943.
11. Barcroft, H. and O. G. Edholm. On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. *J. Physiol. (Lond.)*, 104:161, 1945.
12. Beaconsfield, P. and J. Ginsburg. The effect of body posture on hand blood flow. *J. Physiol. (Lond.)*, 130:467, 1955.
13. Blair, D. A., W. E. Glover, A. D. M. Greenfield, and I. C. Roddie. Excitation of cholinergic vasodilator nerves to skeletal muscle during emotional stress. *J. Physiol. (Lond.)*, 148:633, 1959.
14. Blair, D. A., W. E. Glover, and B. S. L. Kidd. The effect of continuous positive and negative pressure breathing upon the resistance and capacity blood vessels in the human forearm and hand. *Clin. Sci.* 18:9, 1959.
15. Blair, D. A., W. E. Glover, B. S. L. Kidd, and I. C. Roddie. Peripheral vascular effects of bretylium tosylate in man. *Brit. J. Pharmacol.*, 15:466, 1960.
16. Blair, D. A., W. E. Glover, and I. C. Roddie. Vasomotor fibres to skin in the upper arm, calf, and thigh. *J. Physiol. (Lond.)*, 153:232, 1960.
17. Blair, D. A., W. E. Glover, and I. C. Roddie. Vasomotor responses in the human arm during leg exercise. *Circulation Res.* 9:264, 1961.
18. Blair, D. A., W. E. Glover, and I. C. Roddie. Cutaneous vasomotor nerves to the head and trunk. *J. Appl. Physiol.* 16:119, 1961a.
19. Bolton, B., E. A. Carmichael, and G. Sturup. Vasoconstriction following deep inspiration. *J. Physiol. (Lond.)*, 86:83, 1936.

## CONTROL OF PERIPHERAL CIRCULATION

20. Brigden, W., S. Howarth, and E. P. Sharpey-Shafer. Postural changes in the peripheral blood flow of normal subjects. *Clin. Sci.*, 9:79, 1950.
21. Cooper, K. E., O. G. Edholm, and R. F. Mottram. The blood flow in skin and muscle of the human forearm. *J. Physiol. (Lond.)* 128:258, 1955.
22. Edholm, O. G., R. H. Fox, and R. K. MacPherson. Effect of body heating on the circulation in skin and muscle. *J. Physiol. (Lond.)*, 134:612, 1956.
23. Edholm, O. G., R. H. Fox, and R. K. MacPherson. Vasomotor control of the cutaneous blood vessels in the human forearm. *J. Physiol. (Lond.)*, 139:455, 1957.
24. Fenn, W. O. and L. E. Chadwick. Effect of pressure breathing on blood flow through the finger. *Am. J. Physiol.* 151:270, 1947.
25. Fox, R. H. and S. M. Hilton. Sweat gland activity as a contributory factor to heat vasodilatation in the human skin. *J. Physiol. (Lond.)*, 133:68P., 1956.
26. Fox, R. H. and S. M. Hilton. Bradykinin formation in human skin as a factor in heat vasodilatation. *J. Physiol. (Lond.)*, 142:219, 1958.
27. Gaskell, P. Are there sympathetic vasodilator nerves to the vessels of the hand? *J. Physiol. (Lond.)* 131:647, 1956.
28. Gellhorn, E. and I. E. Steck. The effect of the inhalation of gases with a low oxygen and an increased carbon dioxide tension on the peripheral blood flow in man. *Am. J. Physiol.* 124:735, 1938.
29. Gollenhofen, K. and G. Hildebrandt. Psychische Einflüsse auf die Muskeldurchblutung. *Pflüger's Arch. ges. Physiol.* 263: 637, 1957.

30. Grant, R. T. and R. S. B. Pearson. The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. *Clin. Sci.*, 3:119, 1938.
31. Hilton, S. M. and G. P. Lewis. The mechanism of the functional hyperaemia in the submandibular salivary gland. *J. Physiol. (Lond.)*, 129:253, 1955.
32. Howard, P. and J. S. Garrow. Changes in the vascular resistance of the forearm and hand during radial acceleration. *J. Physiol. (Lond.)*, 143:83P., 1958.
33. Hurley, H. J. and J. Mescon. Cholinergic innervation of the digital arteriovenous anastomoses of human skin. A histochemical localization of cholinesterases. *J. Appl. Physiol.*, 9:82, 1956.
34. Lewis, T. and G. W. Pickering. Vasodilatation in the limbs in response to warming the body, with evidence for sympathetic vasodilator nerves in man. *Heart*, 16:33, 1931.
35. McArdle, L., I. C. Roddie, J. T. Shepherd, and R. F. Whelan. The effect of inhalation of 30% carbon dioxide on the peripheral circulation of the human subject. *Brit. J. Pharmacol.*, 12:293, 1957.
36. McGirr, E. M. Rate of removal of radioactive sodium following its injection into muscle and skin. *Clin. Sci.*, 11:91, 1952.
37. Muth, H. A. V., P. N. Wormald, J. M. Bishop, and K. W. Donald. Further studies of blood flow in the resting arm during supine leg exercise. *Clin. Sci.* 17:603, 1958.
38. Roddie, I. C. The decrease in hand blood flow following inflation of an arterial occlusion cuff on the opposite arm. *J. Physiol. (Lond.)*, 112:204, 1951.
39. Roddie, I. C. and J. T. Shepherd. The reflex nervous control of human skeletal muscle blood vessels. *Clin. Sci.*, 15:434, 1956.

## CONTROL OF PERIPHERAL CIRCULATION

40. Roddie, I. C. and J. T. Shepherd. Receptors in the high-pressure and low-pressure vascular systems. Their role in the reflex control of the human circulation. *Lancet*, i:493, 1958.
41. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. Evidence from venous oxygen saturation measurements that the increase in forearm blood flow during body heating is confined to the skin. *J. Physiol. (Lond.)*, 134:444, 1956.
42. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. Reflex changes in vasoconstrictor tone in human skeletal muscle in response to stimulation of receptors in a low-pressure area of the intrathoracic vascular bed. *J. Physiol. (Lond.)*, 139:369, 1957.
43. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. The vasomotor nerve supply to the skin and muscle of the human forearm. *Clin. Sci.*, 16:67, 1957. a.
44. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. The contribution of constrictor and dilator nerves to the skin vasodilatation during body heating. *J. Physiol. (Lond.)*, 136:489, 1957. b.
45. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. A comparison of the heat elimination from the normal and nerve-blocked finger during body heating. *J. Physiol. (Lond.)*, 138:445, 1957. c.
46. Roddie, I. C., J. T. Shepherd, and R. F. Whelan. Reflex changes in human skeletal muscle blood flow associated with intrathoracic pressure changes. *Circulation Res.*, 6:232, 1958.
47. Sharpey-Shafer, E. P. Effects of coughing on intrathoracic pressure, arterial pressure and peripheral blood flow. *J. Physiol. (Lond.)*, 122:351, 1953.
48. Sharpey-Shafer, E. P. Effect of Valsalva's manoeuvre on the normal and failing circulation. *Brit. Med. J.*, i:693, 1955.
49. Sharpey-Shafer, E. P. The effects of squatting on the normal and failing circulation. *Brit. Med. J.*, i:1072, 1956.

50. Stein, I. D., K. Harpuder, and J. Byer. Effects of sympathectomy on blood flow in the human limb. *Am. J. Physiol.* 152: 499, 1948.
51. Uvnas, B. Sympathetic vasodilator nerves. *Physiol. Rev.*, 34: 608, 1954.
52. Wilkins, R. W. and L. W. Eichna. Bloodflow to the forearm and calf. 1. Vasomotor reactions: role of sympathetic nervous system. *Johns Hopkins Hosp. Bull.*, 68:425, 1941.
53. Woollard, H. H. and R. Phillips. The distribution of sympathetic fibres in the extremities. *J. Anat.*, 67:18, 1932.

HEAT DISSIPATION FUNCTIONS FOLLOWING  
EXPERIMENTAL ANTERIOR HYPOTHALAMIC LESIONS  
IN CATS

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For the past decade or so there has been a remarkable uniformity in the usual discussions of the central nervous mechanisms for the control of the various processes by which a homeotherm maintains its body temperature within normal limits. The basic theory has been that there are separate regions for integration of those activities which enable an animal to increase the rate of heat loss and for those which promote heat conservation. This proposal was originally made by Myers (1913). Among the important papers which led to partial localization of these centers are those of Ott (1884, 1891, 1895), Isenschmid and Schnitzler (1914), Nikolaides and Dontas (1911) and Keller and Hare (1932). Figure 1 is one method of expressing the dual center concept. In a poikilotherm the body temperature as shown by the solid line is a function of the environmental temperature, while the true homeotherm (dash dot line) can maintain its body temperature constant over a wide range of environmental temperatures. Only in extreme heat does its body temperature rise. Only in extreme cold does its body temperature drop. Animals in which the region where heat loss activities are activated has been destroyed should react as well as normal animals in a cold or cool environment; however, their body temperature should rise progressively on exposure to a mild heat load (as indicated by the dash line). Finally animals with ablation of the region where heat maintenance activities are integrated should tolerate heat loads as well as normals but should not be able to withstand cold (as indicated by the dotted line). The current dual center theory which implies exact localization of the two areas has been thought to be validated by the work of Ranson and his co-workers. The usual reference is to a review by Ranson in the volume on the hypothalamus (Volume 20, 1940) of the series sponsored by the Association for Research in Nervous and Mental Disease. The basic data in this review were taken from four papers, two of which must be considered in some detail in order to summarize the current localization concept. I have

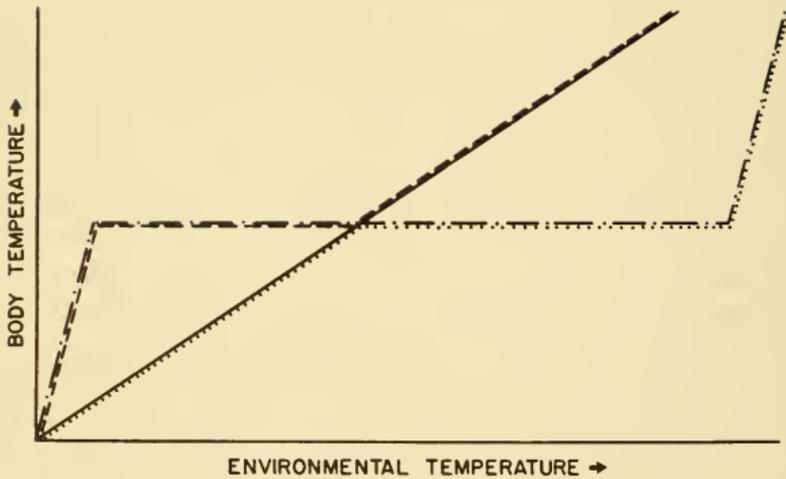


Figure 1: Diagram showing theoretical relationships between body temperature and environmental temperature in a poikilotherm (solid line), a homeotherm (dash dot line), a homeotherm with ablation of heat loss "center" (dash line) and a homeotherm with ablation of heat maintenance "center" (dotted line).

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a perfect and perhaps a peculiar right to erect this strawman for, of the four papers alluded to, I am the senior author on two, the sole author on one, and was present in the laboratory when the experimental work on the fourth was done. This fourth paper (Magoun, Harrison, Brobeck, and Ranson, 1938) is a report on the partial exploration of the hypothalamus with dual electrodes and an RF source of power. This use of a high frequency current for localized heating of the brain was a remarkable advancement in technique. Earlier workers (and some later ones) heated the carotid blood, heated the head, or used diathermic electrodes inserted into the subarachnoid space. With none of these techniques is it possible to exclude the heating of the great vessels at the base of the brain and with most of them it is not possible even to exclude the heating of the skin or mucous membranes. By using electrodes inserted into the brain and high frequency non-stimulating current, rather exact localization is possible for the sensing elements; such localized heating must be in the neurons or on the blood vessels in the brain. With threshold power Magoun and co-workers showed that a shift two mm in depth might alter markedly the response, which demonstrates the exactness of localization with this method.

Figure 2 is a partial summary of their work. The location of active points -- active in that localized heating at these points would result in panting -- are projected onto a parasagittal section of a cat's brain. The most sensitive area -- that with the lowest threshold -- is an oval region ventral to the anterior commissure, dorsal to the optic chiasma and extending rostrally into the preoptic region. Caudal from this active area is a region sensitive to heat but with a higher threshold than the rostral portion. The caudal limit of this less sensitive area is not indicated but it apparently reaches into the anterior mesencephalon. Unfortunately the method of reporting -- a method which migrated to the Southwest -- gives only two dimensions. There are no indications of the lateral or medial limits of the area sensitive to heating, so anyone wishing to extend this work must repeat the original experiments before proceeding. It is hoped that this inadequate method of reporting will be discontinued.

The other three papers are studies of the effects of various lesions on the thermoregulatory ability of cats. Figure 3 is a diagram of the lesion in one of these animals (Clark, Magoun, and Ranson, 1939). It is evident that the lesion is primarily in the lined

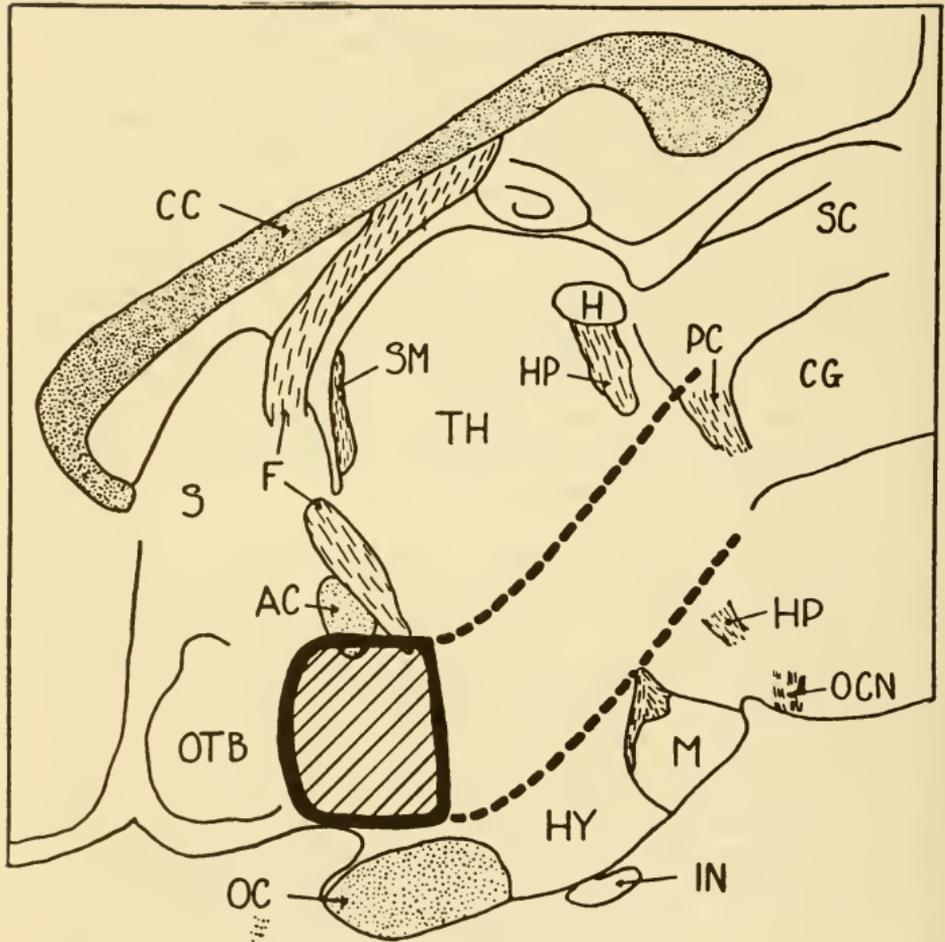


Figure 2: Schematic outline of the region reactive to heating, projected on a paramedian sagittal section through the brain of the cat.

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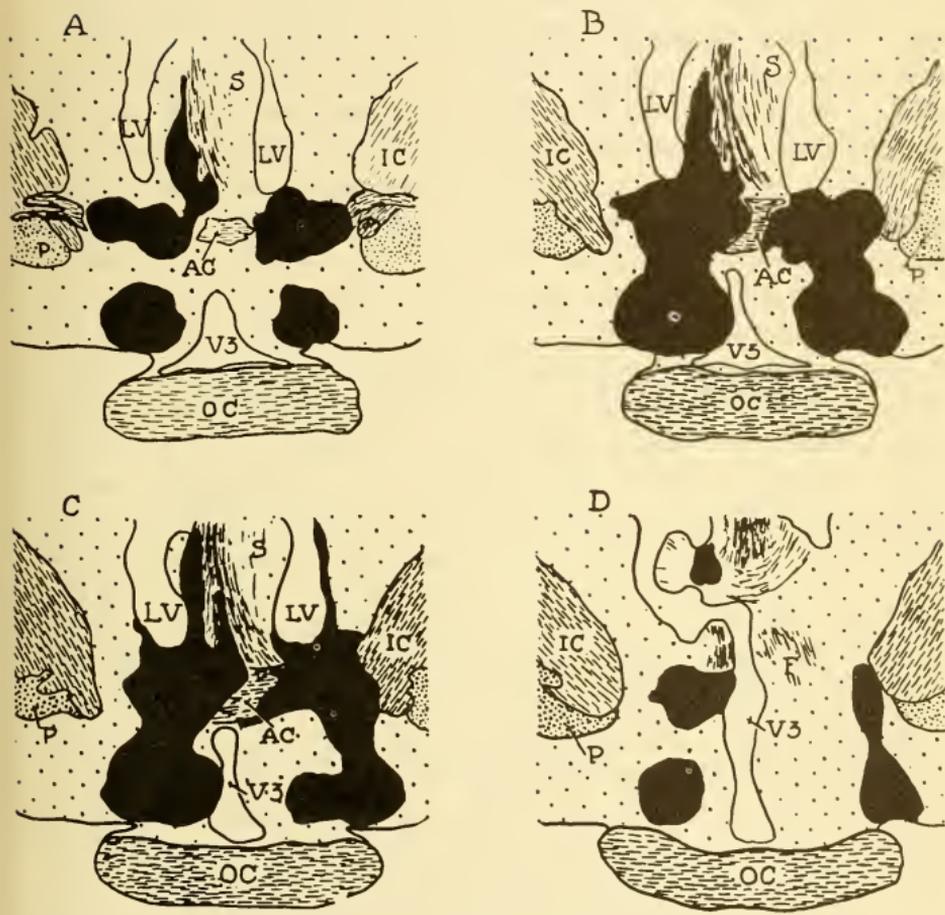


Figure 3: The lesions in Cat 51 indicated in solid black on four drawings from transverse sections through the brain at the level of and behind the anterior commissure.

area shown in the previous slide, that is, the lesion is largely in the area most sensitive to heat. It is also obvious that the lesion is slightly asymmetrical and also incomplete. The heat load test for these animals was an exposure to  $40^{\circ}\text{C}$  in a thermostatically controlled box with the animal confined to a reasonably comfortable hammock. Under these conditions a normal cat's temperature will rise rapidly and panting soon ensues. The average rectal temperature at which panting occurs is  $39.7^{\circ}\text{C}$  which is about  $0.8^{\circ}\text{C}$  above the normal temperature for a cat. The effects of lesions similar to the one previously shown at various levels in the anterior hypothalamus and anterior to the anterior hypothalamus are summarized in Figure 4. In cat 53 the lesion was anterior to the heat sensitive area while in the other cats the lesions were either in the region sensitive to heating or caudal to it. In these remaining seven animals in heat load tests made one month or more after the operation there was little or no change in respiratory rate even though their body temperatures rose markedly. In all but one of these the respiratory rate was less than 40 per minute even when the body temperature was elevated to  $41.1^{\circ}\text{C}$  at which level the tests were concluded. The results of these tests, then, are in perfect agreement with the localization obtained with local heating of the brain. Destruction of the heat sensitive area results in an inability to withstand heat. Figure 5 shows tests in a series of cats with lesions in the lateral portion of the caudal hypothalamus. These animals showed the same loss in ability to tolerate an acute heat load as seen in the cats with anterior lesions. The animals, however, also had marked falls in rectal temperature when exposed to a moderately cool environment. In similar tests the cats with anterior lesions withstood a cold load as well as normal animals. Although some of these animals with caudal lesions were tested two months or more after their operation, they showed no improvement in ability to withstand heat; however, there was one group of cats which had only a temporary loss. These are shown in Figure 6. Here are two groups of cats with small lesions in the anterior portion of the lateral hypothalamus. In heat load tests one week postoperatively similar results were obtained in both groups. The slides show results obtained in tests one month after the operation. It will be seen that the cats with asymmetrical lesions withstood the acute heat load with only slightly more difficulty than normal animals while those with symmetrical lesions were unable to withstand the heat. Presumably in the cats with asymmetrical lesions there had been

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Cat no.	Days after operation	Level of lesion	Temp. at end of test °C	Rise in temp.	Final re-spiratory rate	Panting	Sweating
53	35	A. A. C.	40.3	2.0	140	yes	yes
51	38	A. C.	41.3	2.4	72	no	not tested
94	30	A. C.	41.2	7.5	16	no	no
96	81	A. C.	41.3	4.5	22	no	no
97	64	A. C.	41.2	4.2	24	no	not noticed
12	104	A. H.	41.3	2.4	36	no	no
81	71	A. H.	41.1	1.9	24	no	no
83	28	A. H.	41.2	3.1	32	no	no

Figure 4. Hot box tests on cats with large anteriorly placed lesions.

Cat no.	Preoperative tests					Postoperative tests					
	Temp. at end of test °C	Rise in temp.	Final respiratory rate	Panting	Sweating	Days after operation	Temp. at end of test °C	Rise in temp.	Final respiratory rate	Panting	Sweating
46	39.5	1.2	208	yes	no	7	41.2	4.7	42	no	no
						20	41.1	4.1	30	no	no
47	39.7	0.9	300	yes	no	7	41.1	1.9	26	no	no
						42	41.1	1.7	28	no	no
100	38.9	-0.05	240	yes	yes	28	41.2	2.5	66	no	no
107	39.6	0.6	230	yes	no	26	41.3	3.4	30	no	no
						42	41.3	2.4	40	no	no
109	39.7	0.6	180	yes	no	33	41.1	3.0	20	no	no
						66	41.1	1.8	36	no	no
110	38.8	0.5	210	yes	yes	32	41.3	2.2	30	no	no
						56	41.1	2.5	30	no	no
114	39.2	0.5	240	yes	yes	35	41.1	1.0	140	no	no

Figure 5. Hot box tests on cats with lateral lesions in the caudal part of the hypothalamus.

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Cat no.	Preoperative tests					Tests one month postoperative				
	Temp. at end of test °C	Rise in temp.	Final respiratory rate	Panting	Sweating	Temp. at end of test °C	Rise in temp.	Final respiratory rate	Panting	Sweating
Sym.										
8	40.3	1.9	176	yes	no	41.2	2.1	70	no	yes
20	40.2	1.3	230	yes	yes	41.1	4.3	26	no	no
40	39.6	0.7	246	yes	yes	41.1	1.6	36	no	no
Asym.										
23	39.5	-0.1	206	yes	yes	39.9	1.5	220	yes	yes
39	39.3	0.2	252	yes	yes	41.1	2.1	140	yes	no
42	40.0	0.8	176	yes	yes	40.5	2.2	120	yes	yes
43	39.3	0.3	240	yes	yes	41.1	1.5	222	yes	no

Figure 6. Hot box tests on cats with lateral lesions in the rostral part of the hypothalamus. Cats 8, 30 and 40 had symmetrical lesions; the other four had asymmetrical lesions.

temporary and reversible damage to the heat sensitive area probably as a result of edema which subsided in the first postoperative month. If this is the case then it would appear probable that the results in the animals with symmetrical lesions were not due to edema. For this reason it was assumed that a steady state was present in the animals with symmetrical lesions, or in other words, that the damage was solely due to loss of tissue and therefore permanent.

The foregoing was thought to supply a localization of the dual centers for temperature regulation. In his text Ranson (1947) summarized this theory as follows (Figure 7): "On the basis of all the available evidence it now seems clear that a center controlling heat-loss functions such as panting and sweating is situated in the pre-optic region and that a pathway from this center runs backward through the lateral hypothalamus. The center for preventing heat loss by vasoconstriction and for increasing heat production by shivering is situated in the hypothalamus proper; and its descending pathway also runs backward through the lateral hypothalamus. Both descending pathways run close together dorsolateral to the mammillary body and enter the mesencephalic tegmentum. Bilateral lesions in the caudal part of the lateral hypothalamus interrupt both pathways and interfere with both heat loss and heat conservation mechanisms. Bilateral lesions in the preoptic region destroy the heat-loss center leaving the heat conservation center intact; and as a result the body temperature either remains normal or may be temporarily elevated."

It has been routine in studies of the effects of various lesions on the thermoregulatory ability of experimental animals to utilize only external heat or cold loads. There are, however, other conditions where the dual center theory appears to make definite predictions. Upon assumption of a constant work load it is generally found that when a steady state is achieved the body temperature is at a new and higher level. The dual center theory implies that animals with the anterior hypothalamus destroyed would never attain a new steady state unless the increased heat production were by chance balanced by the increased heat loss occasioned only by the increased body temperature. In most cases in such animals a fatal hyperthermia should rapidly ensue. As far as I know such experiments have never been made and yet they are badly needed.

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Similarly the readjustments to pyrogen administration have only been perfunctorially studied. In our early studies (Ranson, Clark and Magoun, 1939) we had found that in cats with medial lesions in the anterior hypothalamus (animals which had no disturbances in ability to withstand cold or heat) the fever curves were markedly altered and there were fatal and near fatal hypothermic responses to pyrogens. On the other hand an occasional cat with disturbed temperature regulation had essentially the same responses as a normal animal. This is difficult to explain within the confines of the dual center theory for presumably animals with damage to the central apparatus for promotion of heat loss should have fatal hyperthermias to dosages of pyrogens producing only a high fever in normal individuals. Most of the other studies on pyrogens such as Chambers, Koenig, Koenig, and Windle (1949), add little knowledge to the field although two recent reports are of interest. Thompson, Hammel and Hardy (1959) reported that four hypothalactomized dogs failed to develop a fever following injection of a pyrogen. This was confirmed by Bard and Woods (1959) who found that cats with the brain stem sectioned at various levels between the upper mesencephalon and rostral third of the pons fail to develop a fever following injection of an adequate amount of typhoid vaccine. The brain stem of an animal similar to these (Bard and Macht, 1958) is shown in Figure 8. Despite the failure to develop a fever, these animals do show the typical transient leucopenia and other blood changes observable in normal animals. Both reports then indicate the importance of the functional integrity of the hypothalamic mechanisms which enable an animal to regulate against cold in the development of a fever. The problem is: how is a rise in temperature in fever terminated in the presence of damage to the mechanisms for regulation against heat?

It is also difficult to understand the maintenance of normal body temperatures by cats with hypothalamic lesions in the relatively optimum temperatures of the usual animal room. If a cat is placed postoperatively in an incubator of  $32.2^{\circ}\text{C}$  after most lesions the body temperature will be normal or slightly above normal on the morning after the operation. However a majority of the animals with lesions in the heat sensitive zone will have hyperthermias, in some cases even above  $42.2^{\circ}\text{C}$ . When removed to the animal room, these hyperthermias subside over 2-3 days or so and thereafter the body temperature remains within the normal range. However in cats

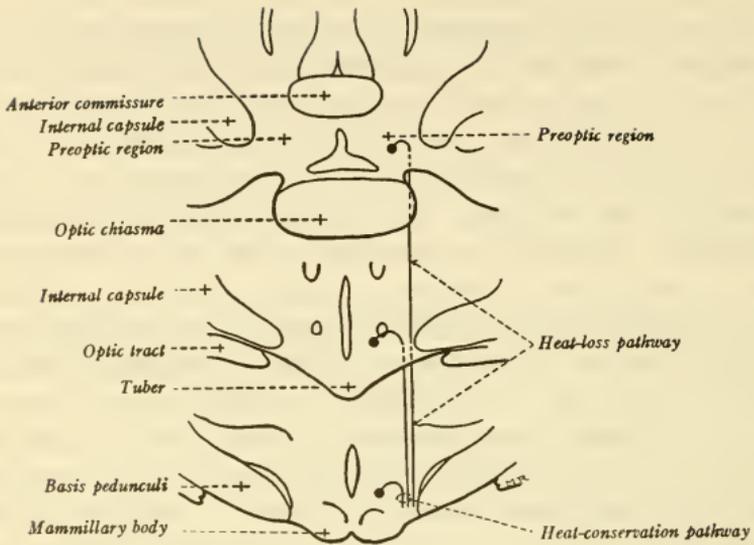


Figure 7: Diagrammatic representation of the mechanism for temperature regulation superimposed upon schematic drawings of three transverse sections through the preoptic region and hypothalamus.

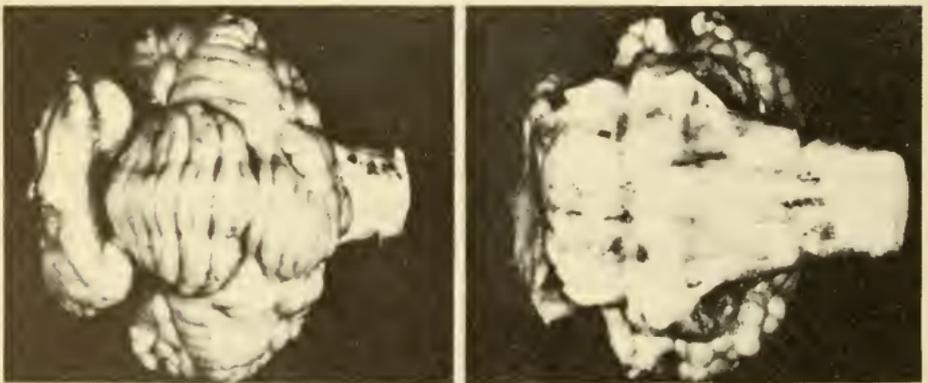


Figure 8: Dorsal and ventral views of truncated brain stem of Cat 4.

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with damage to the posterior hypothalamus or in animals with extremely large lesions anywhere in the hypothalamus, hypothermias are routine and many of these last a week or more. This finding with posterior hypothalamic lesions fits the dual center theory fairly well but with more anterior lesions the fit is not so good. These hypothermias following large anterior lesions have also been reported by McCrum (1953); however, Keller (1960) has stated that this is not the usual occurrence in his series. The difference may lie in the type of lesion for Keller's have routinely been produced by suction or thermocoagulation while ours and those of McCrum (1953) were electrolytic. On the other hand, such hypothermias usually do not result from large purely unilateral electrolytic lesions. One might assume that the reversible hypothermias and hyperthermias might be due to some type of reversible damage to remnants of the dual centers, or, on the other hand, that these normal body temperatures are due solely to vasomotor responses which remain active but not fully integrated even in the chronic midbrain dog (Keller, 1960). However an explanation rather than an assumption is needed.

These three questions--the effect of exercise, the course of fever, and the maintenance of normal body temperature at the usual ambient temperatures in the presence of damage to one or both of the dual centers--present fields for research rather than insurmountable difficulties for the dual center hypothesis. However, neglect of these problems and continued overgeneralization on insufficient evidence (such as was perpetuated by Ström (1960) in the new so-called Handbook of Physiology) will not lead to clarification of the problems of thermoregulation. These three questions were not considered in Ranson's review and there have been no answers in the past two decades. There has appeared, however, much that has been considered confirmatory evidence for the dual center theory and some work which may be contradictory. Some of the confirming studies will be briefly discussed, then some of the contradictory data, and finally some of my own recent work.

In these intervening years there have appeared a number of papers which have purported to confirm the localization for the dual centers as outlined by Ranson. In particular there have appeared a number of reports from Scandinavian workers who have heated the

brain with diathermy or have cooled or heated with thermodes. In one of the early papers of this series (Folkow, Ström and Uvnäs, 1949) there was also confirmation of the caudal higher threshold portion of the heat sensitive area of Magoun. In most cases, however, extensive explorations were not made and in few have the anatomical checkups been complete or even reported. They have found it difficult and in most cases impossible to repeat the observations of Magoun et al. on panting. In cats anesthetized with urethane and alpha chloralose circulatory responses were readily obtainable while respiratory responses were slight to non-existent. This difficulty, I, also can confirm for although I have been able to elicit panting by localized diathermic heating, more often there were no respiratory changes even to heating in the most sensitive area. Figures 9 and 10 summarize one of these papers. The area sensitive to local heating has a greater rostro-caudal extent and is much narrower ventrally than indicated by Magoun et al. (1938). Like Magoun et al. (1938) Eliasson and Ström (1950) used cats and inserted paired electrodes equidistant from the midline. As they state, the reactive area could very well extend further laterally than their figures indicate. It is worth noting that their use of two figures gives a good three-dimensional diagram of the reactive area. In the goat (Andersson, Grant and Larsson, 1956) it proved possible to delineate an area where mild electrical stimulation would elicit panting and vasodilation of ear vessels. As shown in Figure 11 the area is very similar to that found in the cat. Perhaps as they state the larger brain made possible slightly more exact localization. It is, of course, also true that spread of stimulus would be much less with electrical than with thermal stimulation.

Figure 12 from a paper by Birzis and Hemingway (1957) would probably have been hailed by Ranson as convincing proof of the localization he assumed for the dual centers. Electrical stimulation (at points marked X) and in more caudal levels elicited shivering as demanded by the theory. It should be noted that after lesions confined to this particular medial region dogs have no more difficulty than normal dogs in combating a cold load (Keller, 1960). However, after much larger lesions, as shown in Figure 13, there is a severe damage in ability to withstand a cold load. This is shown in Figure 14. In this test a normal dog would have a normal or slightly elevated body temperature but in the two dogs, one of whose lesions you have just seen, the rectal temperature dropped precipitously

## ANTERIOR HYPOTHALAMIC LESIONS

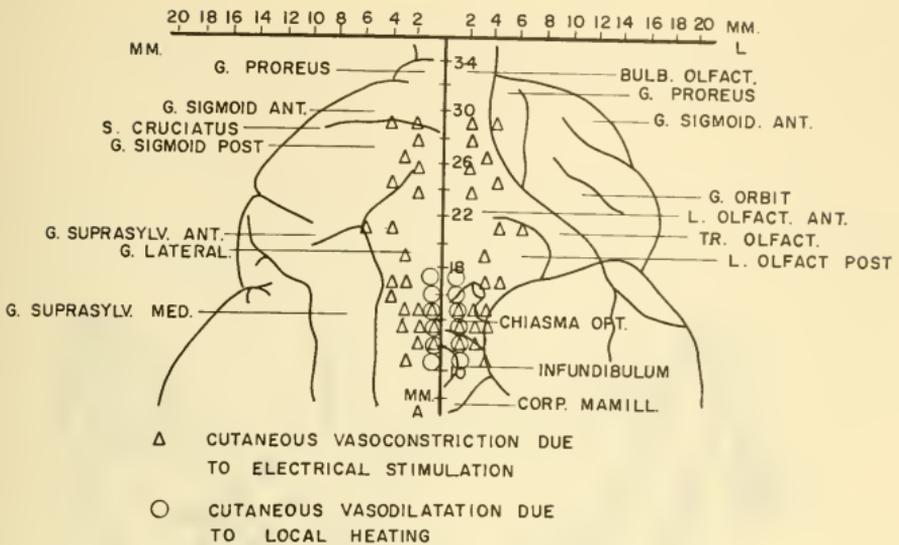


Figure 9. Dorsal and ventral views of the frontal lobe and hypothalamus of the cat, showing the localization of cutaneous vasomotor regions. The anterior and lateral coordinates of the Horsley-Clarke system are given in the figure. The size of the brain corresponds with that of a cat of 3.0 kg. body weight.

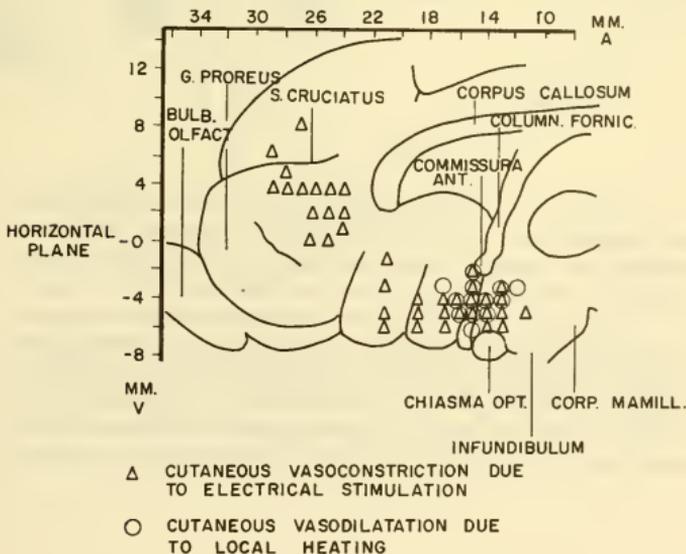


Figure 10. Median section of the frontal lobe and hypothalamus of the cat, showing the localization of cutaneous vasomotor regions. The anterior and vertical coordinates of the Horsley-Clarke system are given in the figure. The size of the brain is the same as in Figure 9.

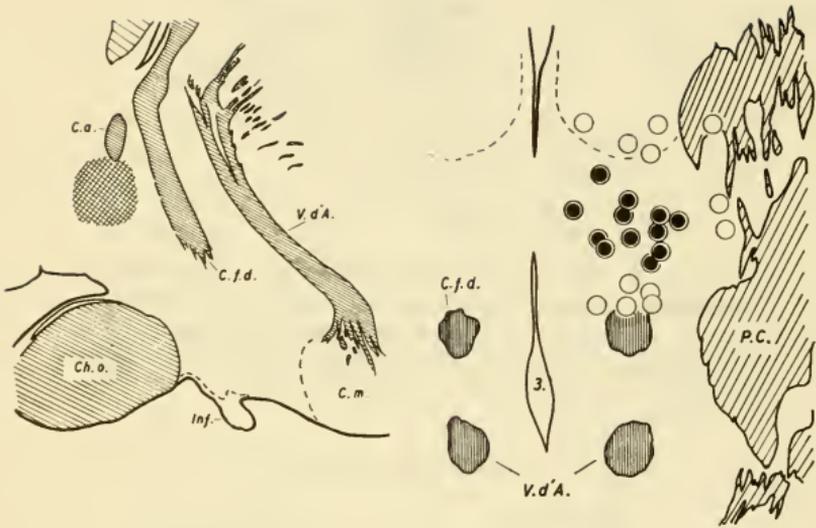


Figure 11. A diagram of a parasagittal section (left) through the preoptic area and the hypothalamus of the goat. The cross-hatched area marks the region where electrical stimulations caused polypnea, vasodilatation in the ears, and inhibition of shivering.

A diagram of a horizontal section (right) of the preoptic area and the hypothalamus of the goat at a level about 2 mm ventral to the anterior commissure. Filled circles mark points where electrical stimulation caused polypnea, vasodilatation in the ears and inhibition of shivering. Open circles mark the localization of adjacent points where electrical stimulation was ineffective in these respects.

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Figure 12. Cross-section through tuberal hypothalamus of Cat 34, showing stimulation points (X) which produced shivering tremor.



Figure 13. Transverse section through area of greatest extent of lesion in Dog 35.

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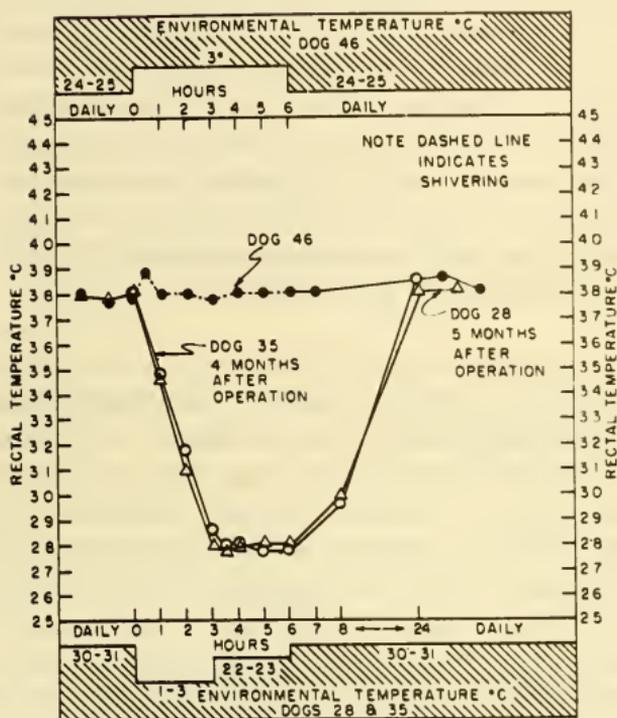


Figure 14. Rectal temperature curves of dogs (28 and 35) in which all central regulation against a cool environment was eliminated by a large lesion placed in the posterior hypothalamus. These dogs' temperature curves are contrasted with an unoperated dog's (46) temperature curve, when stimulated by the same cooling load. Stippling in the curve indicates the presence of shivering.

and there was no shivering. The results of these tests, which were performed months after the operation, are similar to those seen in chronic midcollicular preparations. Figure 15 illustrates the responses of these same two dogs to a heat load. In one dog there was no deviation from the normal and in the other only a slightly higher temperature (Keller, 1950). These dogs, then, are the fourth type required by the dual center theory, that is, animals with much disturbed regulation against cold but with little or no disturbances against heat. This latter finding, though, does raise some serious difficulty with the localization of dual centers as proposed by Ranson. The lateral limits of the lesion apparently include the postulated pathway from the anterior center for regulation against heat. Either there are descending fibers further laterally than had been originally thought or some other lower center is concerned. Neither of these questions can be answered by the available data.

There has appeared one paper (Sherwood, Massopust, McCrum, and Buchanan, 1954) on the localization in the hypothalamus of the rat of thermoregulatory integrating processes. In this species it was found that bilateral lesions involving any portion of the lined area shown in Figure 16, whether anterior, posterior, or tuberal, resulted in an inability to maintain normal body temperature when exposed to a cold load. There was no mention of usual body temperatures of these rats in the animal room nor of any heat load tests. It is probable that they were tested entirely too soon after operation but the findings are not compatible with current dual center theory.

It was mentioned earlier that Birzis and Hemingway had been able to elicit shivering in cats by electrical stimulation. In their experiments the active areas fit in very well with the dual center concept; however, there are two other reports of the electrical elicitation of shivering. The earliest of these is that of Akert and Kesselring (1951). This was a part of the findings in the long series of studies of the effects of stimulation of the brain in unanesthetized cats conducted in the laboratory of Hess. In this series there was one cat in which stimulation in a location similar to that reported by Birzis and Hemingway (1957) elicited shivering but in the other ten cases the active region was adjacent to the lateral ventricle and included six locations in the septum pellucidum, three in the caudate nucleus, and one in the anterior thalamus. There is no mention of how often stimulation in these same locations did not elicit shivering.

# ANTERIOR HYPOTHALAMIC LESIONS

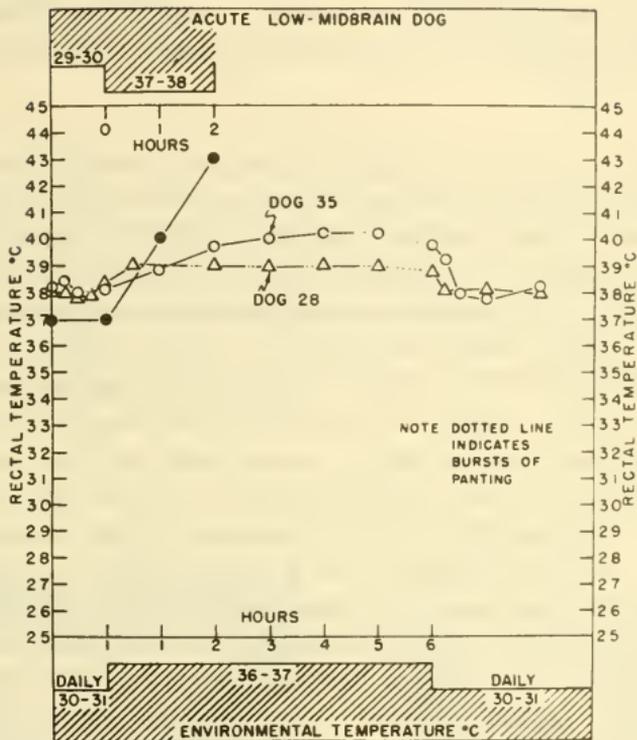


Figure 15. Rectal temperature curves, of the same operated dogs shown in "a", during the six-hour exposure to an environmental temperature of 37° C to 38° C. These dogs' entirely normal regulation against a heavy heat-load is contrasted with the rectal temperature response of another dog (72-D) in which all heat dissipating abilities were absent. Stippling indicates the presence of panting.

Andersson has reported (1957) that by electrical stimulation of the septal region in unanesthetized goats shivering can be easily induced. Figure 17 is a diagram of the active points he found. It should be reiterated that removal of the septum does not in any way interfere with a dog's ability to withstand cold or heat and the body temperatures of such preparations are within normal range (Keller, 1960). The role of the septum in temperature regulation is very difficult to visualize but any role at all is not in accord with the dual center theory of Ranson.

Freeman and Davis (1959) have recently reported some results obtained by heating or cooling the brain of the cat that are not compatible with the localization of the dual centers as proposed by Ranson. Their results from heating are shown in Figure 18, which again is one of those unfortunate parasagittal projections. Heating in the chiasmatal region would be expected to bring about a fall in body temperature but a fall in body temperature on heating the anterior pons and a rise in body temperature on heating the midbrain and caudal hypothalamus are not in accord with the dual center hypothesis. The results with cooling as seen in Figure 19 are even less explicable. Cooling should give no response in the chiasmatal region yet both a rise in some cases and a fall in others was observed. In the caudal hypothalamus only falls in body temperature were observed to result from cooling and the points extend well into the midbrain while the only rises in body temperature from posterior cooling were in the anterior pons. None of these results are in accord with the localization that was proposed for the dual centers nor would they be predicted on the basis of results of extirpations.

This work I have covered maybe summarized as follows: In the past two decades, that is, since the dual center theory was thought to be validated by exact localization, there has appeared some confirmatory work, none of which was crucial, and there has also appeared a body of work not explicable in terms of the localization proposed. Furthermore, none of the primary questions neglected by Ranson have been answered.

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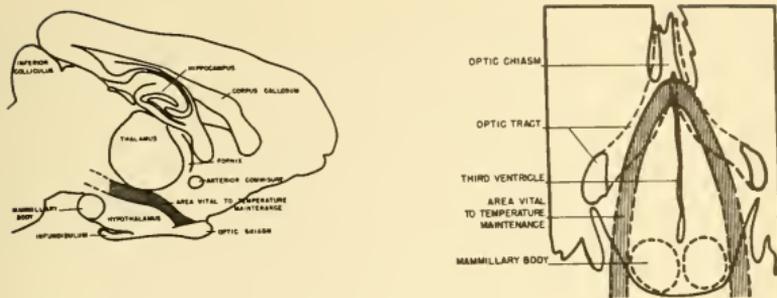


Figure 16. The cross hatched area indicates the portion of the hypothalamus the integrity of which is suggested to be vital to temperature maintenance in the rat. It has been projected upon a mid-sagittal section of a rat brain (left) and represents the loci of the sites of bilaterally symmetrical lesions in twelve animals which could not regulate their body temperatures while in a cold environment.

On the right is the same area shown as a projection upon a horizontal section of a rat brain.

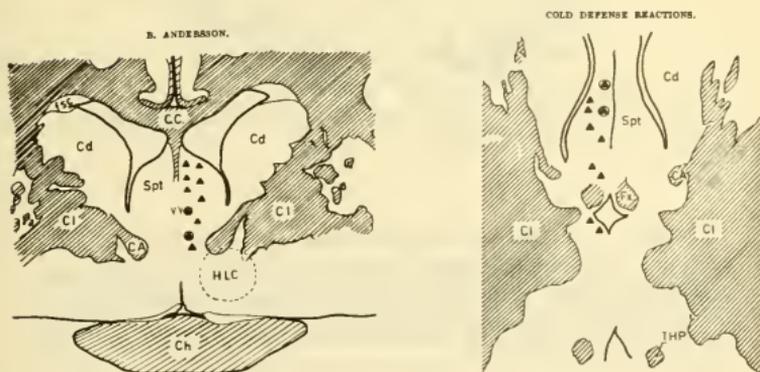


Figure 17. A diagram of a transverse section through the fore-brain of a goat slightly in front of the anterior commissure. Black triangles indicate points where shivering, peripheral vasoconstriction and inhibition of polypneic panting were obtained as effects of electrical stimulation. Encircled triangles indicate points where in addition to the above mentioned effects piloerection and a huddling up of the animals were observed.

At right is a diagram of a horizontal section through the septal area and the thalamus of the goat at a level slightly dorsal to the anterior commissure.

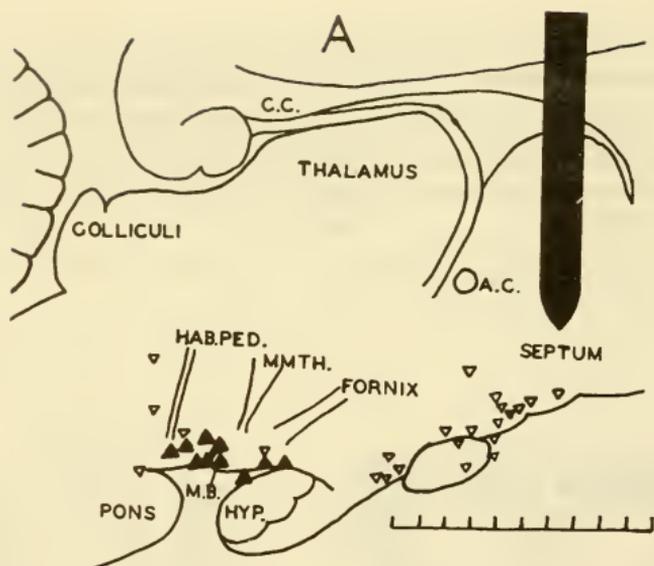


Figure 18. Sites of reaction to heating, shown in parasagittal section 3 mm from the midline. A thermode is shown in scale; the probable effective range of stimulation is 1 mm from the surface. Open triangles represent a fall, solid triangles a rise in rectal temperature. Scale in mm.

## ANTERIOR HYPOTHALAMIC LESIONS

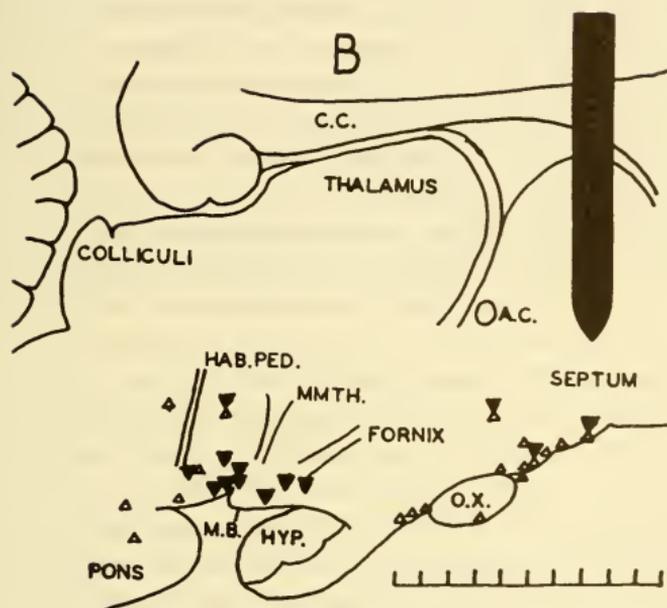


Figure 19. Sites of reaction to cooling, shown in parasagittal section 3 mm from the midline. A thermode is shown in scale; the probable effective range of stimulation is 1 mm from the surface. Scale in mm. Open triangles represent a rise, solid triangles a fall in rectal temperature.

The next four figures, 20, 21, 22, and 23, represent some of my own recent work\*. These are animals with rather unusual lesions. Routinely, extensive lesions were placed unilaterally in the anterior hypothalamus and contralateral to these large lesions were placed in the posterior hypothalamus. It was anticipated and found that such preparations would not present extremely grave nursing problems. As seen in the tests performed one month after the operation these cats would all be considered to have rather severe disturbances of regulation against heat. In this respect these cats are identical with those on which Ranson based much of his validation and localization of the dual center theory. In some of these cats even four months after the operation there remained a severe deficit in regulation. In all cases, however, the only permanent result was an increased panting level. In Cats 1 and 2 (Fig. 19) with the longest survival it is evident that this is probably a steady state defect and that no further improvement would have occurred; presumably this was also true in the others as well. A reasonable assumption would be that some sort of a learning process had occurred. This is negated by the fact that the first four animals spent most of their survival period in an air conditioned room in which the temperature rarely exceeded  $23.8^{\circ}\text{C}$  and then only for very short periods. The animals were given short heat load tests at widely separated intervals. No opportunity for learning occurred. What then can be the mechanism for this return of function? In our original work the assumption was made that the effects of edema, etc., had disappeared by one month after the operation. This assumption was thought to be validated by the fact that in cats with asymmetrical lesions there was an early loss in ability to withstand heat but one month postoperative responses were within the normal level. The assumption still seems reasonable and is supported by the studies of Prados, Strowger and Feindel (1945). No explanation is in sight but one wonders what sort of an explanation would have been devised originally if we had continued to study our animals over a prolonged period of time. Of course it is probable that if we had waited for four months or so before testing the animals we would have found nothing to explain.

\*The initial phases of this were conducted under a contract with the USAF 33 (616)-5657.

## ANTERIOR HYPOTHALAMIC LESIONS

What, then, are the essential details on which a theory of the neural mechanisms of temperature regulation must be based? The most important of these is that there is a separation of integrating areas for heat conservation from those regions essential for heat dissipation. This has been shown by two different types of preparations. In the dog, Keller (1960) has established that it is possible for an animal to have minimal ability to withstand cold while having normal responses when exposed to a heat load. Our own original work and my own recent work indicates that the other type of preparation is also possible and we have been able to produce such animals. However the return of function in these cats poses more problems than it solves. While we have good evidence for the localization of heat maintenance activities, the location or locations of these areas where heat loss activities are integrated are obscure. Certainly the anterior hypothalamus must play some role but what the role is remains for the future to determine.

CLARK, G.

	Cat #1		Cat #2	
	Final		Final	
	Temp.	Resp. Rate	Temp.	Resp. Rate
1 month	41.0	27	41.4	32
3 months	41.4	36	40.7	120P
5 months	41.2	192P	41.4	190P
7 months	41.3	160P	39.5	200P
8 months	41.2	132P	40.3	200R

	Cat #3		Cat #4	
	Final		Final	
	Temp.	Resp. Rate	Temp.	Resp. Rate
1 month	41.0	24	41.0	68
3 months	40.8	160P	41.4	104P
5 months	41.2	128P	41.3	122P
6 months	41.2	130P	41.0	150P

Figures 20-23. Time and results of damage to heat loss mechanisms. The only permanent effect is an increase in panting level.

## ANTERIOR HYPOTHALAMIC LESIONS

	Cat #5		Cat #6	
	Final		Final	
	Temp.	Resp. Rate	Temp.	Resp. Rate
1 week	41.2	70	41.1	68
1 month	41.1	120	41.1	40
4 months	41.2	140	41.0	60
6 months	41.0	130P	40.2	120P

	Cat #7		Cat #8	
	Final		Final	
	Temp.	Resp. Rate	Temp.	Resp. Rate
1 week	41.1	34	41.0	24
1 month	41.0	20	41.0	40
4 months	41.0	60	41.0	50
6 months	40.5	120R	40.4	130P

Temperatures in degrees Centigrade, respiratory rates per minute.  
 This work was begun under USAF contract AF 33(616) - 5657.

CLARK, G.

DISCUSSION

DR. STUART: Do you have the histology of the animals that were shown in the last two slides?

DR. CLARK: I do not have them with me, but the lesions were virtually unilateral hemisections. They were good, big-sized lesions.

DR. FREEMAN: Since this question of the compatibility of my data with the dual center hypothesis came up, I might say that we were trying to prove this hypothesis when we started off with this work in 1950, with the idea that there was a cold center posteriorly and heat center anteriorly. If you stimulated them with conductive thermal changes, you should get appropriate activation of a mechanism for heat loss by heating the anterior hypothalamus, and nothing if you cool. You should get opposite effects with the posterior hypothalamus. What we found was, as you see, that sensitivity to both heat and cold could be demonstrated to exist anteriorly and that the inverse changes took place in the posterior hypothalamus. This sent me back to Ranson's original description of this hypothesis, and it struck me then--and it does so now--that there was a peculiar confusion or ambiguity in his expression of this thing. He described heat loss mechanisms or centers in the anterior hypothalamus and in the posterior hypothalamus and did not specify whether these were sensory or motor or both. He never said, as we thought he had said, that these were heat-sensitive and cold-sensitive mechanisms. He was simply describing his results in more general terms without specifying as to whether temperature sensitivity exists in either one of these areas.

DR. CLARK: At that time, it was thought that the work with the diathermy had conclusively proved that the region beneath the anterior commissure was a heat-sensing area, but we had no data whatsoever about a cold sensing area. The only thing we had was the fact that the caudal and lateral hypothalamus lesions produced animals that could not withstand cold as well as normals; those lines he drew were entirely hypothetical.

## ANTERIOR HYPOTHALAMIC LESIONS

DR. FREEMAN: We developed our own interpretation of this which we still think is compatible with a dual center data. The anterior hypothalamus consists of heat-sensitive and cold-sensitive neurons, and these have an inhibitory effect upon neurons in the posterior hypothalamus which in turn are responsible for activation of heat-conservation and heat-production mechanisms. Heating anteriorly will, in effect, increase this inhibition and depress the mechanisms, whereas cooling anteriorly will do the reverse, cause a release from inhibition. An inhibition of inhibition, if you will, allows these mechanisms to spring up. Now, if you make a lesion anteriorly, you remove this inhibition, you produce an animal with tendency to excessive heat production. This animal has no difficulty in maintaining himself in the face of cold stress, whereas an animal with a lesion posteriorly will tend to lose the capacity for heat production. When the temperature now goes up, there is no automatic mechanism; when the temperature goes down, there is no preventative mechanism left. We think that these are compatible if you express the dual center in terms different from those originally proposed.

DR. CLARK: They are not compatible with the rest of the evidence.

DR. FREEMAN: In what way?

DR. CLARK: You can produce a cat with a large electrolytic lesion just caudal to the optic chiasma. These are large lesions, say from L four to R four and from zero down to the base; those cats will show low temperatures; at a room temperature of 22° C the temperatures will be so low you cannot read them on a clinical thermometer, and I have had temperatures as low as 25° C. Those are electrolytic lesions; if you make a lesion with a knife mounted in the stereotaxic frame at the same location, you do not get these hypothermias. The only trouble is that a knife wound like that is very hard to see in histological sections. You cannot be sure. You know that you went down and hit bottom, but in the sections, you cannot show where the edges of the lesion are. In fact, you may hardly be able to see the lesion at all.

CLARK, G.

DR. FREEMAN: I am not sure that I see the basis of the incompatibility.

DR. CLARK: There is a tremendous difference in the effects of the electrolytic lesions as compared to either section or knife cut.

DR. FREEMAN: That is something entirely new.

DR. STUART: When you make the knife lesion, how much hypothalamic and subthalamic tissue is left intact caudal to the section?

DR. CLARK: All of it.

DR. STUART: And this animal can regulate against the cold?

DR. CLARK: Yes.

DR. STUART: I cannot see where this would disagree with the classical literature.

DR. CLARK: I was thinking primarily of the hypothermia that you obtain with the electrolytic lesion. As far as the rest, it is not too bad, but I still do not see that area in the anterior pons.

DR. FREEMAN: Is there sensitivity back there?

DR. CLARK: Yes.

DR. FREEMAN: Well, you had the old data, yourself. This was not the anterior pons, by the way. This was the anterior midbrain. You yourself showed this trailing off of the region of sensitivity.

DR. CLARK: Yes, that region is way dorsal.

DR. FREEMAN: Well, do not forget that the stimulus we apply here is largely applied dorsally. Those points on the diagram represent the tip of the thermode, and this is the greatest extent of projection.

DR. CLARK: You did not try just going down a little way?

## ANTERIOR HYPOTHALAMIC LESIONS

DR. FREEMAN: We lowered the thermode routinely by short steps and stimulated each stage until we got a response. If you push it all the way to bottom, there is maximal damage to the structure that one is generally trying to stimulate. We went by easy stages.

DR. CLARK: But, you did not get anything until you got deeper?

DR. FREEMAN: Well, the points represent the position of the thermode at the time of an effective response.

DR. CLARK: Presumably the thermode was in the area that is sensitive to heating. You did not get anything because that area should be up around the aqueduct.

DR. FREEMAN: That is true; however, your pathway swings somewhat laterally there, is that correct?

DR. CLARK: Well, there are no data on that. As far as the pathway for panting, yes, because if you leave just lateral extremities of the midbrain, you still get panting, and those dogs cannot regulate against cold.

DR. FREEMAN: This is Keller's work you are describing?

DR. CLARK: Yes.

DR. FREEMAN: That, I think, is also quite compatible with the finding of this region of sensitivity, that is, the anterior midbrain.

DR. CLARK: No, I think it is just a question of whether the pathway extends that far laterally. In other words, I think it is rather a diffused pathway that extends through the entire mesencephalon.

DR. STUART: I think in fairness to Ranson and Magoun, it should be stated that they thought that the posterolateral hypothalamus integrated heat conservation rather than heat productive mechanisms. In a 1940 review (*Ergebn. Physiol.* 41:56, 1939) they mentioned the difficulty encountered in instigating shivering pre-operatively with the applied cooling load. Thus they did not wish to attribute the integration of shivering to that particular region of the hypothalamus.

DR. CLARK: The only thing I did was to take the cat's temperature and put it in a box; after three hours, I would go back and pull the cat out and put him on my lap and take his temperature and feel if he was shivering, and that is not too satisfactory.

DR. STUART: Birzis and Hemingway stimulated a locus in the tuberal hypothalamus to produce shivering. Didn't you say that a lesion that spares this region has no effect on shivering?

DR. CLARK: No, Keller has some dogs where he has had just that medial part destroyed, and they regulate against cold quite well. It takes a tremendous lesion to get any long-term effects.

DR. FREEMAN: There is another point about your data that has always interested me. This also applies to the data from Igor and Ranson on exposing these animals to high ambient temperatures. Their body temperatures will go up in their terms to  $42^{\circ}\text{C}$  and level off there despite continuance of the heat stress, and I notice in your data that almost all these animals have temperatures that range from  $41.11^{\circ}\text{C}$  to  $41.18^{\circ}\text{C}$ , a very narrow range.

DR. CLARK: Well, that is very simple. I did not want to hurt the animal.

DR. FREEMAN: You were watching for it then?

DR. CLARK: When the temperature reached  $41.11^{\circ}\text{C}$ , I stopped the test; but since I only took the temperatures at intervals, in some cases the temperature went above that.

DR. FREEMAN: That is humanitarian, yes, but how about the data of Teague and Ranson's studies, showing that with continuation of the heat stress there is prevention of hypothermia in all their animals?

DR. CLARK: Well, I do not think that is quite the way it went because they also stopped their tests that way.

DR. FREEMAN: I can recall some of the heat stress. I remem-

## ANTERIOR HYPOTHALAMIC LESIONS

ber this particularly because I am very interested in the phenomena. Teague and Ranson's graph shows rectal temperature against time; it shows a period of stress; the temperature will go up, and then it will level off. This is my question: how come? Why does it not go up to  $43^{\circ}\text{C}$  or  $44^{\circ}\text{C}$ ? You see, if they have lost all ability to regulate against heat, they should be unable to control at any level, but now they have this cut-off level and they survive.

DR. CLARK: I know, but that cut-off level is also due to the temperature that they are exposed to; when their temperature gets above  $41^{\circ}\text{C}$ , they are going to be able to lose heat to the environment.

DR. FREEMAN: Then, they should show some kind of gradual approximation to this thing, but this is not what the curve shows, by and large.

MR. ADAMS: How does this approach the peak? Is it as sharp as you have shown?

DR. CLARK: I would have to check back and see the data. One time I was told to take a cat's temperature up until it panted, and I did; I took his temperature up to, I think it was  $44^{\circ}\text{C}$ , and that was rather an acute preparation. In order to get it up that high, I had to raise the box temperature progressively and so the box temperature was way above  $40^{\circ}\text{C}$  when the cat's temperature reached  $44^{\circ}\text{C}$ .

MR. ADAMS: Dr. Clark may still have a point in this being a net thermal balance. If I remember Andersson's data correctly, during his experiments his goats reached a lower level of heat exchange where there was established a steady state heat balance which had been approached sharply. It was not reached gradually as you might expect.

DR. FREEMAN: There is a good deal of other evidence, however, that this level of  $107^{\circ}\text{F}$ , or about  $41^{\circ}\text{C}$ , is a critical point. DuBois wrote on this issue. He pointed out that fevers above  $41.11^{\circ}\text{C}$  are quite rare, and postulated that there is some kind of

emergency mechanism which will keep body temperature from going above that level and Roché, in 1898, found that same thing; you could drive an animal's temperature up by considerable amounts, up to this level, but to go beyond this level you had to either exhaust the animal by a prolonged application or else really provide a severe stimulant.

DR. CLARK: You are quite correct in that, and it is not the usual thing right after anterior hypothalamic lesion, to get a temperature above  $41.1^{\circ}\text{C}$  or  $41.7^{\circ}\text{C}$ . I have one cat that had a temperature of  $43.6^{\circ}\text{C}$  the morning after the operation.

MR. ADAMS: This point that Dr. Freeman brings out I think is true. It is also seen in bats which may be essentially poikilothermic at lower ambient temperatures at rest but which can be seen to regulate their temperatures at higher levels. Since you mentioned that the upper temperature level is dependent on ambient temperature, I think that this might preclude accepting this explanation completely.

DR. FREEMAN: We have done the same thing with cats given strychnine, where they are given serial convulsions, and you can control this by the amount of strychnine that you give. By pounding on the table at fairly regular intervals, you can induce a series of repetitive convulsions which will drive the animal's body temperature up to about this level, and then it will flatten off, even though convulsions continue. About this time, also, they will start to pant. Another way of doing it is to put them in a very hot environment. This is an intact normal cat. Put him in an environment of  $48^{\circ}\text{C}$ , which is quite uncomfortable, and he will make vigorous attempts to escape but will not pant. Now, their body temperature will rise rapidly during this period. I could not get continuous records because they were too active, but abruptly they will collapse and start to pant vigorously. They just lie down; if you take them out at that point, you will find that their body temperatures are  $40.7^{\circ}\text{C}$ . They go so high and then no further. So, there is something that goes on here, and this something, this mechanism--whatever it is--is still intact in the animals you described.

MR. ADAMS: Dr. Clark, were those lesions you reported on this afternoon or this morning dual lateral lesions?

## ANTERIOR HYPOTHALAMIC LESIONS

DR. CLARK: They were unilateral at two levels. You see, I have a virtual hemisection anteriorly on one side, and caudally on the other side. The third ventricle is convenient. There are no commissural fibers in it.

DR. HENSEL: May I make a more general comment on the evaluation of impairment of thermode regulation of the lesion, here? I think I had better explain it on the blackboard. Mostly, we are speaking of a loss of the ability of the regulation against cold. We choose the temperature for testing this rather at random. I think it would be quite useful to test the ability of regulation systematically and quantitatively over the whole temperature range, because if you consider the curve of the poikilothermic and homeothermic organisms as you showed in Figure 1, then the loss of the ability to keep the temperature at a certain level might have two explanations: one explanation is just limitation in the quantitative output of your regulating center; and the other might be a disturbance of the center -- the feedback mechanism itself. So, if you have just a quantitative disturbance, the curve might regulate in a smaller range of temperature, but in Figure 24, your mechanism in terms of cybernetics and feedback is perfectly all right. It might be as precise as this one. This is the case, for example, in the premature infant, and there are many wrong conclusions because the infant can not keep its temperature at this point, but it can maintain a perfectly normal temperature in this smaller range.

DR. CLARK: That goes back to Isenschmid.

DR. HENSEL: Yes, and I think it would be useful if you would do this.

DR. CLARK: I have done it with some cats, but I did not have a good enough controlled room to really do it. You would have to have a pretty accurate room in order to test your animals properly.

DR. HEMINGWAY: About this dual theory which we have been hearing of since before my time: the problem, I think, is trying to interpret the data. I was listening to Dr. Clark, who gave a very stimulating discussion of this. I just wonder if we have to be careful about being too rigid in defining the location and the functions of these centers. That is what it amounts to. You have a center in one

place which has certain properties and certain functions, and another center in another place. I wonder if there is not considerable overlapping in these centers. For example, there are two problems that have come up with shivering and panting. It is possible to control shivering by stimulation in the septum, which is certainly not in the posterior hypothalamus, and it is possible to inhibit shivering by stimulation in the anterior hypothalamus, which is far from the posterior hypothalamus. The other thing is the problem of panting. That is certainly a controversial problem, whether panting can be produced by heating or stimulating the anterior hypothalamus. There is not general agreement on that, is there?

DR. CLARK: No, there is not. Magoun, Harrison, Brobeck, and Ranson (1938), when they did that, were getting it routinely. I saw many of their animals and remember their rectal temperatures; they would be panting with a body temperature as low as 35° C. Of course, the Scandinavian workers (Strom, 1960) state that they had a hard job, and I do not know whether they ever saw panting or not. Do you know, Dr. Hensel?

DR. HENSEL: Do you mean Andersson?

DR. CLARK: No, I do not mean Andersson. I mean the von Euler group, using diathermy in cats.

DR. HENSEL: I think so. I think he saw panting. The only thing he could not see was the vasoconstriction during cooling. As far as I remember, he could see panting.

DR. FREEMAN: But it was very uncommon in his animals.

DR. HENSEL: Yes.

DR. LIM: And also in Hardy's work?

DR. CLARK: Hardy was getting panting in the dog quite readily, and I have been doing some heat experiments with cats and occasionally getting it, in animals under chloralose and animals under urethane and animals under both. I have had trouble getting

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it in unanesthetized preparations, probably because there I cut down the power output of my diathermy apparatus. But we have a lot to learn. As far as the localization of these centers is concerned, I think we know quite a bit about heat conservation because Keller has had several animals that could regulate quite adequately in the heat, but could not in the cold.

DR. HEMINGWAY: Does that include shivering, heat conservation, and heat production?

DR. CLARK: Yes. These animals when put in the cold would show a drop in body temperature similar to that you might see in a chronic midbrain preparation.

DR. HEMINGWAY: Does that include shivering and cutaneous vasoconstriction, both in that one term?

DR. CLARK: Yes. Of course, even these will show some vasomotor changes. You get those even in the chronic midbrain dog.

DR. LIM: From your recent data, do you suggest that chronic preparation should be made at least six months after operation?

DR. CLARK: Well, there I do not know, but I do know that you have to differentiate between acute and chronic effect of lesions, and I think that any report that is based on animals a week, two weeks, one month, or two months after the operation should be questioned.

DR. STUART: If the function does not return?

DR. CLARK: Yes. Now, of course, determining the things that an animal can do a week after the operation as well as a normal dog is important, but one may be misled concerning the loss of function, for a week or up to two months or maybe three months. Of course, the questions are: Is it due to tissue that regains function? Is it due to some other center vicariously functioning? You have a lot of problems in there, but the important thing after any brain operation is what the animal can do that approaches normal, not what is lost.

DR. HEMINGWAY: That raises a question which Dr. Freeman and I have talked about many times. He thinks that if there is des-

truction of part of the brain necessary for some function, then some other part of the central nervous system can take over that function. This is certainly true in your asymmetric lesions, that you can destroy one side and the other side will take over the functions of both sides.

DR. CLARK: Yes, but with the asymmetric lesions, I think you still have really intact tissue; as for complete vicarious functioning of the new area, I think we have to see that before we buy it.

DR. FREEMAN: Well, you can see it in some, say, lesions of a sort in the peripheral end of the nervous system. For example, recall Sperry's transplant in which he exchanges tendons to different muscles and then forces these monkeys to perform various tasks with the tendons reversed. There is indication there that some form of reorganization does take place. It is not basically a structural modification. That is to say, from all available tests, the pattern of nerve organization, anatomically, has not changed, but the functional abilities of the animal to use this limb have changed.

DR. CLARK: That is true, but of course you remember, too, in Sperry's spider monkeys that after he moved postcentral gyrus, they lost that ability. And his rats never did learn how to use the muscles right in their legs, but continued as long as he kept them to step harder on a tack.

DR. FREEMAN: On the other hand, in any form of higher, more highly organized activity, it is possible to see this sort of thing. For instance, Fleuron showed that by reversing nerves supplied to the extensor and flexor muscles in the wing, one could alter a bird's innervation, but yet the bird could still fly. So some form of reorganization obviously takes place.

DR. CLARK: In the salamander, complete reorganization takes place.

DR. FREEMAN: Well, that is a different story.

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DR. STUART: The way to get around this is to use our ablation and lesion studies as a preliminary investigation to studying the intact brain. What is going on in the normal animal during the heat conservation and dissipation events?

DR. CLARK: Well, it is obvious that work in the future should not be two men working here and two men working there looking at a slightly different picture. What we need is a rather large team working together on all of this.

REFERENCES

1. Akert, K. and F. Kesselring. Kältezittern als zentraler Reizeffekt. *Helv. Physiol. Acta.* 9:290-295, 1951.
2. Andersson, B. Cold defense reactions elicited by electrical stimulation within the septal area of the brain in goats. *Acta Physiol. Scand.* 41:90-100, 1957.
3. Andersson, B., R. Grant and S. Larsson. Central control of heat loss mechanisms in the goat. *Acta Physiol. Scand.* 37: 261-280, 1956.
4. Bard, P. and M. B. Macht. The behavior of chronically decerebrate cats. *Ciba Foundation Symposium, Neurological Basis of Behavior.* Boston, Little, Brown and Co., p. 55, 1958.
5. Bard, P. and J. W. Woods. Central site of pyrogenic action of bacterial endotoxin. *The Physiol.* 2:5-6, 1959.
6. Birzis, L. and A. Hemingway. Shivering as a result of brain stimulation. *J. Neurophysiol.* 20:91-99, 1957.
7. Chambers, W. W., H. Koenig, R. Koenig, and W. F. Windle. Site of action in the central nervous system of a bacterial pyrogen. *Am. J. Physiol.* 159:209-216, 1949.
8. Clark, G., H. W. Magoun, and S. W. Ranson. Hypothalamic regulation of body temperature. *J. Neurophysiol.* 2:61-80, 1939.
9. Eliasson, S. and G. Ström. On the localization in the cat of hypothalamic and cortical structures influencing cutaneous blood flow. *Acta Physiol. Scand.* 20:(Suppl. 70) 111-118, 1950.
10. Folkow, B., G. Ström, and B. Uvnäs. Cutaneous vasodilatation elicited by local heating of the anterior hypothalamus in cats and dogs. *Acta Physiol. Scand.* 17:317-327, 1949.

## ANTERIOR HYPOTHALAMIC LESIONS

11. Freeman, W. J. and D. D. Davis. Effects on cats of conductive hypothalamic cooling. *Am. J. Physiol.* 197:145-148, 1959.
12. Isenschmid, V. R. and W. Schnitzler. Beitrag zur Lokalisation des Wärmeregulation vorstehenden Zentralapparates im Zwischenhirn. *Arch. f. exper. Path. u. Pharmacol.* 76:202-223, 1914.
13. Keller, A. D. The role of circulation in the physiology of heat regulation. *Physical Ther. Rev.* 30:1-8, 1950.
14. Keller, A. D. Personal communication, 1960.
15. Keller, A. D. and W. K. Hare. The hypothalamus and heat regulation. *Proc. Soc. Exper. Biol. and Med.* 29:1069-1070, 1932.
16. McCrum, W. R. A study of diencephalic mechanisms in temperature regulation. *J. Comp. Neurol.* 98:233-282, 1953.
17. Magoun, H. W., F. Harrison, J. R. Brobeck and S. W. Ranson. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* 1:101-114, 1938.
18. Meyer, H. H. Theorie des Fiebers und seiner Behandlung. *Verh. Kongr. inn. Med.* 30:15-25, 1913.
19. Nikolaides, R. and S. Dontas. Warmezentrum und Warm-polypnea. *Arch. f. anat. u. Physiol. Anat. Abt.* 249, 1911.
20. Ott, Isaac. The relation of the nervous system to the temperature of the body. *J. Nerv. Ment. Dis.* 11:141-152, 1884.
21. Ott, Isaac. The interbrain: its relations to thermotaxis, polypnea, vasodilation, and convulsive action. *J. Nerv. Ment. Dis. New Series* 16:433-436, 1891.
22. Ott, Isaac. The thermogenic center in the tuber cinereum. *Med. Bull.* 17:246-248, 1895.

23. Prados, M., B. Strowger, and W. H. Feindel. Studies on cerebral edema. I. Reaction of the brain to air exposure; pathologic changes; II. Physiologic changes. *Arch. Neurol. Psychiat.* Chicago, 54:163-174; 290-300, 1945.
24. Ranson, S. W. Regulation of body temperature. *Res. Publ. Ass. Nerv. Ment. Dis.* 20:342-399, 1940.
25. Ranson, S. W. (revised by S. L. Clark) *The Anatomy of the Nervous System*, 8th Edition, Saunders, Philadelphia, 1947.
26. Ranson, S. W. Jr., G. Clark, and H. W. Magoun. The effect of hypothalamic lesions on fever induced by intravenous injection of typhoid-paratyphoid vaccine. *J. Lab. and Clin. Med.* 25:160-168, 1939.
27. Sherwood, C., L. C. Massopust, Jr., W. R. McCrum, and A. R. Buchanan. The effect of hypothalamic lesions upon body temperature maintenance in the albino rat while in cold environments. *J. Neuropath. and Exp. Neurol.* 13:191-208, 1954.
28. Ström, G. Central nervous regulation of body temperature, in *Handbook of Physiology Vol. II, Chapter 46:1173-1196, 1960.* (Editors: J. Field, H. W. Magoun, and V. E. Hall.)
29. Thompson, R. H., H. T. Hammel, and J. D. Hardy. Calorimetric studies in temperature regulation: the influence of cold, neutral, and warm environments upon pyrogenic fever in normal and hypothalamicectomized dogs. *Fed. Proc.* 18:159, 1959.

# NEURO-MUSCULAR ORGANIZATION OF SHIVERING

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Shivering in response to a cold stress normally waxes and wanes in intensity. Studying patterns of muscular activity at different levels of such intensity is a method of investigating certain neural aspects of shivering. In this experiment jaw and limb muscles were analyzed electromyographically during shivering and the effects of some physiological variables on such activity were noted.

## EXPERIMENTAL PROCEDURE

Thirty-five male and female adult dogs (9.0 - 11.5 kg.) were anesthetized with sodium isoamylal barbiturate (0.6 mg/kg I. V.) and electromyograms of jaw, fore and hind limb flexor and extensor muscles were recorded simultaneously while the animals were shivering in the waning stages of anesthesia. The animals were not restrained, but rather positioned in normal sleeping posture. The electromyograms were recorded with a concentric bipolar electrode, C-R coupled amplifier, cathode ray oscilloscope and electromagnetic oscillograph. Respiratory movements were recorded by strain gauge transduction of pressure variation of a chest tambour. Shivering movements were additionally recorded by strain gauge transduction of limb vibrations.

## RESULTS

The Pattern of EMG Recordings During Shivering

Preceding visible shivering a generalized increase in muscle tone was evident. This increase was reflected in the bipolar electrode recording of single unit discharges from one motor unit (NMU) (Fig. 1). Such NMU discharges from a single fiber motor unit ranged from 6-26/sec and 100-200  $\mu$ V. They were detected from the mylohyoid, external oblique, flexor, limb, or tail muscles. There was no clear relationship of the discharge of any given motor unit with that of any other motor unit of the same or other muscles. At first these discharges had no close relationship to the respiratory cycle, but, as shown in Figure 2, as the number of unit discharges increased they tended to become grouped into the inspiratory phase. When shivering became visible, though still feeble, the EMG record illustrated grouped discharges consisting of fused NMU activity, together with separated NMU discharges. These grouped discharges were concomitant with lung inflation (Fig. 3).

The intervals between both NMU and grouped discharges were longer at the beginning and end of lung inflation than at peak inflation. Similarly, the amplitudes of grouped discharges were spindle shaped, concomitant with one respiratory cycle and illustrated the fusing of additional NMU's into each grouped discharge at peak lung inflation (Fig. 4).

As shivering became more intense, the NMU discharge had a frequency of 10-12/sec (Fig. 5). One grouped discharge corresponded to one cycle of limb movement discharge and one given NMU occurred per given grouped discharge. At this stage there was no relationship between grouped discharges and they had an amplitude of 1 mV or more. During intense shivering these grouped discharges had a duration double that during feeble shivering. Vigorous

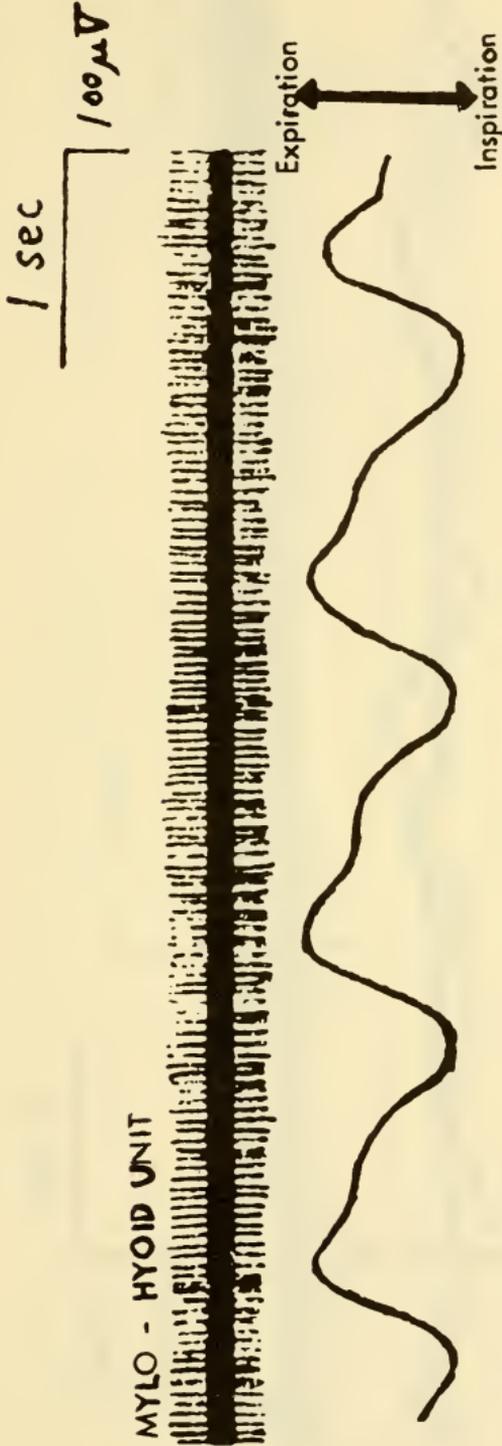


Figure 1. Single neuromuscular units (NMU) preceding visible shivering - Stage 1.

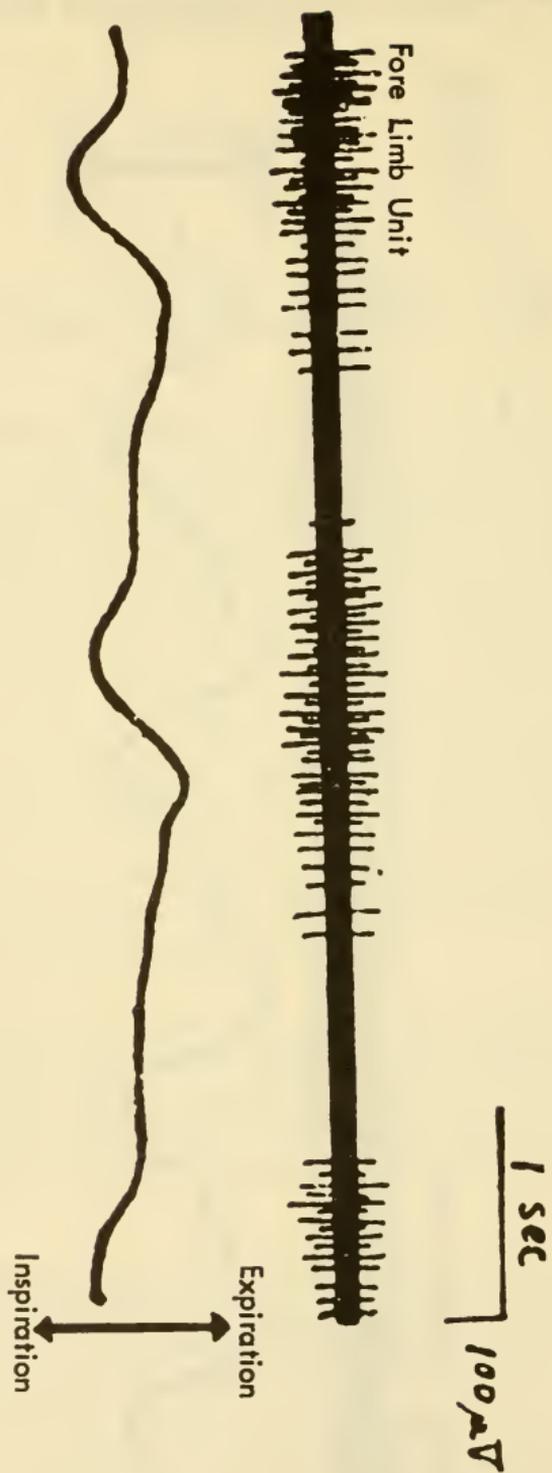


Figure 2. Single neuromuscular units (NMTU) preceding visible shivering - Stage 2.

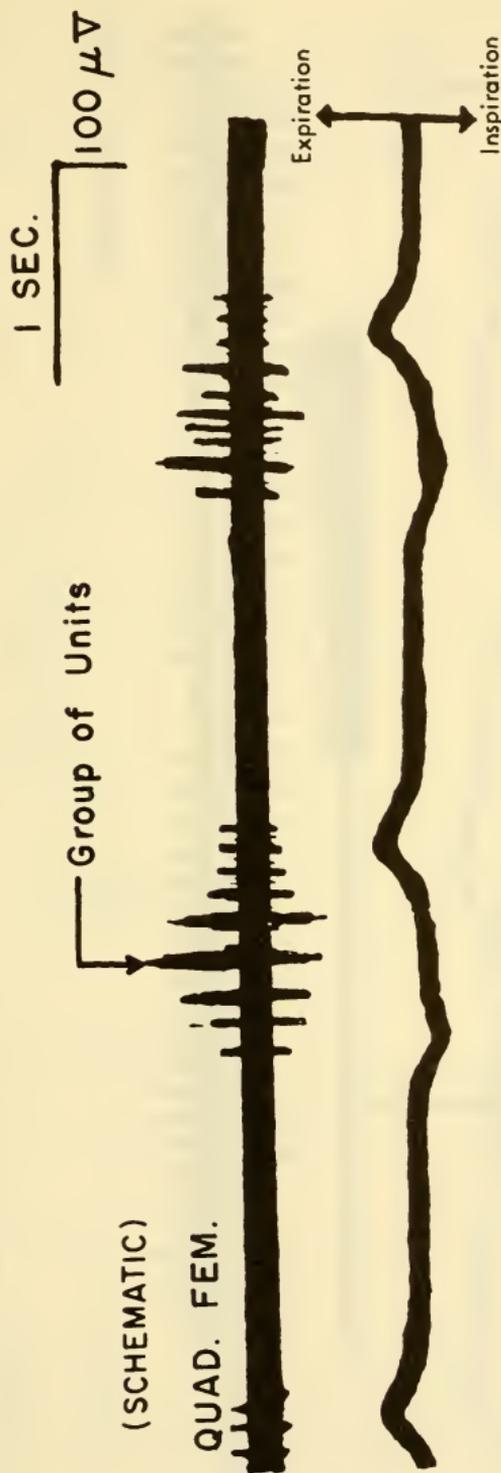


Figure 3. Visible shivering - Stage 1. (The amount of deflection does not indicate the depth of respiration.)

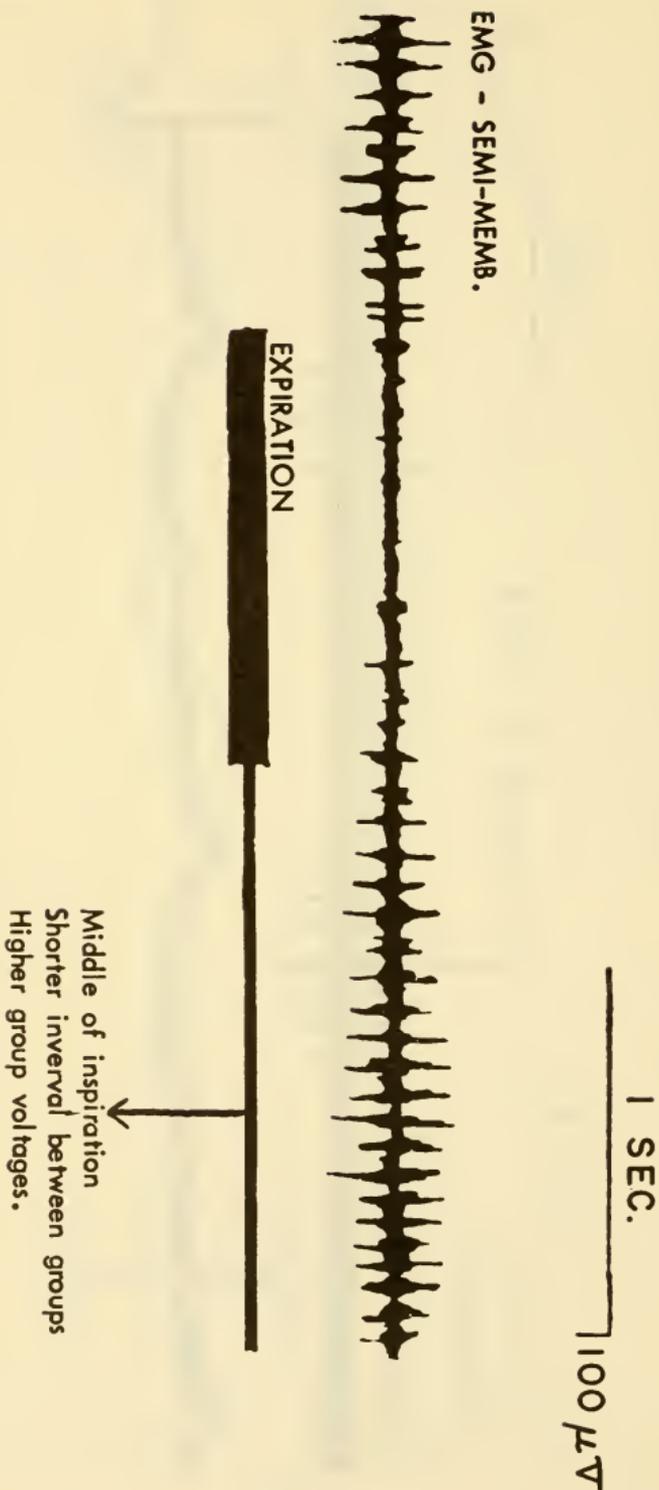


Figure 4. Alterations in grouping discharges during inspiration.

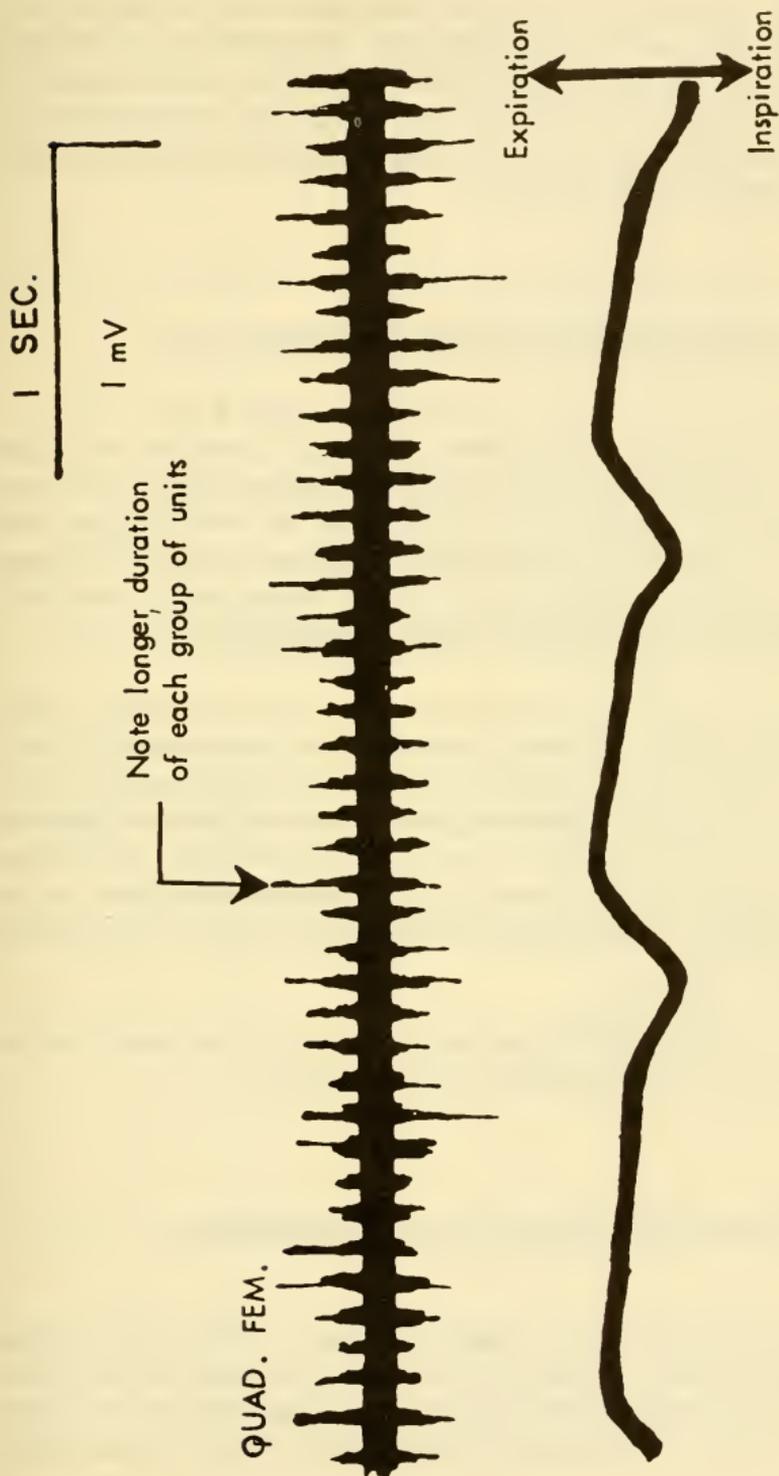


Figure 5. Visible shivering - Stage 3.

shivering continued for four to five hours and in the waning stages of anesthesia was again concurrent with lung inflation. The duration of grouped discharges shortened thus reflecting a lesser number of NMU discharges fusing into the group discharge. Intervals between each elongated grouped discharge lengthened and at this stage visible limb movements ceased (Fig. 6).

### Differences Between Muscles During Shivering

Grouped discharges and NMU discharges were observed in jaw, tongue, and neck muscles before limb and trunk muscles and as shivering waned it disappeared earlier from jaw muscles than from others. The above pattern was not evident when the head or limbs were restrained by being tied to a board which usually resulted in inhibition of the specifically restrained body part.

Muscles of the hind limb had a tendency to become active earlier than the fore limb. Extensor muscle groups became active before flexor muscle groups, agonist and antagonist discharges being concurrent rather than reciprocal; there was one grouped discharge from any one muscle fiber per one full limb cycle (Fig. 7). Additionally there were a greater number of NMU discharges fused into the grouped extensor discharges than NMU discharges fused into grouped flexor discharges.

Jaw muscle shivering and electrical activity was most predominant in the horizontal position of the lower jaw.

### The Relation of Shivering to the Level of Anesthesia

Under deep anesthesia (light mydriasis - corneal reflex absent) none of the animals shivered. Three of the 10 animals shivered concomitant with lung inflation when a weak corneal reflex was evident. At this level of anesthesia shivering was induced in the other 7

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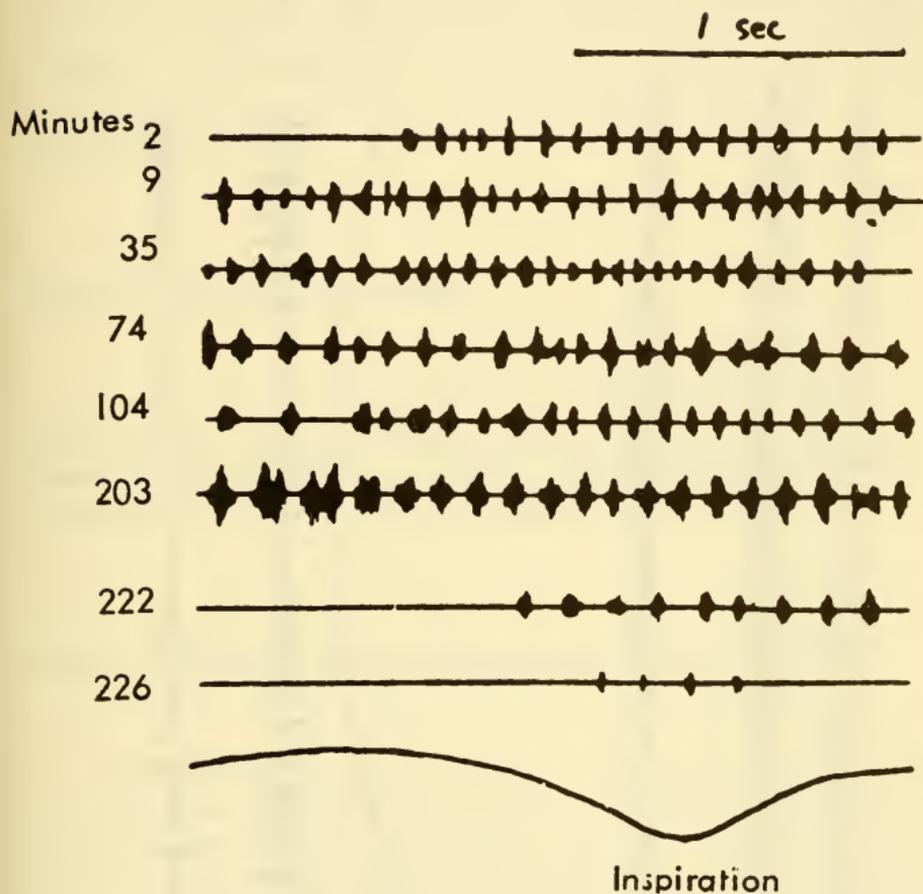


Figure 6. The development of shivering in a typical muscle (schematic).

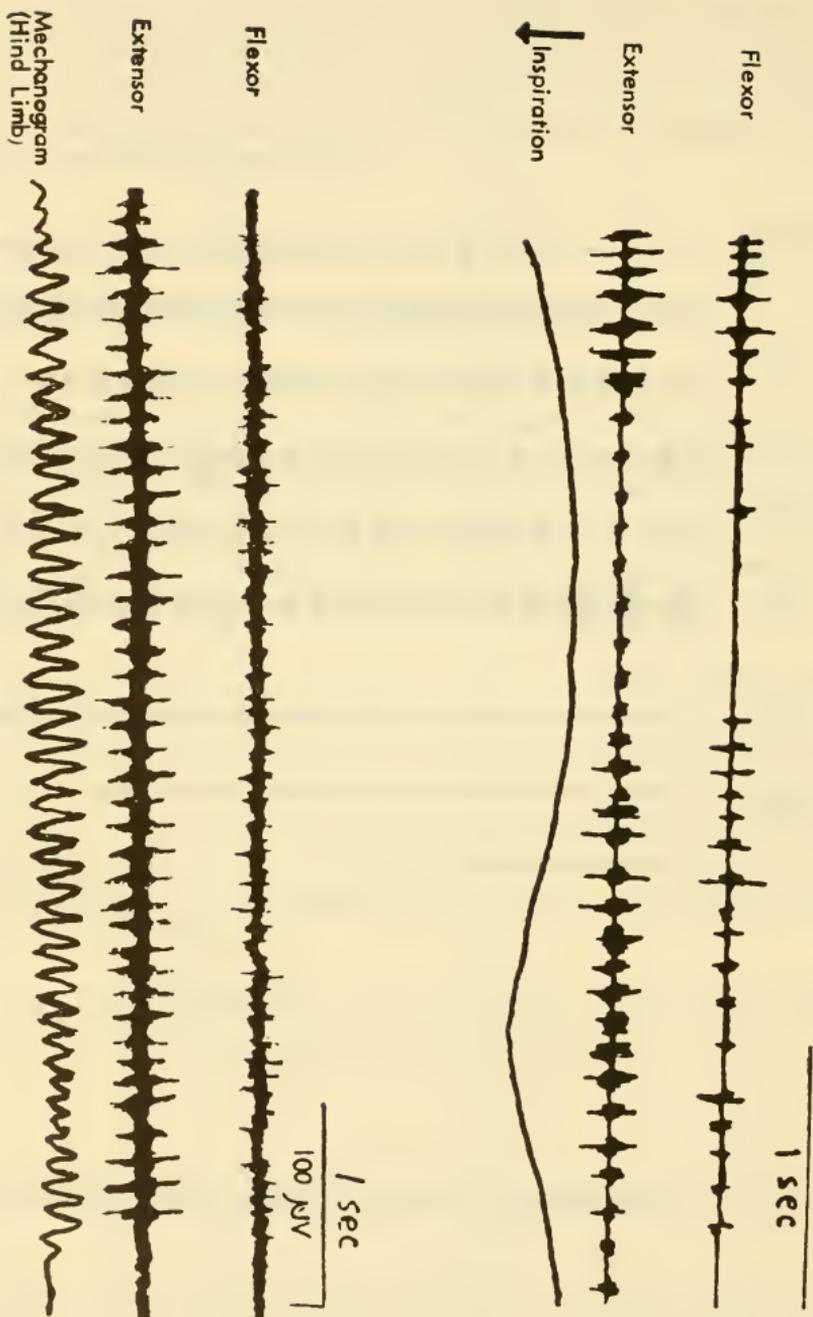


Figure 7. Flexor (Biceps Femoris) versus extensor (Quad. Femoris) during shivering.

animals by a noxious stimulus (pinching the skin) irrespective of rectal temperature (Fig. 8). Sometimes the rectal temperature continued to fall but at a slower rate after such noxious stimulus induction of active and continuous shivering. When the animals were at a light enough anesthetic level to display a conjunctival reflex, shivering weakened, and it was evident only during inspiration and sometimes it was coupled with limb extension, twitches, or locomotor movements.

### Effect of Vagotomy on Shivering

Respiratory movements became mild, absent, or irregular immediately post bilateral vagotomy (Fig. 9). While respiration was so disturbed shivering was completely depressed and its return was concomitant with the recovery of regular respiration.

### Effects of Acetylcholine (ACH) and Epinephrine on Shivering

Twenty seconds after the I. V. or I. P. injection of acetylcholine (5 mg/kg) the blood pressure of shivering animals fell 30 mm Hg. approximately for about 10 minutes or more. Respiration rate then rose from 9 to 20 breaths/min. Immediately after the blood pressure fell, shivering became feeble and was depressed completely within 5 to 50 seconds. Shivering did not return post ACH injection until respiration and blood pressure returned to pre-injection levels. Epinephrine injection (30 mg subcutaneous) facilitated the recovery of shivering after ACH induced inhibition (Fig. 10) After ACH injection, cortical, thalamic, and subthalamic brain waves did not illustrate any remarkable changes in wave frequency but wave amplitudes were somewhat depressed (Fig. 11). There seemed to be a relationship between the disappearance of shivering after ACH injection and the decrease in cortical EEG wave amplitudes and subsequent appearance of cortical barbiturate spindling. However,

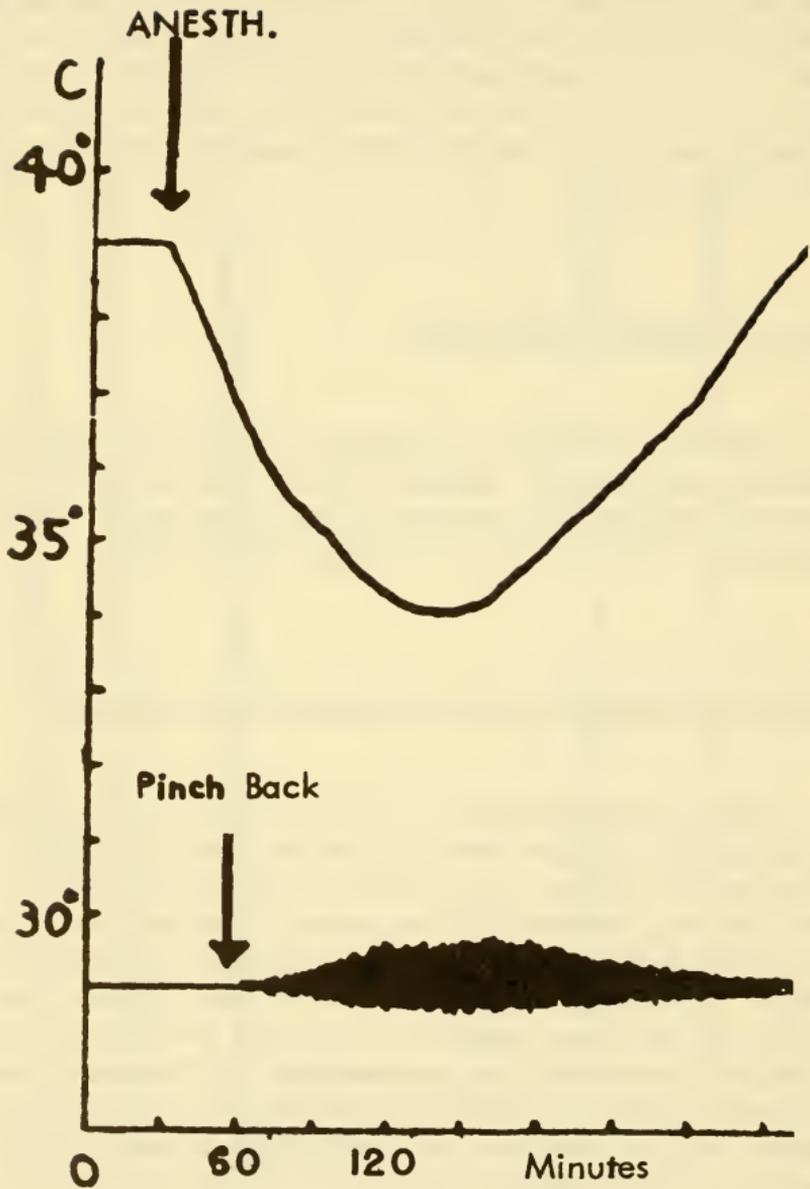


Figure 8. Noxious stimulus inducing shivering at low body temperature.

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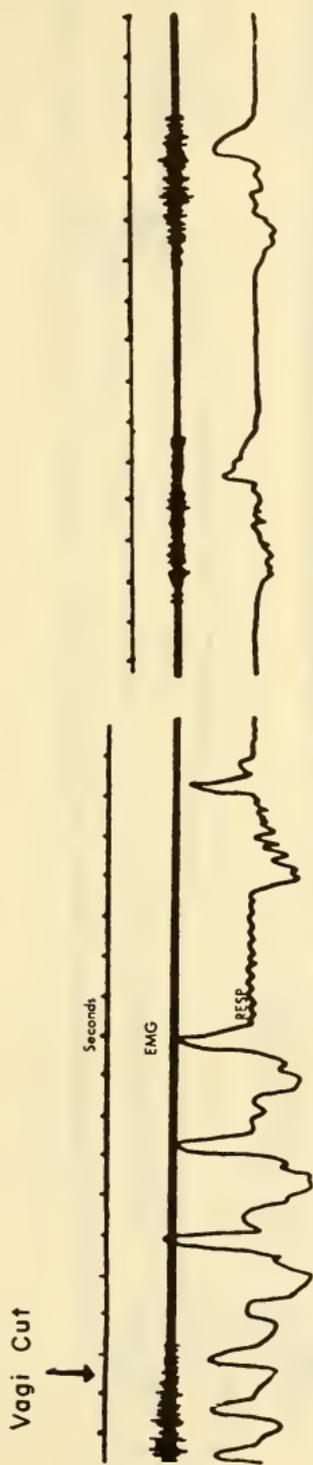


Figure 9. Effects of bilateral vagotomy on shivering.

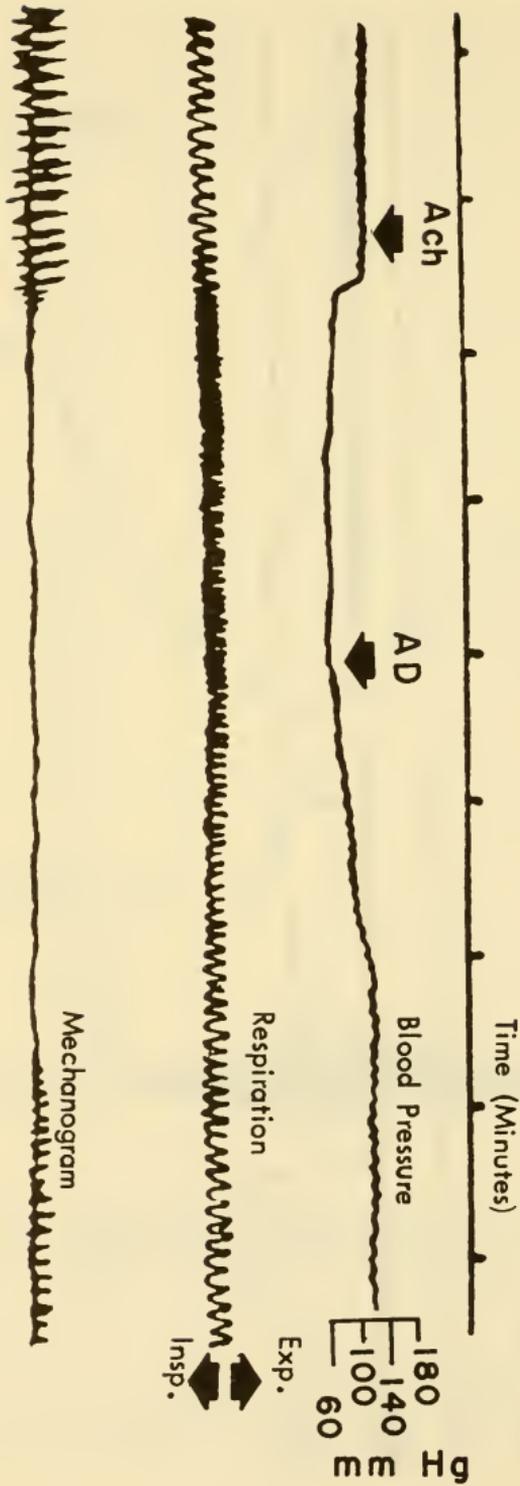


Figure 10. Effects of acetylcholine (ACh) and epinephrine (AD).

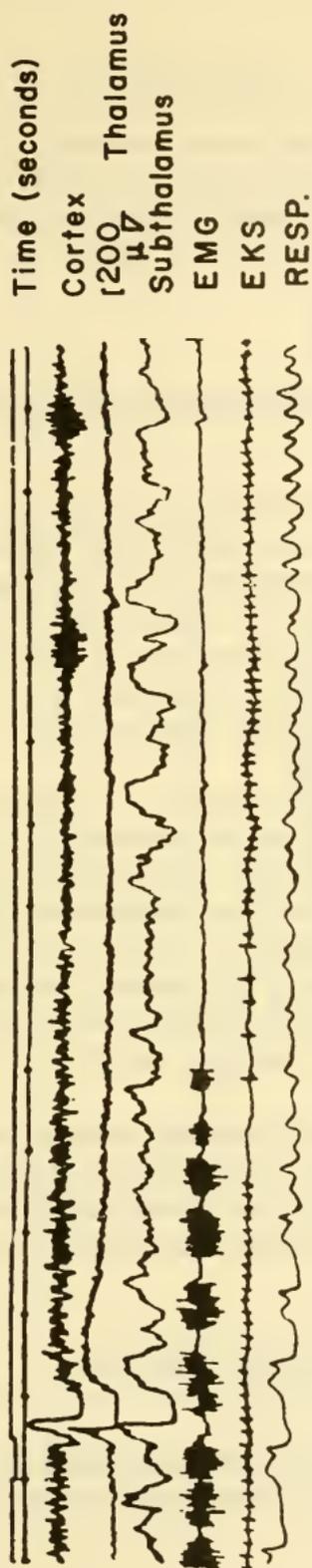


Figure 11. Effects of acetylcholine (ACH) on cortical subcortical and shivering activity.

shivering can occur in the presence of cortical barbiturate spindling without ACH injection. After ACH injection the frequency and number of NMU discharges decreased; after epinephrine injection, both increased, as did the number of NMU's per grouped discharge.

### Relationship of Body Temperature to Shivering

As mentioned earlier shivering did not occur during deep anesthesia. At room temperature ( $15^{\circ}\text{C}$  to  $20^{\circ}\text{C}$ ) the rectal temperature of animals gradually declined post Na-amytal injection and shivering occurred spontaneously at a mean rectal temperature of  $34.4^{\circ}\text{C}$  (range  $30.7^{\circ}\text{C}$  to  $38.5^{\circ}\text{C}$ ) when animals were left unmolested. Such shivering was inhibited by radiant heating on the back with a mean time of 77 sec (range 15 to 180 sec) (Fig. 12).

Shivering returned an average of 71 secs (range 20 to 260 secs) after the radiant heating was removed despite rising rectal temperature. Slow body warming by dipping one hind limb in  $43^{\circ}\text{C}$  water inhibited shivering at a rectal temperature of  $39.5^{\circ}\text{C}$ , but if the limb was removed from the water, shivering occurred at a rectal temperature of  $39.2^{\circ}\text{C}$ . Shivering at high rectal temperature was inhibited by radiant back heating and resumed when the heating was removed without change in rectal temperature (Fig. 13).

With a summer environmental temperature of  $26^{\circ}\text{C}$  or more, it was always difficult to produce shivering under barbiturate anesthesia even if the animal's environmental temperature was lowered to  $10^{\circ}$  -  $15^{\circ}\text{C}$ , the normal winter environmental temperature.

### Effects of Noxious Stimuli on Shivering

As mentioned earlier, shivering could be produced by noxious stimuli when the animals were at an anesthetic level associated with

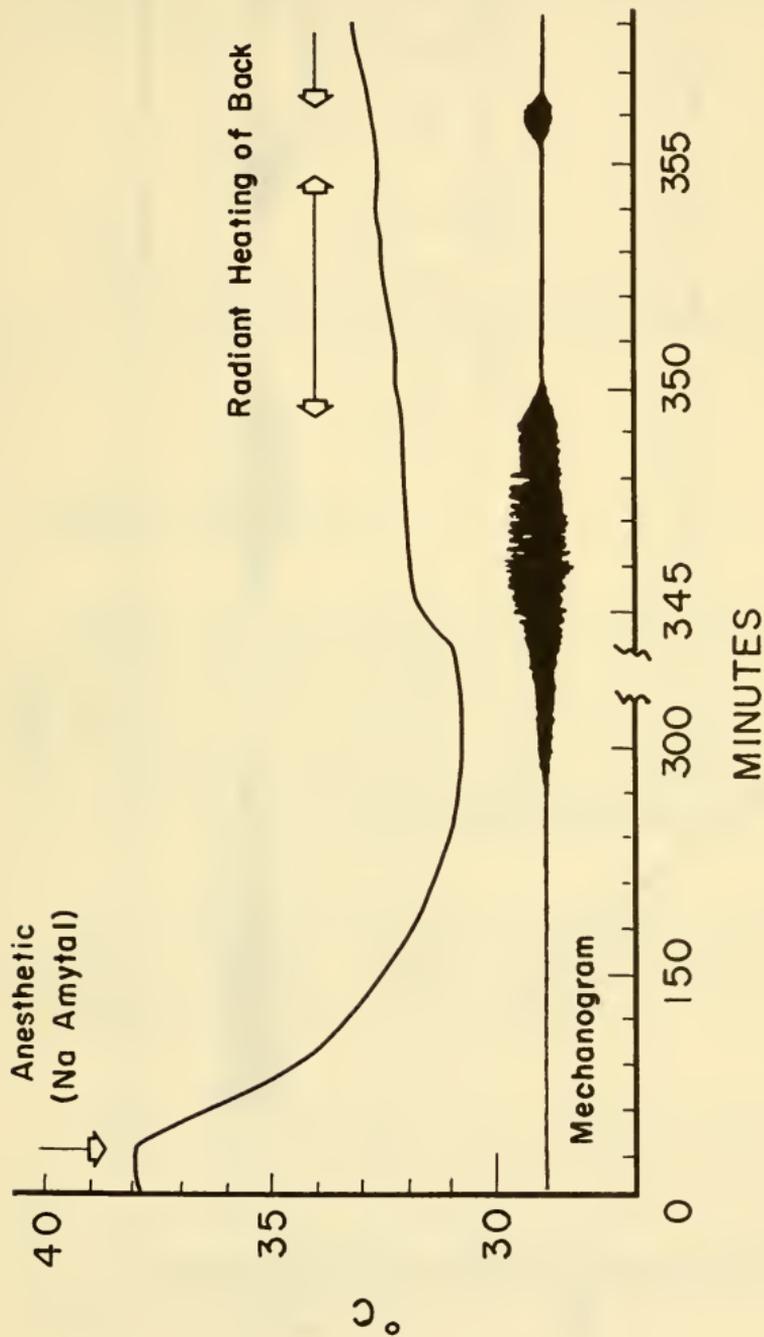


Figure 12. Suppression of shivering by radiant heating at low body temperature.

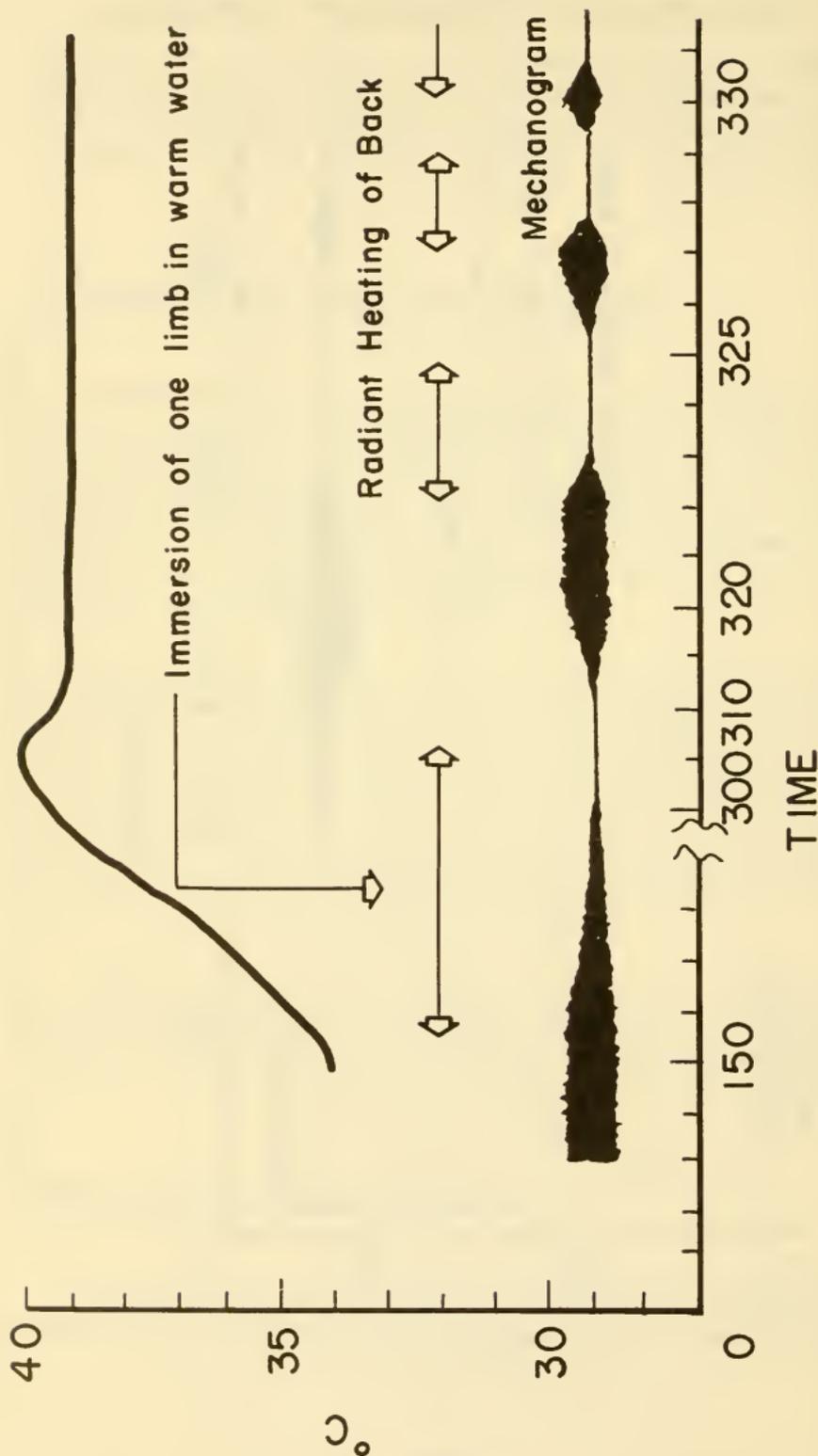


Figure 13. Suppression of shivering at high rectal temperature.

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a weak corneal reflex. At much lighter anesthetic levels noxious stimuli tended to inhibit shivering but such inhibition was followed by rebound facilitation (Fig. 14).

### DISCUSSION

These observations must be considered in terms of neural mechanisms which serve to activate, inhibit, and regulate the rhythm of shivering.

#### Activating Considerations

Magoun et al. (1938), Ström (1950), Von Euler (1950), Hemingway et al. (1954), and Andersson et al. (1956) have localized a primary inhibitory region at the junction of the antero-lateral hypothalamus and the lateral pre-optic region. A primary shivering activating system has been shown by Stuart, Hemingway, and Kawamura (1960) to exist in the dorso-medial portion of the posterior hypothalamus. The results here reported suggest that:

First: The shivering activating region may have a stronger resistance to barbiturate anesthesia than the shivering inhibitory region. Shivering, once initiated during light anesthesia, continues as the rectal temperature rises above  $38^{\circ}$  C.

Second: The excitability of the activating region is possibly affected by blood hormone levels particularly the thyrotropic hormone or thyroid hormone levels because in winter the thyroid function is active and it is somewhat depressed in the hot summer season. This is suggested by the fact that it is difficult to induce shivering in anesthetized cats in the summer even though the blood and skin temperatures are low.

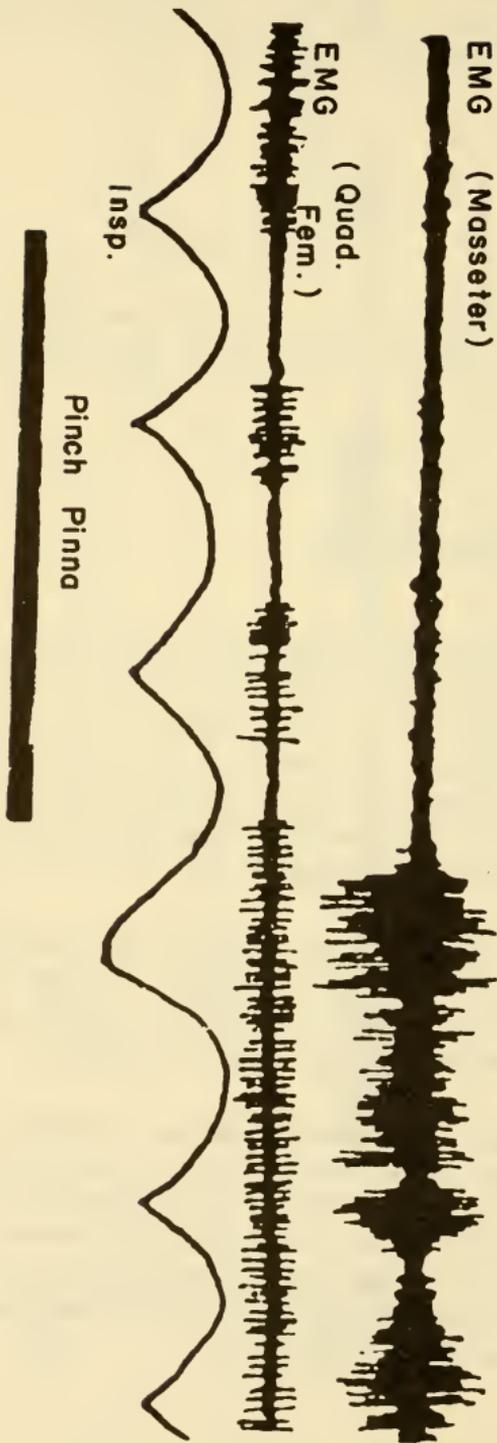


Figure 14. Effect of noxious stimulus on shivering during light anesthesia.

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Third: The shivering activating region and the reticular activating system have a close relationship since (a) strong noxious stimuli which stimulate the reticular activating system have a tendency to induce shivering even during deep anesthetic conditions, (b) the reticular activating system is possibly adrenergic (Bonvallet et al, 1954; Bradley, 1958; and Rothballer, 1956) and as such may be facilitated by epinephrine and depressed by acetylcholine.

These results indicate that acetylcholine inhibits and epinephrine facilitates shivering. Some conflict exists in the literature on this latter point. Cassidy, Dworkin, and Finney (1926) reported that shivering, abolished by insulin injection in anesthetized animals, was restored by large doses of epinephrine. Hall and Goldstein (1940) reported that I. V. injection of 80-150 mg/kg epinephrine causes a transitory facilitation in anesthetized animals. Smaller doses (30-50 mg/kg) produced inhibition without temporary facilitation. Unpublished data of Stuart, George, and Hemingway suggest that shivering is mildly facilitated in unanesthetized cats following subcutaneous injection of 40 mg/kg. The facilitation here reported following subcutaneous injection of 30 mg/kg into anesthetized dogs followed previous ACH injection. Obviously the question cannot be fully resolved until a more extensive study is performed on both anesthetized and unanesthetized shivering animals in which various doses of epinephrine are applied by both intravenous and subcutaneous routes, uncomplicated by previous drug inhibition of shivering.

Fourth. There is a relationship between the activating region and inspiration during shivering that could be organized in one of three ways: (a) Excitatory impulses to the shivering activating region from pharyngeal cold receptors that are stimulated during inspiration (Cort and McCance, 1953); (b) Excitatory impulses ascending to the activating region and/or descending to the spinal cord from pulmonary stretch or from the inspiratory center receptors, maximally stimulated at peak inspiration; (c) A generalized state of increased medullary excitability occurring during inspiration and facilitating descending extrapyramidal activity (Kawamura and Fujimoto, 1958). For example, the jaw opening reflex is facilitated during inspiration.

However, it must be stressed that there was no clear relationship between inspiration and the increase in muscle tonus that pre-

cedes shivering. This may mean that at this stage of anesthesia in which an increase in muscle tone but no shivering is evident, the animal is too deeply anesthetized to permit respiratory facilitation of shivering. However, this lack of relation between shivering and muscle tonus may be due to the latter phenomenon having spinal, rather than central origin. Classical decerebration studies have illustrated the predominantly inhibitory action the rostral nervous system exerts on the spinal cord. Just as decerebration releases the spinal cord from inhibitory influences so it may well be that in the light anesthetic state, the supra-spinal inhibitory regions are more depressed than the spinal cord. Hence, the initial increase in muscle tone is not directly related to temperature regulation but represents a stage of anesthesia in which proprioceptive hyperactivity predominates just as decerebrate rigidity is due to a hyperactivity of myotactic origin.

In addition to a central activating region being necessary to initiate shivering, there is evidence that shivering is facilitated by afferent impulses from proprioceptive nerve endings that may exert these excitatory effects centrally and/or peripherally.

The evidence is as follows:

First. During deep anesthesia the somatic muscles are completely relaxed and no electrical activity as revealed by unit potentials is noted. As the animal recovers from the anesthesia and the muscles regain tonus, unit spike potentials begin to appear and these are followed by shivering. Present results in these observations confirm the earlier work of Burton and Bronk (1937). The work here reported suggests that as the muscle tone increases, the resulting activation in integrative afferent proprioceptive input from annulo-spiral, flower spray, Golgi tendon organ, and deep joint proprioceptors is favorable to the production of shivering. For example, it is well known that increased annulo-spiral discharge from any muscle fiber lowers the alpha motor neuron thresholds of that muscle. Kawamura et al (1958) have shown that there is an increase in the discharge of frequency of the trigeminal mesencephalic nucleus (which is considered to receive proprioceptive information from the jaw muscles) immediately prior to the onset of jaw muscle shivering.

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Second. Shivering is more intense in jaw muscles when the head of the dog is in the normal horizontal position. In this position, the anti-gravity jaw muscles are subjected to more tension with a concomitant increase in proprioceptive activity.

### Inhibitory Considerations

These results suggest the following concepts relating to inhibitory shivering mechanisms:

First. Uprus et al (1935), using unanesthetized human subjects, have shown that shivering ceases as the rectal temperature rises and reoccurs as the temperature falls, even in the presence of a high initial temperature. The results on anesthetized animals would suggest that shivering can be both inhibited by radiant heating and instigated by cold air without any change in rectal temperature. Shivering was inhibited in low rectal temperature dogs when the backs of the animals were briefly heated. This phenomenon may be due to a sudden increase in excitatory impulses to the anterior hypothalamic inhibitory region from dorsal heat receptors. Such a brief and sudden input could be sufficient to inhibit shivering temporarily. Unfortunately, it is not known if such inhibition might be only temporary in the face of consistent low blood temperature since the period of radiant heating was of short duration. At any rate, this phenomenon is a clear example of a peripheral stimulus antagonizing the physiological effects of a contrary central stimulus.

Second. In deep anesthetic states a noxious stimulus can facilitate shivering. But in light anesthetic states noxious stimuli tend to inhibit shivering, even when the blood temperature is below normal. This type of inhibition may be due to the noxious stimuli evoking avoidance behavior in the animal and as such voluntary avoidance movements would tend to inhibit shivering by successful seizure of the motor neuron pool. Such a concept is supported by Stuart, Freeman and Hemingway's unpublished findings that restraint devices inhibit shivering in unanesthetized chilled cats. It is difficult to account for the earlier appearance of shivering in tongue, jaw, and neck muscles than in limb muscles. At first glance it appears analogous to the development of tetanus and tetany. However, restraint and

proprioceptive input is more prevalent in these experiments in the limbs on which the animal is lying than in the freely suspended tongue, jaw, and neck muscles. When inducing shivering by electrical stimulation of the central nervous system, Stuart and Kawamura have found shivering easier to induce in the limb muscles; but in these experiments the animals' heads were held in a stereotaxic frame.

### Regulatory Considerations

Perkins (1945) has suggested that the rhythm of shivering is controlled by proprioception but instigated and maintained by central hypothalamic activity. Such a concept followed his recording a change in the frequency-amplitude characteristics of hind limb shivering following deafferentation. The most characteristic EMG pattern of a shivering muscle is a grouping voltage occurring 10-12 times per second, the same frequency as the hind limb oscillations recorded by Perkins. When we cut the dorsal roots the grouping voltages became randomized and shivering lost its characteristic rhythm. This finding is a confirmation of Perkins' original findings. However, as mentioned earlier it is suggested that proprioceptive input as well as regulating the rhythm of shivering also facilitates its initial occurrence.

### SUMMARY

Following electromyographic analysis, the muscles of dogs at various stages of shivering intensity, rectal temperature, and anesthetic level, the following conclusions appear in order:

1. The order of appearance of shivering in muscles is (a) jaw and tongue, (b) neck, (c) hind limb, (d) forelimb, with extensor muscle shivering more intense and appearing earlier than flexor muscle shivering.

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2. The increased muscle tonus that occurs in anesthetized dogs prior to shivering is not necessarily a phenomenon of temperature regulation origin.
3. Lung expansion facilitates shivering.
4. Proprioceptor activity may facilitate as well as coordinate shivering.
5. Acetylcholine inhibits and epinephrine facilitates shivering, and suggests a relationship of shivering to the level of excitability of the reticular activating system.

### ACKNOWLEDGMENT

I wish to thank Dr. A. Hemingway, Professor of Physiology, UCLA School of Medicine, for his help and encouragement in presenting this paper, and I also wish to extend my appreciation to Mr. D. Stuart for editing this paper.

DISCUSSION

DR. MINARD: Is it not possible that the ACH acts by cutaneous vasodilation, warming the skin and reducing the afferent input from the skin, whereas epinephrine might have the opposite effect? Is it possible that acetylcholine, instead of acting on the ascending reticular formation, might act peripherally by vasodilation in the skin, thereby reducing the thermoreceptor inflow to the center?

DR. KAWAMURA: Yes, there may be two processes. One is the effect of the autonomic function on the vasomotor system; the other is the direct effect of these drugs on the central somatic system. I would guess that the effect is either on the autonomic or somatic central mechanisms and that they are more important in this case than the peripheral ones.

DR. RODDIE: How was the acetylcholine given?

DR. KAWAMURA: By injection into the femoral vein.

DR. RODDIE: It is just that the action of acetylcholine in the body is a very short one; it is destroyed very quickly. That was shown by the heart rate records. But the inhibition of shivering lasted for quite a long time, right until the end of the record. I wonder whether there was any other effect that acetylcholine might have.

DR. STUART: I do not think he showed heart rate. He showed blood pressure dropping.

DR. RODDIE: There was an EKG record, and it came back to normal whereas shivering was inhibited throughout the record.

DR. FREEMAN: Also, acetylcholine passes very slowly across the blood-brain barrier so that unless one gave it by intrathecal injection into the purported centers one would find it hard to see how it could escape destruction by acetylcholinesterase in the blood.

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DR. HENSEL: In the record, I saw that after administration of acetylcholine the blood pressure fell from about 120 to about 60; and I wonder whether there is any possibility that the blood supply of the brain might have changed. We know that shivering is very much influenced by changes in oxygen pressure and  $\text{CO}_2$  pressure. Might this not be the cause of your change? I do not know, but how did you exclude this possibility?

DR. STUART: To say that the particular activating system is adrenergic and that it would be facilitated by an injection of epinephrine and inhibited by acetylcholine, is a point of great controversy today, I think, among neuropharmacologists. I did not think that Dr. Kawamura meant to imply that this was necessarily so; but he is suggesting that this is one alternative.

DR. CLARK: That difference in shivering intensity between summer and winter is intriguing. Did you, by any chance, give any of your winter-summer dogs thyroxin?

DR. KAWAMURA: No, I have never applied thyroxin to the dogs in this experiment.

DR. CLARK: And was the difference between summer and winter shivering only observed under sodium amytal anesthesia as well?

DR. KAWAMURA: Yes, I tried anesthesia with other barbiturates too. Pentobarbital, thiopental, and ether were used. The summer-winter differences in shivering were the same, independent of the anesthetic drug. Sometimes I could induce weak shivering even in summer in the dog, but it was very difficult to get and was short lasting.

DR. CLARK: I operate under nembutal and routinely I see my animals shivering when they are coming out of the anesthesia regardless of the season.

DR. JOHANSEN: In regard to the interrelations you have proposed between respiration and shivering, have you ever tried to manipulate with the respiratory phases in an anesthetized animal?

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DR. KAWAMURA: This would be an interesting problem.

DR. JOHANSEN: I was thinking that you might try artificial respiration and attempt to interfere with the phases of the respiration, in order to exclude, for instance, the stretch receptors.

DR. KAWAMURA: I have made a study of the relationship of artificial respiration and shivering. Through my experience I can tell you that shivering movement is always followed by the inspiratory phase, under fast or slow rhythm of artificial respiration.

DR. FREEMAN: We found the same relationship between shivering and inspiration when we were recording unit activity in the brain stem associated with the shivering. These unit potentials come with shivering and go when shivering stops, but during the early part when shivering is phasic with inspiration these bursts are synchronous with inspiration. Also, your observation of a painful stimulus is true of these units as well. There are many units in the nervous system which can be driven by painful stimuli. Their activity can be either started or increased and there are relatively few that will be inhibited; but these shivering unit potentials are very strikingly shut off, and when the painful stimulus is removed, there is a striking rebound phenomenon. Their frequency increases abruptly above the preceding level.

DR. HENSEL: Have you any observation of the topography of shivering in the proximal and distal parts of the limb? We found in our investigations in the cold chamber that shivering starts in the proximal parts of the limbs as measured by the EMG. After prolonged cold exposure, then the increased muscular tone in the proximal parts will disappear, and increased tone in the distal parts appears; so there is a temporal shift in the topography of shivering.

DR. KAWAMURA: Yes, I believe there is a problem, and I visually recognized that usually the peripheral region begins shivering earlier than the proximal vibration appears, but no exact recordings were made on the proximal and distal distribution of shivering.

DR. FREEMAN: If you asphyxiate an animal or impair his respiration, then instead of having simply the intercostal muscles and

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diaphragm active, you get accessory muscles that are inspiratory and these are predominantly in the neck and jaw. I wonder if you made any attempt to correlate the pattern of onset of shivering in muscles with the pattern of onset of these accessory muscles as asphyxia is brought into play?

DR. KAWAMURA: This was not measured. It would be worthwhile to investigate this to determine whether or not the phasic activity of the accessory muscles facilitates shivering.

DR. LIM: There is one comment. Dr. Hensel tells me that the carbon dioxide inhalation, five to six percent, increases shivering which phenomenon may be in favor of this last possibility in raising the respiratory activity.

DR. HENSEL: Yes.

DR. STUART: One important aspect of this paper is the demonstration of synchronous activity in antagonistic muscles during shivering. This, together with the shivering tremor frequency of 10-12 cps, is distinctly different from the Parkinson tremor (4-7 cps) in which antagonistic muscle activity is alternating. Now, you showed us evidence that the flexor and extensor fire synchronously.

DR. KAWAMURA: Yes, I did.

DR. STUART: I think this is unique in the literature. Have you recorded the tension developed in antagonistic muscles during shivering? Or do you know of any accounts of it?

DR. KAWAMURA: No, I have never measured that.

DR. HENSEL: Did you record hypothalamic temperature during your experiments with local cutaneous heating?

DR. KAWAMURA: No, I did not.

DR. HENSEL: That is the question, because we found in the cat that local cutaneous heating might cause quite considerable changes in hypothalamic temperature without any considerable change in rectal temperature.

KAWAMURA, Y.

DR. HEMINGWAY: I think Dr. Kawamura heated the back, did you not?

DR. KAWAMURA: Yes, I did.

DR. HEMINGWAY: Are you thinking of the head and back or just the back?

DR. HENSEL: I mean just the limb, not the back but the hind limb. The hypothalamic temperature changed very slowly following heating of the hind limb.

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### REFERENCES

1. Andersson, B., R. Grant, and S. Larsson. Central control of heat loss mechanisms in the goat. *Acta. Physiol. Scand.* 37:261-280, 1956.
2. Bonvallet, M., P. Dell, and G. Hiebel. Tonus sympathique et activité électrique corticale. *EEG clin. Neurophysiol.* 6:119-144, 1954.
3. Bradley, P. B. Microelectrode approach to the Neuropharmacology of the reticular Formation. *Psychotropic Drugs.* Elsevier Pub. Co., p. 205-216, 1958.
4. Burton, A. C. and D. W. Bronk. The motor mechanism of shivering and of thermal muscular tone. *Am. J. Physiol.* 119:284, 1937.
5. Cassidy, G. J., S. Dworkin, and W. H. Finney. The effect of various sugars (and of adrenalin and pituitrin) in restoring the shivering reflex. *Am J. Physiol.* 77:211-218, 1926.
6. Cort, J. H. and R. A. McCance. The neural control of shivering in the pig. *J. Physiol.* 120:115-121, 1953.
7. Hall, V. E. and P. B. Goldstone. The influence of epinephrine on shivering and on metabolism in the cold. *J. Pharma. and Exp. Therap.* 68:247-251, 1940.
8. Hemingway, A., P. Forgrave, and L. Birzis. Shivering suppression by hypothalamic stimulation. *J. Neurophysiol.* 17:375-386, 1954.
9. Kawamura, Y. and J. Fujimoto. A study of the jaw opening reflex. *Med. J. Osaka Univ.* 9:377-387, 1958.

10. Kawamura, Y., M. Funakoshi, and S. Tsukamoto. Brainstem representation of jaw muscle activities of the dog. *Jap. J. Physiol.* 8:292-304, 1958.
11. Magoun, H. W., F. Harrison, J. R. Brobeck, and S. W. Ranson. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* 1:101-114, 1938.
12. Perkins, J. F. The role of the Proprioceptors in Shivering. *Am. J. Physiol.* 145:264-71, 1945.
13. Rothballer, A. B. Studies on the adrenaline-sensitive component of the reticular activating system. *EEG and clin. Neurophysiol.* 8:603-621, 1956.
14. Ström, G. Influence of local thermal stimulation of the hypothalamus of the cat on cutaneous blood flow and respiratory rate. *Acta physiol. Scand.* 20:Suppl. 70, 1-118, 1950.
15. Stuart, D., Y. Kawamura, and A. Hemingway. *The Physiologist* 3(3):156, 1960.
16. Uprus, V., G. B. Gaylor, and E. A. Carmichael. Shivering: A Clinical study with especial references to the afferent and efferent pathway. *Brain.* 58:220-232, 1935.
17. Von Euler, C. Slow temperature potentials in the hypothalamus. *J. Cell and Comp. Physiol.* 36:333-350, 1950.

# NERVOUS PATHWAYS IN THE CHEMICAL REGULATION AGAINST COLD AND THEIR CENTRAL CONTROL

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The nervous system can activate heat production in various ways, at least theoretically. Three main processes are usually called upon. First, the nervous system can increase the specific activity of every innervated organ; mechanical activity of muscle is a good example of this. The heat production will increase accordingly, the useful work being very small in the case of muscular tonus of shivering. Second, there are nonspecific reactions of emergency function, which, though they are not directly adapted to the struggle against cold, spend energy and produce heat useful for this purpose. An example of this is the activation of the sympathetic system and epinephrine secretion. Finally, there exists a specific and independent system which activates metabolism and heat production by various organs, especially the liver and splanchnic viscera, without any other efficient activity.

Although the roles of these various means have often been investigated in the past, only few works are at the present directed in this line; however, no definite solution has been found yet. We will consider the problem from the standpoint of the quantitative importance of each of these factors and the conditions under which they are put into action.

Most investigators are concerned with the disturbances of the central temperature after excluding one of the effector mechanisms. Such a method cannot provide sufficient and quantitative information. Also, the estimation of the heat production itself is not of much use in many cases. Indeed, the caloric response to cold depends more or less on physical regulation, chiefly on peripheral vasomotor activity, and it would be preferable if it were suppressed beforehand. Besides, one must be sure that the intensity of the cold action is responsible for the development of the caloric response as it may be the result of an increase of heat loss. Finally, a

difficulty may arise from the great potency of the mechanisms of struggle considered as a whole in some animal species. In the dog, for example, the ability to withstand the cold is very important; the physical regulation may spare the load on heat production and in the severe cold the heat production can increase to very high values without any inefficiency being detected. Only extreme cold can surpass the total capacity for defense in the normal animal. In moderate cold exposure, one effector mechanism may easily be replaced by the others. It is therefore necessary to know the greatest capacity for thermogenesis and, if that requires excessive conditions of temperature, to remove part of these effector mechanisms and to determine then the maximum capacity for heat production. Afterwards, every further reduction of that maximum can be ascribed to the subsequent operation. The comparison of these various levels of thermogenesis is only valuable if they are true maxima and if no substitutes are possible.

### CONTROL OF THE MUSCULAR ACTIVITY

Voluntary muscular activity, shivering, and thermal muscle tone are effected by the same muscle but according to different kinds of stimulation. Of course some parts of the muscular apparatus are concerned more with one sort of activity, but not exclusively.

In the spinal cord, there is some evidence of the existence of descending pathways especially controlling shivering. It is known that corticospinal tracts are not necessary for that control. Moreover, it appears that different patterns of muscular activity can substitute for each other. Indeed, in the dog deprived of reactions of shivering by section of the anterior part of the cord, muscular activity may still increase in cold ambient temperatures, in the form of agitation.

Authors such as Freund and Strasmann (1912) and Isenschmid (1926) tried to measure the importance of thermogenesis provided

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by muscular activity by cutting motor nerves to an extensive region. This procedure pointed out the persistence of a potent increase of heat production against cold. But the active portion of the musculature can still be responsible for that result.

Lesions of the spinal cord have been attempted also, though they are less specific in their meaning. According to Freund (1913), section of the thoracic cord in the rabbit abolishes the whole physical regulation against cold, leaving the chemical regulation unchanged or even more active in compensation. Kayser (1929), experimenting on the pigeon, observed similar results after section of the thoracic cord. Hermann, (1938), using the dog, saw the persistence of an efficient regulation against cold after destruction of the cord below thoracic one level. In cold ambient temperature, there is a distinctly greater increase of heat production in the same animal species we have seen than in the dog before the lesion. The maximum metabolism is not yet reached at  $-15^{\circ}\text{C}$ , and the curve of metabolism is still ascending at this temperature despite extensive paralysis and the lack of epinephrine secretion. In that preparation, of course, a part of the musculature remains active and seems to be able to compensate for exaggerated heat loss in the cold. Indeed, in absence of vasomotor regulation, the heat production has to balance more exactly the thermal demand of the environment and any deficit must appear unmasked.

Issekutz (1937) found that cervical section of the dog reduces the thermogenetic responses in the cold. According to Freund (1913), rabbits then become poikilothermic. These authors explain these results by the assumption of the suppression in that section of important vegetative outflow leaving the cord at this low cervical level. Our results confirm that section or destruction of the cord reaching the inferior cervical segments seriously disturbs the chemical regulation in the dog. In the cold, below  $-10^{\circ}\text{C}$ , a maximum metabolism level of 2 to 2.5 times the basal value is reached with fall in central temperature, but there is no complete poikilothermia. Besides, we think that the difference between cervical and thoracic lesions can be explained more properly by the motor outflow of the brachial plexus at this level.

In order to test this explanation, we tried to ascertain the role of the cervical and brachial plexuses in the potent thermogenetic

capacities of dogs whose spinal cords are severed at thoracic one level (Fig. 1). In 10 to 12 dogs operated on in this manner, bilateral section of the brachial plexus induced an obvious disturbance of the regulation, very similar to those resulting from cervical lesions; below  $0^{\circ}$  C, the regulation failed and the central temperature decreased when the cold exposure continued. Under the same conditions the heat production could not surpass a given level; we obtained a true maximum.

Therefore, the muscular activity in the narrow field controlled by the cervical and brachial plexuses is able to provide an important though unmeasured part of the regulatory thermogenesis (Figs. 2 and 3). Also, one can suppose that the regulatory power remaining after that operation depends on the activity of musculature in the neck and face, which is almost impossible to eliminate.

Many other results point out the importance of the muscular factor in the heat production elicited by cold exposure. Hammel and Hardy (1960) observed a very close parallelism between the bursts of shivering and the curve of heat production in the dog. During the intervals between these bursts the metabolism drops down to basal values. Carlson (1955) made similar observations in the rabbit.

The old experiments on curarization are liable to objections because of the non-specific actions of drugs. Davis (1955), using curare, assigns the extra-motor reactions for 40 per cent of the heat production by the mouse in the cold. Werner and others (1956) found spontaneous rewarming of curarized dogs with blankets after anesthesia in a room at  $24^{\circ}$  C, but the role of basal combustion is not taken into account. Cottle and Carlson (1954) noted a distinct increase of heat production of curarized rats exposed to cold, chiefly in adapted animals.

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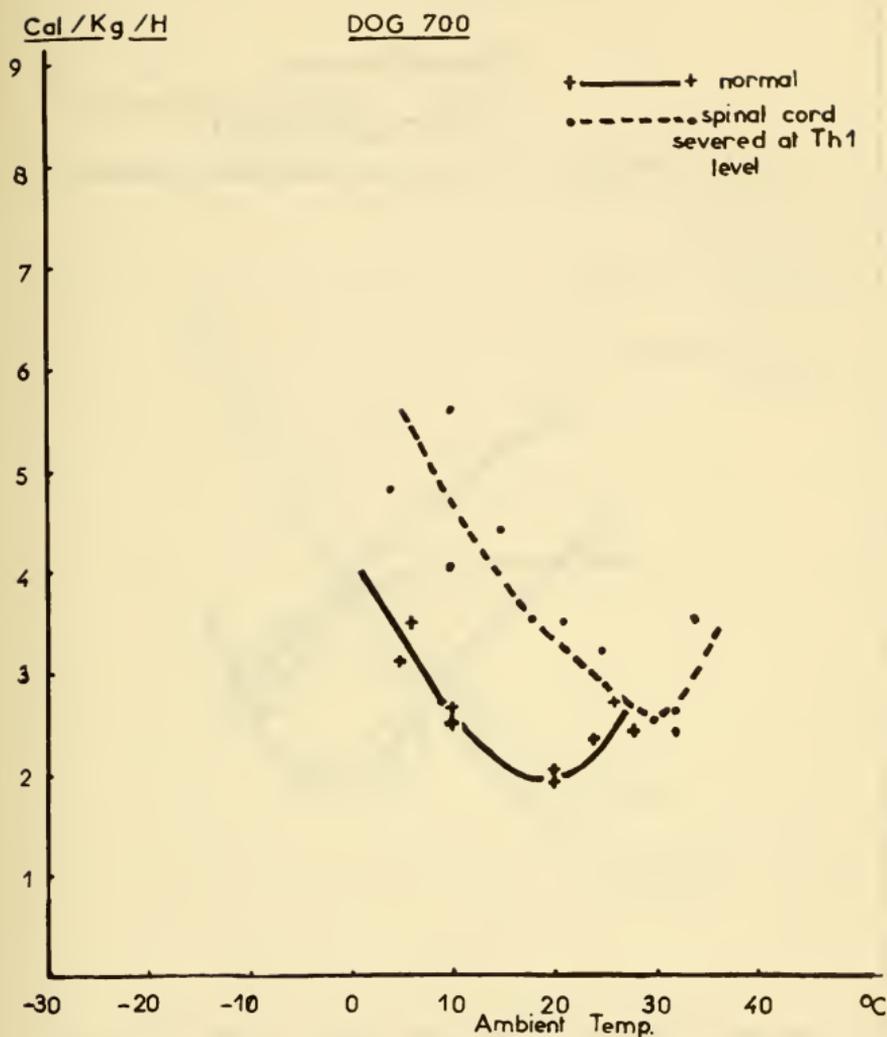


Figure 1. Heat production of dogs plotted against ambient temperature. The normal dog and dog after spinal cord had been severed at thoracic one level.

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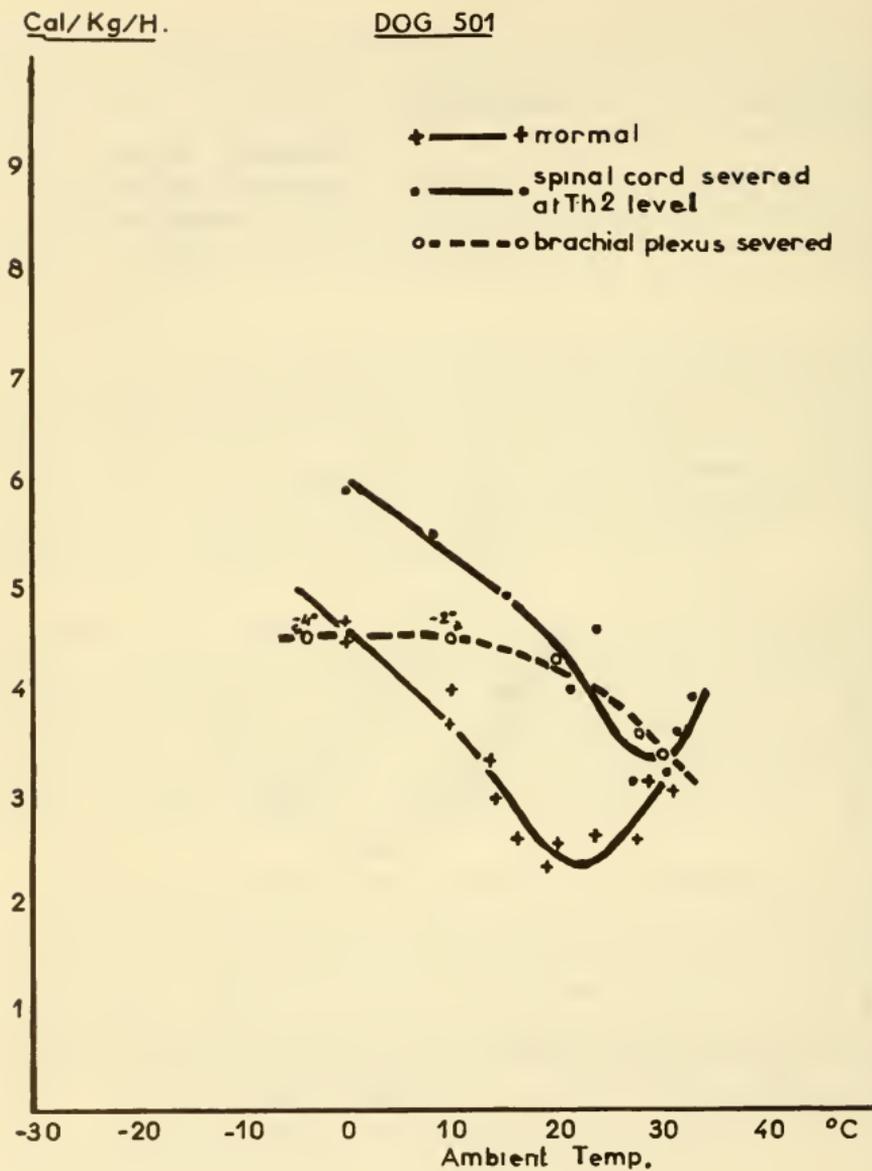


Figure 2. Heat production of dogs. The normal dog, the dog after spinal cord had been severed at thoracic one level, and the dog after severing the brachial plexus.

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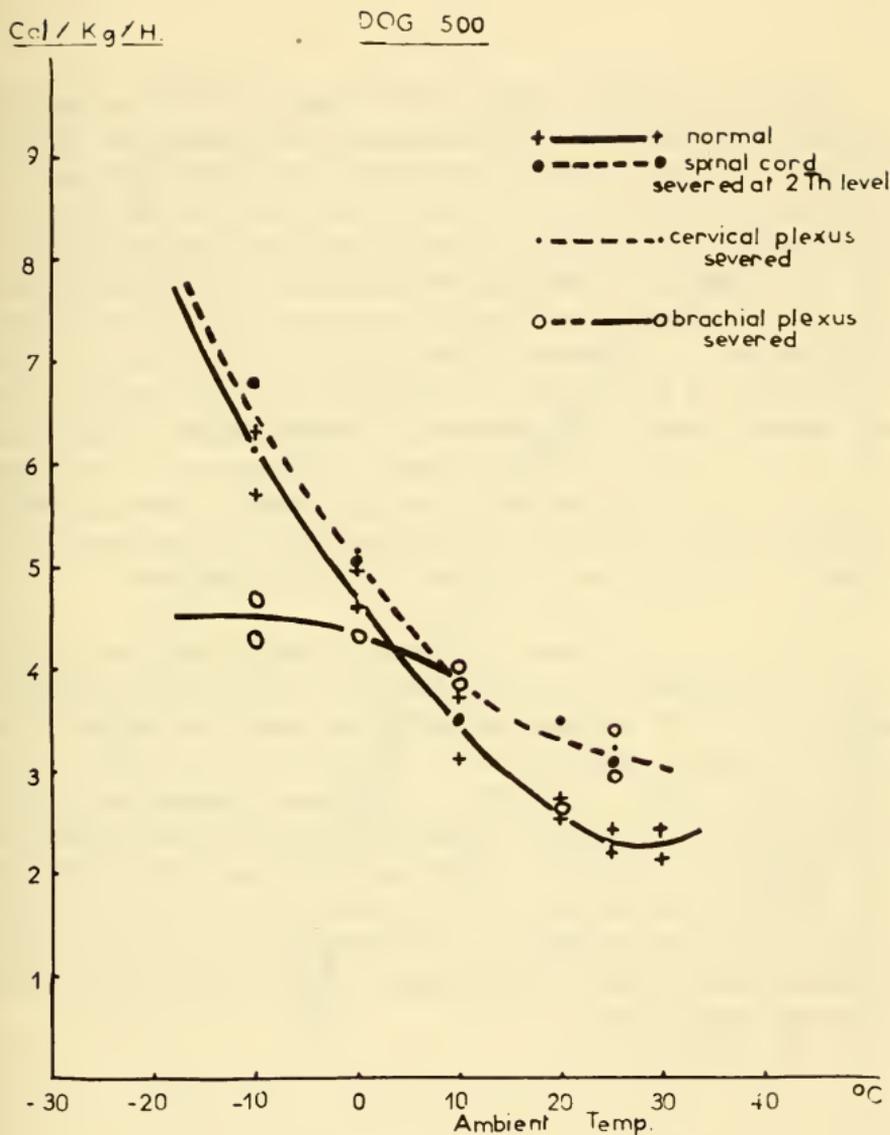


Figure 3. Heat production of dogs. The normal dog, after the spinal cord had been severed a thoracic two level, after the cervical plexus had been severed, and after the brachial plexus had been severed.

## THE ROLE OF EPINEPHRINE SECRETION

Can the calorogenic action of hormones of the adrenal medulla play an important part in the regulatory heat production? In 1941, Hemingway and Hathaway ascribed to this factor the slight increase of metabolism observed at the beginning of the cold exposure, before the onset of shivering. Of course, extraneous injected epinephrine can substitute for the heat required by the cold exposure. However, Lundholm (1949) estimated a maximum augmentation of basal combustions by epinephrine injection of only 28 per cent. But, sensitization of that action can be provided by acclimation (Cottle and Carlson, 1956). In experiments on removal of the adrenal medulla in the rat, Thibault (1948) estimates that epinephrine contributes as much as 35 to 40 per cent to the total power of thermogenesis. In the dog, such a procedure is inefficient, even in very cold environments, because of the importance of other substitutes.

In order to avoid these difficulties, we have tried first to eliminate an important part of the muscular innervation, leaving the spinal control of epinephrine secretion intact, by section of the brachial plexus, associated with section of the roots of the spinal cord below lumbar two level. A maximum metabolism is still reached. Then, one adrenal medulla is denervated and cleaned, and the other gland removed. A significant but rather mild lowering of the maximum metabolism level is obtained (50 to 100 per cent of the basal metabolism) (Fig. 4). Probably the main role of the sympathoadrenal system in the defense against cold consists of the reduction of heat loss.

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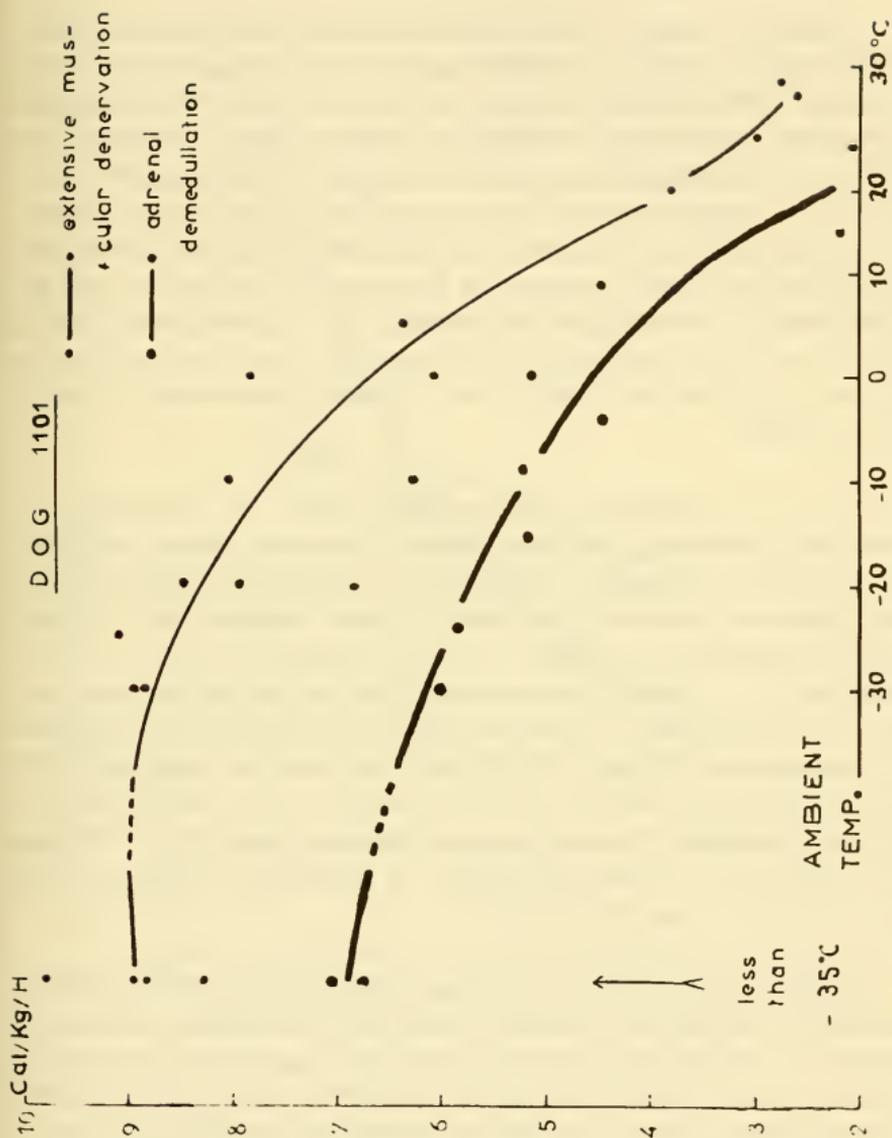


Figure 4. Heat production of dogs. After extensive muscular denervation and adrenal demedullation.

## SPECIFIC CALORIFIC INNERVATION

A specific control of heat production has sometimes been assumed. For the muscles, no recent experience can support the views of Freund (1914) and of Wenger (1933) that a nervous apparatus controls the metabolism without any other activity. Certainly, the muscle can present various kinds of activity according to the conditions of stimulation (tonus, shivering). During acclimation, motor and electric activity could decrease (Sellers, 1954), or become different (Carlson, 1955) despite an increase in metabolism and the development of vascularization pointed out in these conditions by Heroux, and Saint-Pierre (1957). However, these reactions can be the result of hormonal control, and no special innervation is necessary for them.

It may be questioned, also, whether there is any special innervation of abdominal viscera, chiefly of the liver, subjecting their heat producing activities to the thermoregulatory control. Some investigators stress the importance of these organs in the chemical regulation against cold (Fedorov and Shur, 1942; Jitariuet al., 1941, Donhoffer et al., 1959). But evaluating the role played by these organs is very difficult. A nervous control of their activity has also been considered; Freund (1913) first, and then von Issekutz (1937) explained the importance of the low cervical cord for chemical temperature regulation because nervous impulses leave the cord here, and cross over the stellate ganglia or possibly the vagi, and thus they are able to reach the liver.

On three dogs, whose active muscular fields were reduced beforehand by section of the spinal cord at fourth thoracic level and section of the brachial plexus bilaterally, and which exhibited a "plateau" of metabolism in the cold, we performed a section of both pneumogastric nerves in the thorax. After this operation the maximum metabolism remains unaltered (Fig. 5). On two other dogs prepared in the same way for a limitation of muscular activity, bilateral stellectomy failed to induce any change of the plateau level (Fig. 6). These results confirm the above-mentioned interpretation of a muscular destination of the cervical outflow controlling chemical

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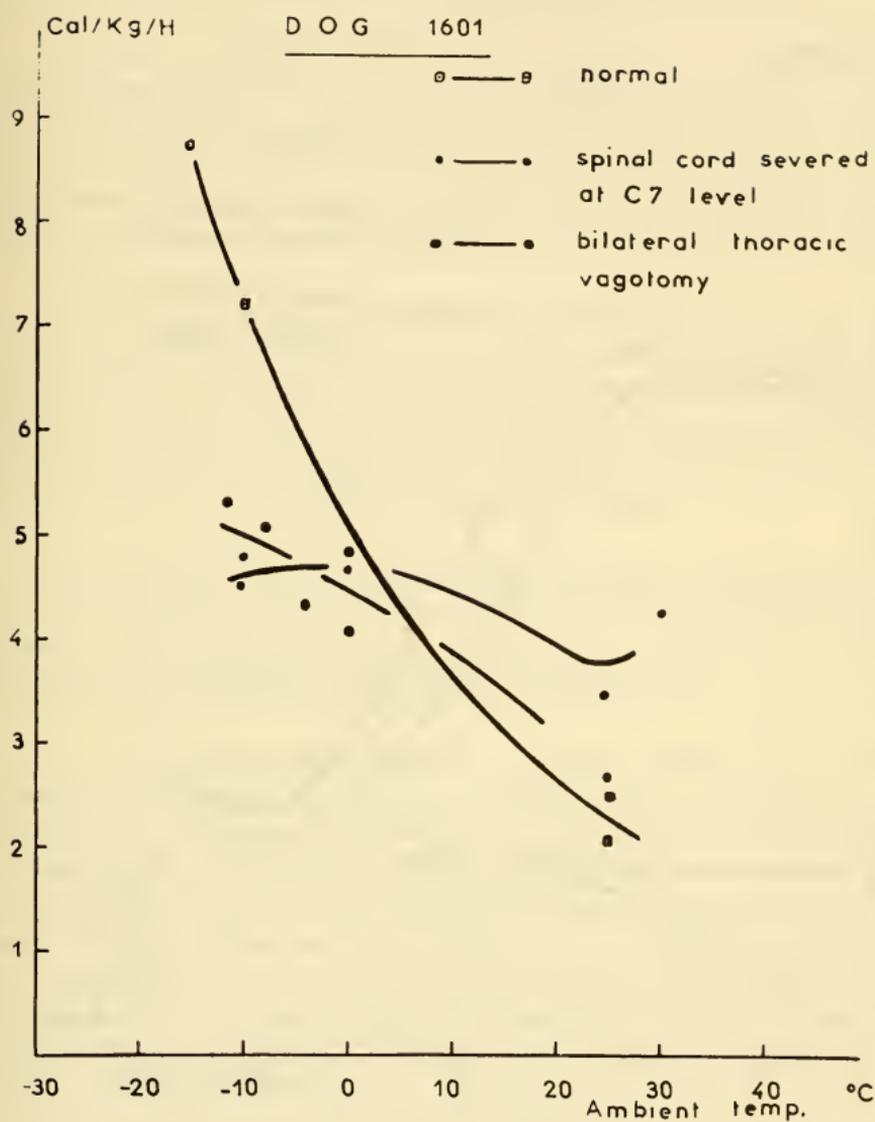


Figure 5. Heat production of dogs. The normal dog, after the spinal cord had been severed at C7 level, and after bilateral thoracic vagotomy.

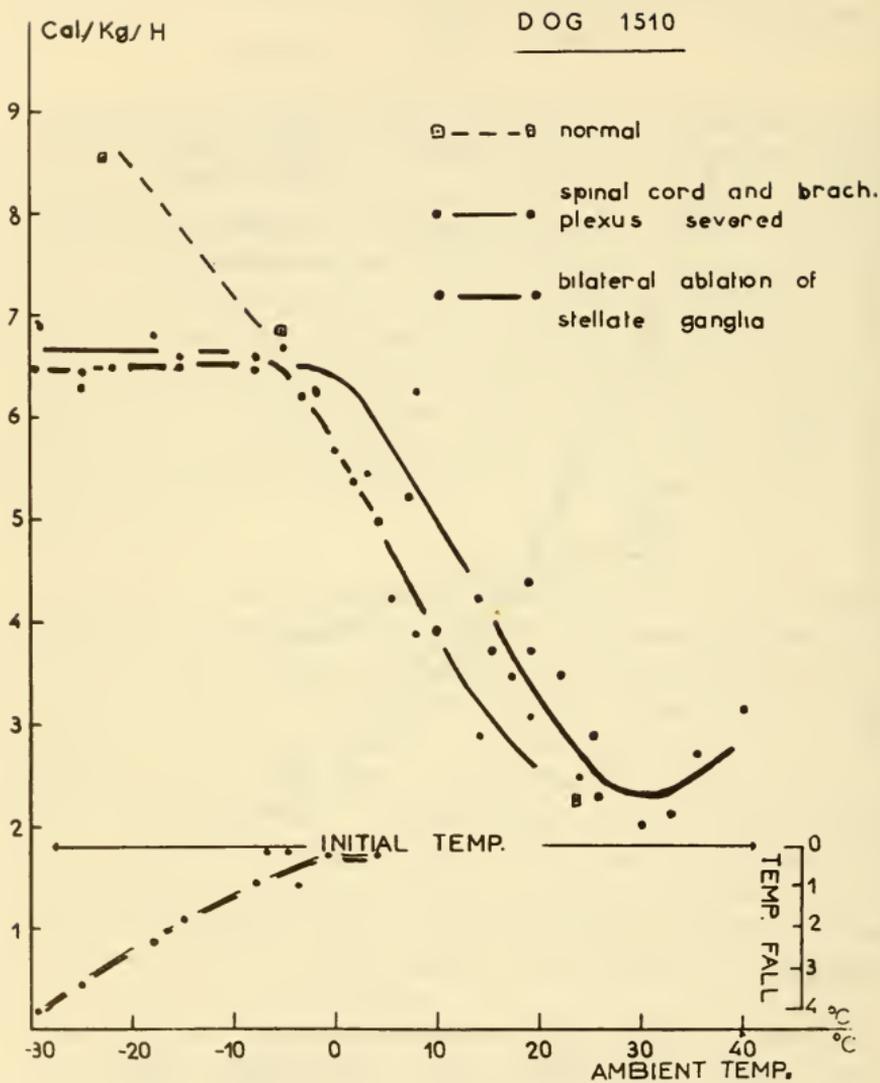


Figure 6. Heat production of dogs. Normal dog, after severing the spinal cord and brachial plexus, and after bilateral ablation of the stellate ganglia.

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regulation. However, a control of that sort by splanchnic nerves remains possible, but it is not yet thoroughly investigated.

Thus the control of the musculature in its motor activity seems to be the chief nervous factor in chemical regulation in the dog, since the remaining thermogenetic power after extensive muscular denervation is poor. Moreover, the part of the hormonal control appears very small and restricted to the effects of epinephrine secretion, at least if one lays aside the slow processes of adaptation.

All of our preceding results are expressed as a correlation between thermal production and ambient temperature. Now, by varying ambient temperature we try to submit the animal to various thermal demands. One can ask whether the correlation is with ambient temperature or with peripheral skin temperature. In the latter case, the value of our results must be questioned.

Indeed, there is often in those animals a great reduction of the thermal sensitive skin area by nervous section. It is then necessary to know the significance of the measured calorification and of its maximum, and what kind of reaction is reflected by it.

Besides the ambient temperature, two other values can be investigated, the mean skin temperature and the difference between skin temperature and ambient temperature. This last value can provide information on the thermal gradient, and hence on heat loss. We made such an estimation on some of our animals which were paralyzed or which lacked nervous section, by measuring three or four skin temperatures in the still sensitive area at different ambient temperatures in steady conditions. The calorific production,  $P$ , measured during a period of 20 minutes, is plotted against superficial temperature  $t_s$ , or  $t_s - t_a$  where  $t_a$  is ambient temperature. The difference between superficial and ambient temperature ( $t_s - t_a$ ) appears to give a good correlation, while there is no correlation with  $t_s$  (Fig. 7).

The deficit in thermoregulation of the dog with extensive muscular denervation remains unchanged for months. Besides, it becomes apparent only in severe cold. In mild cold exposure, heat production develops in a progressive and adapted manner. There is a limitation of but not a disorder in the regulation.

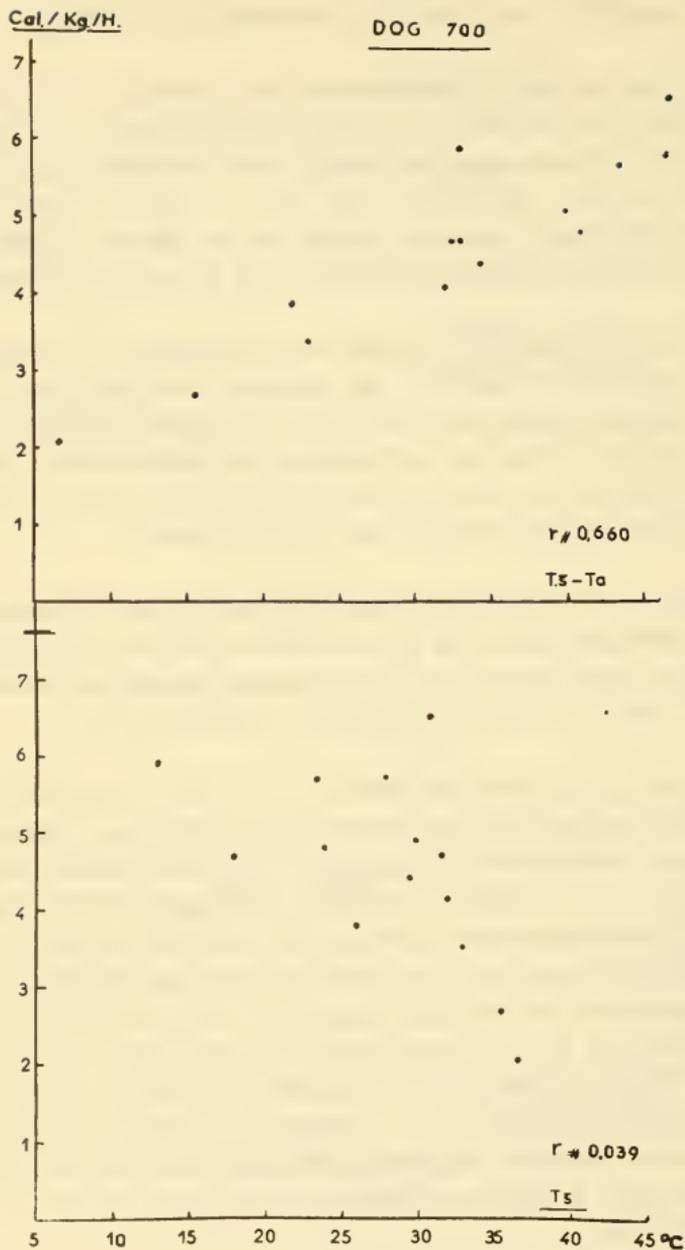


Figure 7. Heat production of dogs plotted against  $t_s - t_a$  and plotted against  $T_s$  where  $t_s$  is the skin temperature and  $t_a$  is the ambient temperature.

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However, the existence of a central sensitivity towards the cold is still in question. Numerous attempts to demonstrate this sensitivity are negative, according to the work of Ström (1950), Forster et al. (1952), and Brendel (1960); such a central mechanism is sometimes judged useless since, on exposure to cold, the immediate reaction is an increase of the core temperature. Positive results of Barbour (1912) are criticized because of the tremendous lowering of brain temperature required for the experiment.

Since 1954, we have made several approaches to this problem, in order to know whether chemical regulation and particularly muscular activity and shivering can be put into action by a central action of the cold. At the beginning of this work we tried to obtain, by several means, a shift in the normal temperature gradient of the body. Thus, the internal body temperature might decrease (in order to trigger any central sensitivity) but the superficial skin temperatures would remain constant or even increase (in order that superficial cold receptors would not be stimulated).

Experiments were performed systematically on unanesthetized dogs bearing chronically implanted thermocouples in the brain; several subcutaneous temperatures were also registered. Shivering and muscular tone were registered by electromyograph, and sometimes by respiratory exchanges.

In a chronic spinal dog, or in a dog whose spinal cord is destroyed up to thoracic one level, central cooling may be induced by wrapping ice bags around the posterior part of the body which is deprived of sensitivity. In such a case, warm blankets and infrared lights induce a warmer temperature on the anterior part of the body and particularly on the face. In other cases, for reflex cold stimulation, the face could be refrigerated.

The results may be summarized as follows on a graph (Fig. 8): on the ordinate is central temperature; on the abscissa is mean superficial temperature. It is possible to show the existence of a "shivering zone" above a threshold curve. Thus, during the same experiment, shivering may be induced by the decrease of superficial temperature (with a constant central temperature) or by a decrease of central temperature (with no change or even an increase

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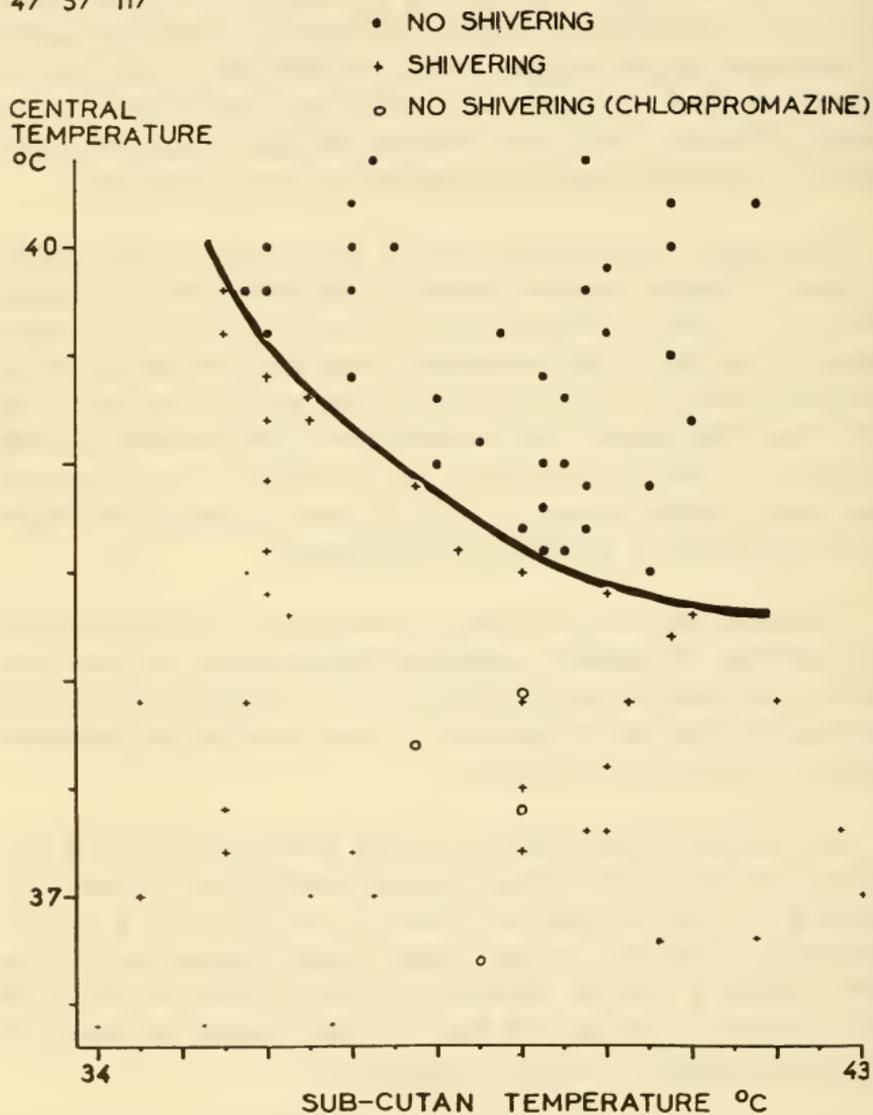


Figure 8. Thermal shift through ice water ingestion. In normal unanesthetized dogs, ingestion of one liter of ice water induces a rapid fall of central temperature with much shivering.

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of superficial temperature). The threshold curve changes with the animal's conditions and may go up during fever (spontaneous, or induced by intravenous injection of vaccine).

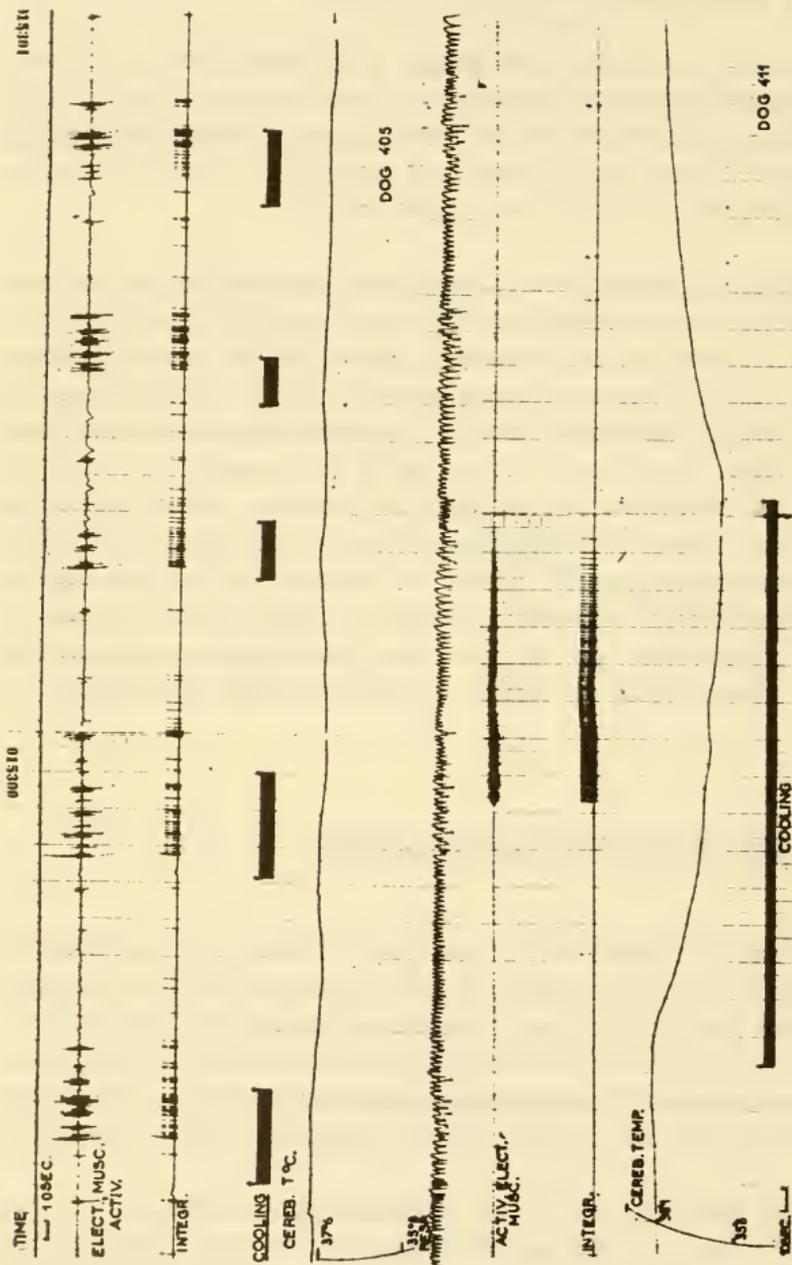
In normal unanesthetized dogs, with intracerebral thermocouples, ingestion of one liter of ice water induces a rapid fall of central temperatures with much shivering, even when the superficial temperature is kept high. Shivering disappears when the central temperature comes back to the normal level.

Finally, cold exposure on the thermal equilibrium can be compensated for by heat production of the muscular work that is experimentally imposed on the organism. There are two possibilities in this case. The autonomic thermogenesis of the organism may be regulated by the superficial stimuli; this thermogenesis would thus add to the heat production of the work. If the regulation is made by the need of constancy of central temperature, which is almost accomplished, there is substitution. We have shown that, in spinal dogs, the muscular work induced in muscles of the hind legs by electric stimulation increases the oxygen consumption only in neutral ambient temperature. In the cold, this consumption replaces the need for oxygen which is induced by cold, but does not increase it.

### Direct cooling of the central nervous system

We implanted aseptically and stereotaxically in the brains of eleven dogs a thermode producing cold by gaseous detent of propane. The central temperature near the thermode was registered with a thermistor, at the same time as the rectal and three or four superficial temperatures. The electromyograph was recorded in the awake dog with an ink-writer, with or without integration (Figs. 9 and 10).

Results show that there is a close correlation between the central temperature and the electromyograph. Every decrease of the cerebral temperature is associated with an increase of the muscular tone or even with a clear-cut shivering. The most striking results are obtained when the thermode is located at the middle hypothalamus. In such a case, only a decrease of 1/10 degree centigrade is



Figures 9 and 10. Electromyographic record showing shivering during brain cooling.

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sufficient to trigger a muscular response. These reactions are obtained even with a constant superficial temperature; nevertheless, the superficial temperature has some effect on the amplitude of the muscular reaction induced by cold central stimulation.

These results agree with those of Hammel, Wyndham, and Hardy (1958), who obtained shivering by local cooling of the dog hypothalamus. Freeman and Davis (1959) and Kruger et al. (1959) were also able to register vasomotor reactions in the cat to cold acting in this region. Donhoffer et al. (1957), cooling the brains of rats, observed an increase of heat production.

Lim (1960), from experiments in cooling carotid blood in the dog, concluded that shivering can be elicited either peripherally or centrally. In this respect, negative attempts can result from the use of anesthesia, from the operative shock, or from defective localization of the thermode, in consideration of the strong convection in the brain.

Exclusion of central sensitivity. Chlorpromazine does not decrease the capacity of resistance against cold in a normal animal. A dog treated with chlorpromazine in a cold environment may shiver normally and increase its thermogenesis, and may be used as a control animal. But the hypothermic dog (spinal dog overstrained by a cold environment) given chlorpromazine, does not react against cold and stays hypothermic if there is no superficial stimulation, that is, if superficial receptors are submitted to a high ambient temperature by heating. But such a dog may shiver and its rectal temperature may increase when it is surrounded by a cold ambient temperature. This paradoxical behavior can be explained by a selective suppression of the central component of the thermal sensitivity to cold by chlorpromazine.

We performed electrolytic destruction of the hypothalamus in nineteen dogs. In several of them we obtained thermoregulatory behavior resembling that of chlorpromazine. Such animals recover some reactions against cold post-operatively, such as increase of thermogenesis when placed in a cold ambient temperature, but this reaction does not permit an exact adaptation of the heat production to the loss. The central temperature remains unsettled and there is

no muscular reaction when the central temperature is selectively decreased (Fig. 11).

Keller (1959), in coagulation experiments on the dog hypothalamus, reports cases of defect in the regulation of central temperature against cold, although potent reactions of shivering, no doubt of reflex origin, take place. On the other hand, the same author succeeded in observing shivering after elimination of the whole peripheral thermal sensitivity by cutting the brain stem except for the pyramidal bundles. In the last case the good resistance in cold exposure could be ascribed to brain sensitivity.

The existence of a central cold-sensitive device in the brain seems well proved; nevertheless, its functional significance remains to be evaluated.

One may also ask whether the thermogenetic response is specific for each kind of activation (central or reflex). According to Davis and Mayer (1955), the chemical regulation, in its restricted meaning (without muscular activity), depends only on the central temperature. On the other hand, shivering and muscular activity would be under a pure reflex control. Some of the preceding results are in conflict with this view. As for the control of epinephrine, no recent direct evidence has been obtained.

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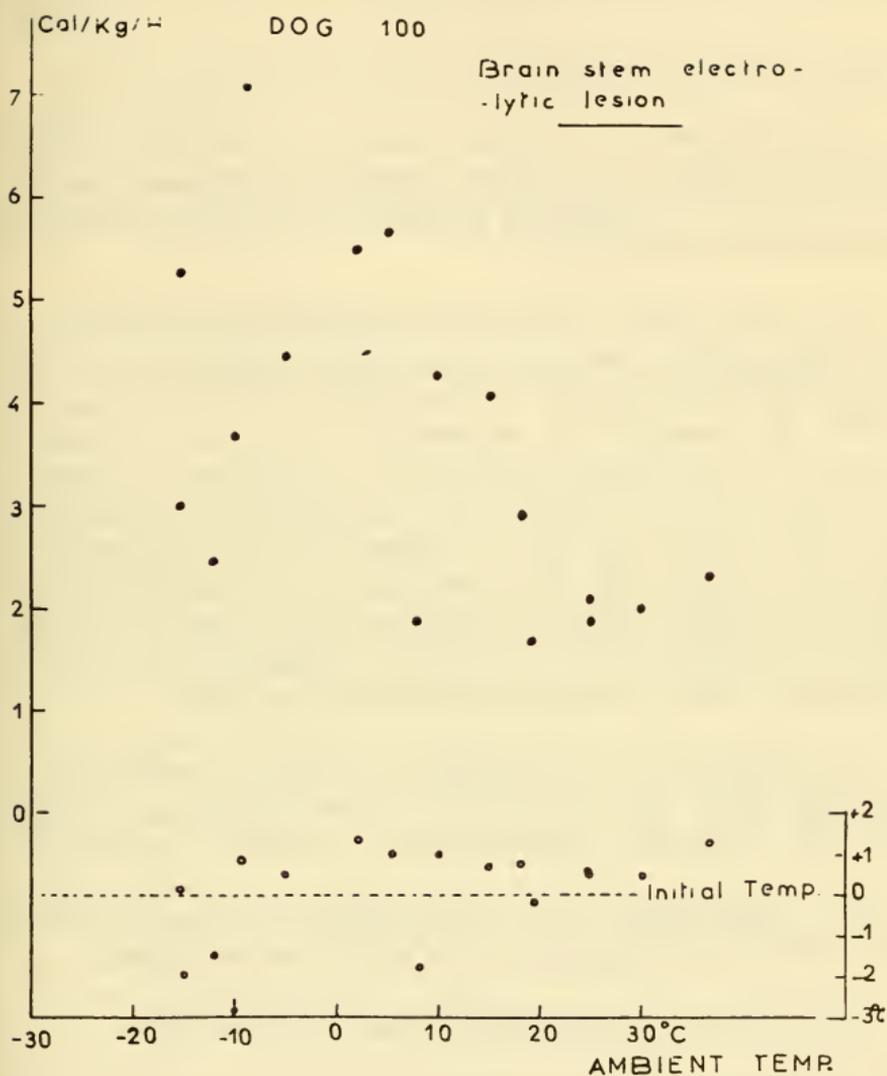


Figure 11. Heat production of dog following brain stem electrolytic lesion.

DISCUSSION

MR. EAGAN: In your first series of experiments, did your metabolism figures at the ambient temperature represent the maximum metabolic rate that you measured at that temperature? Was this the sum of metabolism?

DR. CHATONNET: The metabolism figures represent the metabolic rate actually measured at each ambient temperature. In very cold ambient temperature and only after exclusion of muscular activity by denervation in an extensive field, the maximum is reached. By adrenal demedullation I try to suppress a thermogenetic factor and, in such a way, to evaluate its importance. Of course, the vasomotor effect of adrenal medulla hormones plays some role in heat loss, but in the dog which showed beforehand a maximum of metabolism in the cold, the increase of heat loss following this operation does not modify this metabolism level. It only reduces the range of external temperatures regulated.

DR. CLARK: Since you apparently kept your animals alive a very long time, one wonders about sensitization to circulating hormones. Were they more sensitive to adrenalin than normals?

DR. CHATONNET: Yes, the chronic spinal dog, the acute dog, is very sensitive to epinephrine, as far as the vascular action.

DR. CLARK: I was thinking of action on skin vessels.

DR. FREEMAN: Doesn't enervation take place after spinal section?

DR. CLARK: In the cat it does. And how about pitressin? Did you try pitressin in any of them?

DR. CHATONNET: I did not try it. I do not believe that hypophysis plays an important role in regulation in spinal dogs, at least in the capacity of thermogenesis.

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DR. CLARK: I know the C7 spinal cat becomes exquisitely sensitive.

DR. CHATONNET: I know the sensitivity against posterior pituitary extract.

DR. FREEMAN: Have you discussed your results with Dell or Stutinsky or Bonvallet, who worked similarly?

DR. CHATONNET: Yes.

DR. FREEMAN: They came, I believe, to the conclusion that the hypophysis played a major role in regulation in spinal dogs.

DR. CHATONNET: I do not believe that the hypophysis plays an important role in regulation in spinal dogs, at least in the capacity of thermogenesis that I studied. Bonvallet and Dell (1946) observed that hypophysectomy or the section of the supraoptico-hypophyseal tractus deprived the spinal dog of the ability to maintain his central temperature for exposure to 20° C to 22° C. Injection of posterior pituitary extract again set up this ability. The authors explain the fact at least partly thus: impairment of water metabolism by hypophysectomy lessens the efficiency of the remaining thermogenesis in that animal. But they have not measured the metabolism of their dogs. One can also suppose that the essential disturbance concerned heat loss regulation by vasomotor control. In any way, the thermogenetic capacity of the C7 spinal dog is poor and does not depend on any "per se" thermogenic hormonal control, but on residual muscular activity. However, such a long-acting vascular factor should produce slow adaptation to environmental change. In the Bonvallet and Dell experiments the reactions were very fast. Our chronic spinal dogs and the dogs whose spinal cords have been destroyed control their temperature in a limited range of external temperatures according to the extent of innervation abolished, but in this range their regulation is immediate and the thermogenesis involved is steady from day to day.

DR. FREEMAN: Did you compare your results with theirs?

DR. CHATONNET: I had no results of hypophysectomy.

DR. HANNON: Have you ever studied what I prefer to call non-shivering thermogenesis rather than thermochemical thermogenesis? Have you ever studied this in climatized animals or acclimated animals?

DR. CHATONNET: No.

DR. HANNON: This might prove interesting since these animals have almost completely replaced the shivering thermogenesis with the non-shivering thermogenesis.

DR. CHATONNET: In my experiments, dogs are kept at constant room temperature of 25<sup>o</sup> C, except for cold tests. In these conditions the non-shivering thermogenesis is not very important. And it is doubtful that this mechanism can develop by acclimation in such large animals.

DR. HANNON: I would like to toss out one other question to Dr. Chatonnet or any of the other participants here. In these cold climatized animals, during the process of climatization, they at first have a shivering thermogenesis when they go into the cold. This declines gradually and reaches minimum values after a few weeks. Concomitant with this decline, non-shivering thermogenesis increases and replaces it. Now if you take this animal out of the cold, his thermogenesis generally drops down to about what a control animal would be -- a little higher, maybe, with essentially the same as a cold animal. You put him back in the cold and almost immediately he starts this non-shivering thermogenesis. What is the mechanism?

MR. EAGAN: It is indeed a mystery, because curarized animals and animals that are adrenal demedullated still control this increased potential for cold-induced thermogenesis.

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DR. FREEMAN: As Bonvallet pointed out, this tendency was predominant in small animals; the smaller the animal, the greater his range of variance. I think he quoted figures indicating that a rat can vary it over a range of forty times, whereas, in man, it is greatest at about one or two times. That is a large mammal. This form of regulation is important in the smallest one with a high ratio of surface area to body weight.

DR. HANNON: Yes, this is true.

DR. FREEMAN: So that you would not expect it to be as predominant in dogs, but nevertheless, he thought there existed a mechanism in dogs which was the same as that in other animals, but not as effective.

DR. CLARK: You can demonstrate that in spinal cats.

DR. FREEMAN: How?

DR. CLARK: If you take a cat that has had the cord severed at, say, C6, C7, and you had him alive for months, if you put him in a temperature of 18° C, his temperature will drop way down and then over a course of a few days, it will come up to almost what it was before. You take him then and put him in 29° C, and his temperature goes up to 39° C or 40° C, and it takes about 3 to 5 days for his temperature to come back to normal level.

REFERENCES

1. Barbour, H. G. Die Wirkung unmittelbarer Erwärmung und Abkühlung der Wärmezentren auf die Köpertemperatur. Arch. exp. Pathol., 70:1-26, 1912.
2. Beaton, L. E. and C. R. Leininger. Spinal distribution of thermoregulatory pathways in the monkey. J. Neurophysiol. 6:37-38, 1943.
3. Birzis, L. and A. Hemingway. Descending brain stem connections controlling shivering in cats. J. Neurophysiol. 19: 37-43, 1956.
4. Bonvallet, M. and P. Dell. La régulation thermique du chien spinal sans hypophyse. C. R. Soc. Biol. 140:942-945, 1946.
5. Brendel, W. Die Bedeutung der Hirntemperatur für die Kältegegenregulation. Pflügers Arch., 270:607-647, 1960.
6. Carlson, L. D. Heat production and cold adaptation. Fed. Proc. 14:26, 1955.
7. Chatonnet, J. Importance du frisson dans les capacités de thermogénèse du chien à moelle épinière détruite. C. R. Soc. Biol. 145:1538-1540, 1951.
8. Chatonnet, J. Sur l'origine de la chaleur libérée dans la régulation chimique de la température. J. Physiol. (Paris), 51: 319-378, 1959.
9. Chatonnet, J. et M. Tanche. Sur l'existence dans la moelle épinière de voies nerveuses distinctes pour la commande du frisson. C. R. Acad. Sci. 249:412, 1956.

## NERVOUS PATHWAYS

10. Chatonnet, J. et M. Tanche. Dissociation du frisson "central" et du frisson "reflexe" chez le chien à moelle détruite. *J. Physiol. (Paris)*, 48:439-442, 1956.
11. Chatonnet, J. et M. Tanche. Chlorpromazine et regulation thermique - Zone de froid. *Thérapie* 14:778-792, 1959.
12. Chatonnet, J. et M. Tanche. Influence d'un abaissement de température localisé de la région diencephalique sur l'activité musculaire thermorégulatrice chez le chien éveillé. *J. Physiol. (Paris)*, 52:48-49, 1960.
13. Cottle, W. and L. D. Carlson. Adaptative changes in rats exposed to cold. *Am. J. Physiol.* 178:305-308, 1954.
14. Cottle, W. and L. D. Carlson. Chemical regulation of heat production in cold adapted rats. *Fed. Proc.* 15:41-42, 1956.
15. Davis, T. R. A. and J. Mayer. Demonstration and quantitative determination of the contribution of physical and chemical thermogenesis on acute exposure to cold. *Am. J. Physiol.* 181:675-678, 1955.
16. Donhöffer, S., M. Farkas, A. Haug-Laszlo, I. Jarai, and G. Szegvari. Das Verhalten der Wärmeproduktion und der Körpertemperatur der Rätte bei Lokaler Erwärmung und Kühlung des Gehirnes. *Pflügers Arch.* 268:273-280, 1959.
17. Donhöffer, S., G. Szegvari, I. Varga-Nagy, and I. Jarai. Über die Lokalisation der erhöhten Wärmeproduktion bei der chemischen Wärmeregulation. *Pflügers Arch.* 265:104-111, 1957.
18. Eiff, A. Von, K. Spohn, W. Gnutchel, and F. Hertle. Stoffwechseluntersuchungen am curarisierten nicht narkotisierten Menschen. *Pflügers Arch.* 253:283-285, 1951.
19. Fedorov, N. A. and E. I. Shur. The role of the viscera in regulating the temperature of the body of an animal under physiological and pathological conditions. *Am. J. Physiol.* 137:30-38, 1942.

20. Förster, R. E. and T. B. Ferguson. Relationship between hypothalamic temperature and thermoregulatory effectors in unanesthetized cats. *Am. J. Physiol.* 169:255-259, 1952.
21. Freeman, W. J. and D. D. Davis. Effects on cats of conductive hypothalamic cooling. *Am. J. Physiol.* 197:145-148, 1959.
22. Freund, H. Über die Bedeutung der Vagi für die Wärmeregulation. *Arch. Exp. Path. Pharm.* 72:295-303, 1913.
23. Freund, H. und S. Janssens. Über den Sauerstoffverbrauch der Skelettmuskulatur und seine Abhängigkeit von der Wärmeregulation. *Pflügers Arch.* 100:96, 1923.
24. Freund, H. und E. Schlagintweit. Über die Wärmeregulation curarisierter Tiere. *Arch. exp. Path. Pharm.* 77:258, 1914.
25. Freund, H. und R. Strasmann. Zur Kenntnis der nervösen Mechanismus der Wärmeregulation. *Arch. Exp. Path. Pharm.* 69:12, 1912.
26. Hammel, H. T., J. D. Hardy, and M. M. Fusco. Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. *Am. J. Physiol.* 198:481-486, 1960.
27. Hammel, H. T., C. H. Wyndham, and J. D. Hardy. Heat production and heat loss in the dog at 8° C to 36° C environmental temperature. *Am. J. Physiol.* 194:99-108, 1958.
28. Hemingway, A. and S. R. Hathaway. An investigation of chemical temperature regulation. *Am. J. Physiol.* 134:596-602, 1941.
29. Hermann, H., G. Morin, and J. Vial. Efficacité de la thermorégulation chez le Chien sans moelle au cours du refroidissement. *C. R. Soc. Biol.* 127:1491-1493, 1938.
30. Heroux, O. and J. Saint-Pierre. Effect of cold acclimation on vascularization of ears, heart, liver and muscles of white rats. *Am. J. Physiol.* 188:163-168, 1957.

## NERVOUS PATHWAYS

31. Issekutz, B. von. Die Rolle des Zentralnervensystems und der Schilddrüse bei der Wärmeregulation. *Pflügers Arch.* 238: 787, 1937.
32. Isenschmid, R. Physiologie der Wärmeregulation. *Handbuch der norm. und path. Physiologie.* 12:23, 1926.
33. Jitariu, P., A. Koch, and U. Otto. Über Temperaturdifferenz und Durchblutungsmessungen am Leber und ihre Auswertbarkeit zur Beurteilung von Stoffwechseländerungen im Organ. *Pflügers Arch.* 245:317-341, 1941.
34. Kayser, Ch. Contribution à l'étude du mécanisme nerveux de la régulation thermique. *Ann. de Physiologie,* 5:131-223, 1929.
35. Keller, A. D. Neurologically induced physiological resistance to hypothermia. *Ann. N. Y. Acad. Sci.* 80:457-474, 1959.
36. Krüger, F. J., H. W. Kundt, H. Hensel, K. Brück. Das Verhalten der Hautdurchblutung bei Hypothalamuskühlung an der wachen Katze. *Pflügers Arch.* 269:240-247, 1959.
37. Lim, T. P. K. Central and peripheral control mechanisms of shivering and its effects on respiration. *J. appl. Physiol.* 15: 567-574, 1960.
38. Lundholm, L. The effect of adrenaline on the oxygen consumption of resting animals. *Acta. Physiol. Scand.* 19 (suppl. 67): 1-133, 1949.
39. Morin, G. L'adrénaline, hormone du froid. *Biol. Med.* 37:196-230, 1948.
40. Sellers, E. A., J. W. Scott, and N. Thomas. Electrical activity of skeletal muscle of normal and acclimatized rats on exposure to cold. *Am. J. Physiol.* 177:372-376, 1954.
41. Sherrington, C. S. Notes on temperature after spinal transection with some observations on shivering. *J. Physiol. (Lond.),* 58: 405-424, 1924.

CHATONNET, J.

42. Sinelnikow, E. Über die Wirkungsweise des Wärmezentrum im Gehirn. Arch. f. Anat. und Physiol., p. 279, 1910.
43. Ström, G. Effect of hypothalamic cooling on cutaneous blood flow in the unanesthetized dog. Acta. Physiol. Scand. 20 (suppl. 70):271-277, 1950.
44. Tanche, M. et J. Chatonnet. Sur l'influence d'un apport calorifique impose a l'organisme (travail musculaire) sur les reactions thermorégulatrices au froid. J. Physiol. (Paris). 50:534-537, 1958.
45. Thibault, O. Facteurs hormonaux de la thermoregulation chimique. Ann. Nutrition Paris 2:89-109, 1948.
46. Wenger, H. Nachweis der Wärmebildenden Funktion des Sympathikus im Skelettmuskel. Z. Biol. 93:307-316, 1933.
47. Werner, A. Y., D. Dawson, and E. Hardenbergh. Spontaneous rewarming of hypothermic curarized dogs. Science 124:1145, 1956.

# A CRITIQUE OF THE DOCTRINE OF "CENTERS" IN TEMPERATURE REGULATION

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The title of this presentation was taken from a remark by Dr. Hemingway at the start of this conference, in which he said that he would describe a "center" for shivering, even though he did not like the term. I agree that it is not a good term in some respects, but on the other hand I think that if properly used, it can serve us as well in the future as it has in the past.

## HISTORICAL SURVEY

One of the remarkable features about temperature regulation is that not merely one organ is involved but all the organs in the body. Respiration, digestion, or reproduction predominantly involve one organ and its ramifying parts, but in temperature regulation one cannot simply consider the skin, or the muscles, or the endocrines, but all of them in the patterns of activation imposed on them by the central nervous system. One can make balance sheets of energy exchange during different patterns, or one can study the way in which the central nervous system creates these patterns, by means of which the brain regulates its own operating temperature.

Systematic analysis of this property was initiated about one hundred years ago with the studies by Samuel Goltz in 1874 on the physiological effects of heating and cooling carotid blood. This was a particularly propitious time to begin, for operative intervention in the brain had just become feasible with the introduction of aseptic surgery. Claude Bernard had just published his *Physiologie Generale* in which the doctrine of the constancy of the internal milieu was first set forth, and there was ample evidence for the regularity of

the body temperature from studies of clinical thermometry instigated by Karl Wunderlich of patterns of temperature change in normal cycles and disease. The early workers were impressed by the stability of body temperature, and they introduced three concepts into temperature regulation which have persisted to the present day. One of these was the placing of a line on the clinical thermometer at  $98.6^{\circ}\text{F}$  ( $37^{\circ}\text{C}$ ), which implies a higher degree of constancy of body temperature than is actually the case. The second was the notion that each of the components of thermoregulatory responses was represented by a group of cells in the nervous system, to which was given the name "center." The third was that this collection of centers was under the control of a master center described as a thermostat. Initially, this thermostat was placed in the medulla, and only following work by Isenschmidt and Krehl and others at the turn of the century was it placed in the hypothalamus. Much of the history of temperature regulation since that time has consisted of the attempt to define the location and properties of these centers.

In reality, this has only been part of a much broader application of the same principles to other parts of the brain, with particular attention devoted to parcelation of function in the cortex and the medulla. In some respects this doctrine seems to have been highly successful, notably in the cases of the "respiratory centers" in the medulla and the "feeding centers" in the hypothalamus. In other instances such as the "speech center" in the parietal cortex, the "sleep center" in the thalamus, or the "vasomotor center" in the medulla, identification at first seemed adequate and now has been brought into question. In the case of temperature regulation, with the exception of the so-called "heat center" in the hypothalamus (which actually turned out to be a sensory mechanism), the best that can be said after nearly a century of hard work is that efforts continue.

In view of the large amount of work based on this doctrine and the still continuing doubts as to its validity, one is led to ask how it came into existence in the first place and what the underlying assumptions for it have been. This doctrine represents in essence an attempt to subdivide the brain into its physiological components or parts. There were at least three other methods for subdividing the brain introduced in the last one hundred years, each to a large

## TEMPERATURE REGULATION "CENTERS"

extent the work of one man. J. Hughlings Jackson was led by clinical observations of neurological disease to subdivide the brain in a series of horizontal components, each of which maintained excitatory or inhibitory dominance over the segments below. Analysis of these segments was carried out by transections of the brain at various levels. I. P. Pavlov, on the basis of his conditional reflex studies, divided the brain into a series of vertical segments, or what he called motor and sensory analyzers. These consisted of chains of neurons extending from the sensory receptor through the spinal cord and basal ganglia to the cortex, or in the opposite direction from the cortex down to the effector without significant transverse interaction being postulated at intervening way stations.

Another series of subdivisions was developed by C. Judson Herrick and others on the basis of comparative behavioral studies and the comparative anatomy of the vertebrates. He based his subdivision largely on the phylogenetic differentiation of the parts of the brain, which ultimately led to recognition of the importance of various parts of the limbic lobe in behavior. Each of these views was carefully developed over a period of many years and was based on a systematic observation of total behavior, that is, the behavior of animals in the intact state. The doctrine of the centers had no direct relationship to any of these systems, nor, for that matter, to any other. Rather, it developed from observations of isolated "evoked" responses in non-behavioral contexts. It was not the work of any one man or any one school and has yet to be given a formal and logical description. Yet it has been as widely accepted and used as any of the other three.

Historically, the term 'center' first came into general usage after 1870. Prior to that time it was rarely used in text books, but thereafter it occurred in almost all major text books of physiology and clinical neurology. Specifically, it seems to have followed the discoveries by Fritsch and Hitzig in 1870 (see Brazier, 1959) of the excitable motor cortex and by Claude Bernard of the hyperglycemia produced by stimulation of the medulla. Several kinds of influence seem to have facilitated its immediate acceptance as a method of analyzing or describing brain function. First among these was undoubtedly the development of new techniques for histological staining, which showed that the brain could be subdivided, or was

organized into a series of nuclear masses, which provided the anatomical substrate for 'centers.' A second important influence was the continuing wide-spread interest in phrenology, which was kept before the public in the more acceptable form of localization of mental processes by the writings of Herbert Spencer. This implied that particular functions, which could be observed holistically in behavioral context, could be ascribed to particular parts of the brain.

A less direct, more subtle, and yet equally important influence was the developing science of thermodynamics. This has been introduced earlier by Johannes Müller in his law of specific nerve energies. Throughout this time nerve discharges were described in physical terms such as nerve force or nerve energy. For example, Spencer (1863) stated (quoted from Darwin, 1872, p. 109) as an "unquestionable truth that, at any moment, the existing quantity of liberated nerve-force, which in an inscrutable way produces in us the state we call feeling must expend itself in some direction -- must generate an equivalent manifestation of force somewhere." This is a statement of conservation of momentum. Darwin (1872) remarked: "This involuntary transmission of nerve force may or may not be accompanied by consciousness. Why the irritation of nerve-cells should generate or liberate nerve force is not known; but that this is the case seems to be the conclusion arrived at by all the greatest physiologists such as Müller, Virchow and Bernard, and so on." (Darwin, 1872, p. 70).

As originally stated by Müller, this hypothesis proposed that packets of vital fluid travelled down nerves at immeasurable speed. This was subsequently disproven through studies by Helmholtz, Hermann, and others on the action currents of peripheral nerve and was finally discredited by the clear distinction that came to be drawn between vital spirits and electricity. In its place was introduced the notion of a unit or quantum of electro-chemical energy, the action potential, as the sole vector of information in the nervous system, with the sole attributes of number and location in time and space.

These units of energy were thought to summate algebraically, in space and time, and when concentrated in a local volume of tissue,

## TEMPERATURE REGULATION "CENTERS"

an anatomical center, to constitute a focus of activity. This focus was manifested either by an evoked potential or (much later) by trains of EEG waves. Hypothetical centers were conceived as maintaining levels of such energy of activity, and these levels of activity could be raised or lowered by synaptic activation. Eventually, this localized concentration of energy became identified with the central excitatory state of Sherrington, and subsequently with pools of unit potentials in the spinal cord or other spatially distinct volumes of brain tissue. Sherrington apparently had a great deal to do with the informal application of 19th century thermodynamics to analysis of the brain, perhaps less in his scientific publications than in philosophical works such as *Man on His Nature* (1953), in which he describes his more tenuous analogies. He wrote, for example, "A nerve centre is a place of junction of nerve-lines, and of departure for fresh ones...Signals convergent via many lines may in the centres coalesce and reinforce....It is at such junctions that inhibitions occur. It can there suppress action, or, no less important, can grade it by moderating it. In the network of conductors, it can switch off one line as another is switched on." (p. 164). This was clearly analogous to a telephonic relay system, which is not too different from the idea of a thermostat, a mechanical contrivance, which by analogy was also conceived to exist in the brain.

This conception of the brain as a mosaic of centers, each with its characteristic levels of energy, involved assumptions that were particularly appropriate for the prevailing technique of testing. The electrode inherently has a focal relationship to the brain. The application of an electric current through the electrode was conceived to raise the energy level of a given center in the brain much as the release of energy of a peripheral nerve was increased by electrical stimulation. It is characteristic of the looseness of thinking involving "centers" that the logical possibility that electrical stimulation might increase a central inhibitory state was seldom considered. In the early part of this century the electrode began to be used also for making circumscribed lesions, which were thought to diminish the level of energy available or producible by a center. This was conceived as an algebraic effect rather than in terms of altering a pattern of function in the brain. More recently, the electrode has been used to record the level of electrical activity at various points in the brain, and the assumption has been made that

these changes represent fluctuations in the energy level of centers in which the electrode has been found to lie. In each case, the electrode has been used as a focal tool and the interpretation has been made in focal terms.

This fact of technique is crucial. When it was first introduced, the term center was simply a label applied to a given part of the brain which could produce a discrete response on stimulation, such as the eye-opening center, tongue-twitching center, or finger-moving center, and so forth, without any firm commitment on the part of the user. But its subsequent application to all other parts of the brain was due more to the technology of the electrode than to any rational development of the system. Despite many difficulties with this doctrine, it has been the bulwark of studies in temperature regulation and there is no cliché more firmly entrenched in the medical literature than the term "temperature regulation centers."

I would now like to illustrate some of these assumptions and difficulties by describing three experiments. These have one thing in common. They failed. They gave negative results, or, perhaps better said, "indeterminate" results; and I would like to point out what the assumptions of these experiments were and how at least in two cases the assumptions were wrong.

#### AN INCONCLUSIVE EXPERIMENT INVOLVING RECORDING

The first experiment was to record the electrical activity of the hypothalamus in association with changes in body temperature (Freeman, 1957). This was a prelude to hypothalamic heating and cooling by means of which to evoke electrical changes possibly correlated with thermoreceptor activity. As we conceived the problem initially, the hypothalamus was composed of a series of nuclei, and each nucleus was presumed to have its own characteristic form or pattern of electrical activity; one of these nuclei or collections of cells, even if it was intermingled with others, was sensitive to

## TEMPERATURE REGULATION "CENTERS"

temperature changes; and as temperature changed either the amplitude, the frequency, or the pattern of electrical activity of that site would change with temperature. So we placed our electrodes throughout the anterior hypothalamus and subsequently all through the basal forebrain in a search for electrical changes. We induced changes in temperature ranging from 28° C to 45° C and found no localized pattern of electrical change that we could relate to these temperature changes. Pathological changes were, of course, frequently and widely manifest.

Essentially, the result was zero. Something was wrong with the experiment. We might have attributed it to anesthesia or to surgical trauma or to some other cause, but as it turned out, this was not the case. The fault lay in the fact that we had assumed that the cells under study were producing electrical activity that we could record with this method, and this turned out to be not so.

Figure 1 shows a series of recordings taken from electrodes placed in the hypothalamus. The sets represent a horizontal section through the cat brain showing the lower pole of the caudate nucleus, cerebral peduncle and optic tract around the anterior hypothalamus. There were five electrodes spaced 1.5 mm to 3.0 mm apart, dorsoventrally halfway between the optic chiasm and anterior commissure. Each of these electrodes was recorded from with respect to one of two indifferent electrodes on the scalp, the top tracing showing the activity occurring between the reference points. There was a remarkable similarity between the records taken from these different points in the hypothalamus. We had anticipated that there might be some overlap of wave forms in different records from this region. We did not anticipate, however, the fact that these different records could be superimposed after appropriate adjustment of gain in the different channels, the only difference between them being that there was a gradient of amplitude from anterior to posterior. Only as far back as the level of the mammillary bodies (Fig. 1, C, 5G) or laterally near the hippocampus was there introduction of other elements into the records, and there they were very difficult to see. But anteriorly where we were particularly concerned with temperature changes, the entire region had one pattern of electrical activity.

The recordings in Figure 1 were monopolar. We also tried bipolar recording to see whether or not the universal electrical

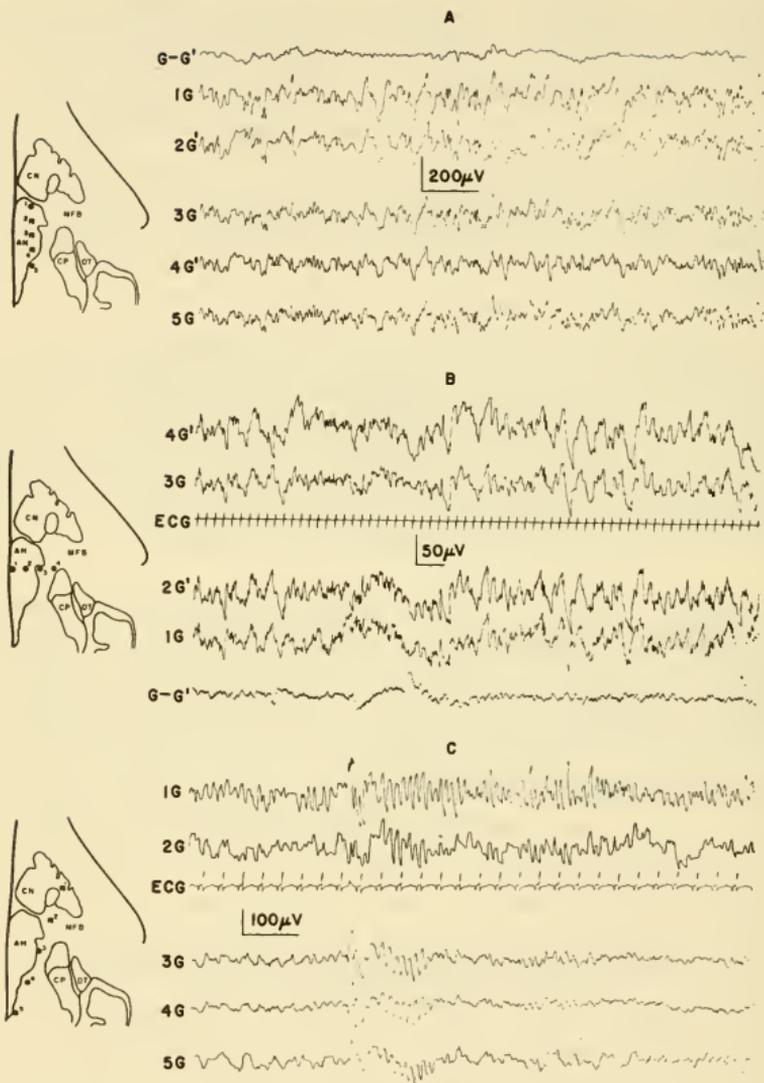


Figure 1. Monopolar recordings from basal forebrain showing gradients of amplitude. The schematics represent horizontal sections through the cerebrum of the cat's brain; the location of each electrode is indicated by a numbered point. The notation "G-G'" indicates the recording between two reference electrodes. Electrode "G" was placed on the ipsilateral scalp and "G'" on the contralateral scalp. For abbreviations, see text. Time, 1 sec.

## TEMPERATURE REGULATION "CENTERS"

activity was masking local changes which might best be picked up by two electrodes as close together as 0.5 mm. The amplitude was clearly much less (Fig. 2) than that from either with respect to a distant electrode, but there was no other difference. This was also true for tip separations of 1.5 mm, 3.0 mm, and 6.0 mm, the records from which were nearly identical except in amplitude. There was no disclosure of any other signal than that recorded with monopolar electrodes, implying that the hypothalamus had a uniform electrical activity under the conditions of this experiment, which did not involve evoked transients or abnormal temporal synchrony. This identity of pattern was true not only of the hypothalamus proper, but also of much of the surrounding region, i.e., inferior pole of the caudate nucleus, the olfactory striatum, parts of the septum and the cerebral peduncle.

We attempted by diathermic heating locally in the hypothalamus to elicit local changes in the hypothalamic electrical pattern. There were four electrodes in this experiment with monopolar recording from each; the diathermy current was passed between the outer two, there being a thermocouple centered between the middle pair of electrodes for control of the hypothalamic temperature. The middle pair permitted study of the electrical activity without having to use the heating electrodes, around which the tissue was destroyed. Figure 3B shows that after heating to a temperature of  $50^{\circ}\text{C}$ , which is quite high for hypothalamic temperature, not only was the electrical activity from the intervening electrodes substantially unaltered but so also was the electrical activity recorded from generating electrodes. There was some difference in wave form, which was of the type which was seen to occur spontaneously during the course of an experiment and did not represent a significant change.

In Figure 3C, the intervening thermocouple was heated to  $70^{\circ}\text{C}$ , almost, one might say, the boiling point of the brain, and there was substantially no change in subsequent records. Histologically at post-mortem there was coagulative necrosis of the hypothalamus, parts of the septum, the caudate nucleus, and the thalamus. We did find a way of abolishing this activity, and that was to make transections of the brain ventrolateral to the hypothalamus. Transections could be made anteriorly, laterally, dorsally, and posteriorly (Fig. 3F) with little change as long as the medial forebrain bundle was

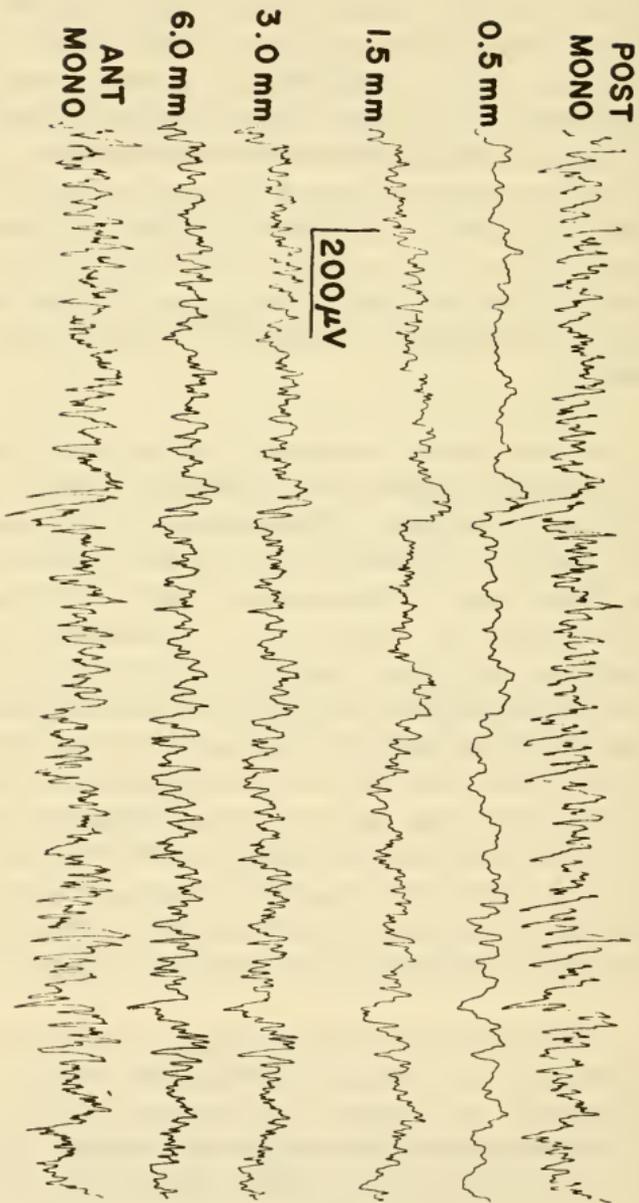


Figure 2. Concomitant monopolar and bipolar recordings show that the amplitude of the bipolar signal is dependent on the distance of separation of the electrodes, and that its form is dependent on the form of the regional component. The electrodes are arranged as in Figure 1: A, except that the electrode at 0.5 mm is coaxial with and immediately below the posterior monopolar electrode. Time, 1 sec. All bipolar records are with respect to the posterior electrode, No. 5.

# TEMPERATURE REGULATION "CENTERS"

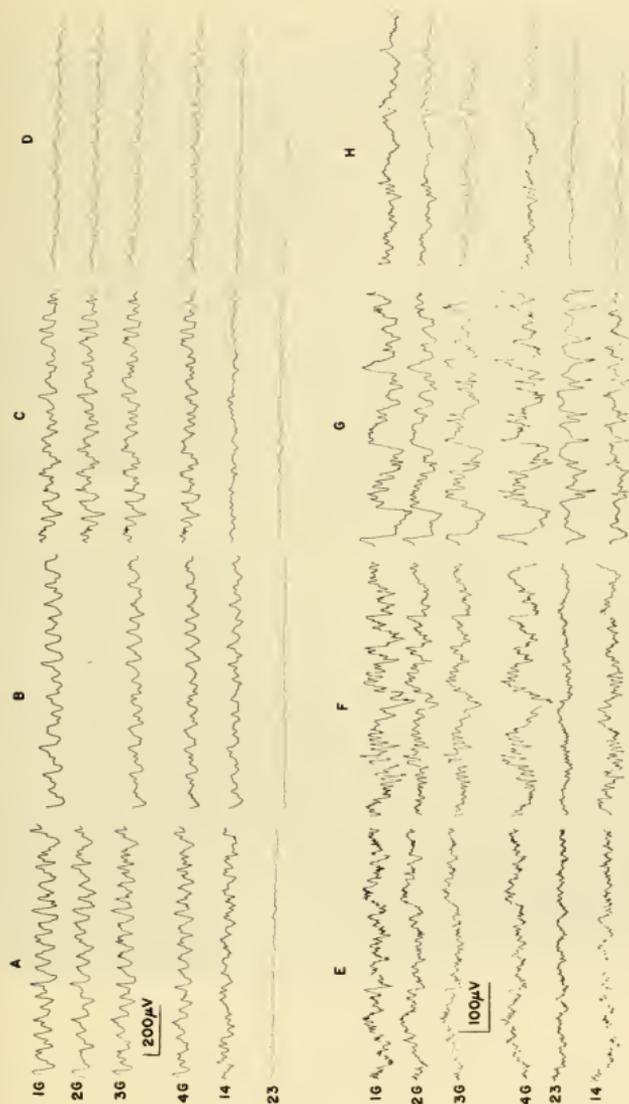


Figure 3. The effects on normal electrical activity (A, E) of coagulation and (B-C, F-G) of surgical isolation of (D, H) the hypothalamus are compared. The electrodes are arranged as in Figure 1: A. Of each set, the upper four lines are monopolar, and the lower two are bipolar. The pair in "14" are 6 mm apart. Time, 1 sec.

left intact. As soon as that was cut, hypothalamically recorded electrical activity (before or after coagulation) was greatly diminished (Fig. 3, D, H). This implied that the tacit assumption we made, that the electrical changes were generated locally by the tissue in which the electrodes were located, was not tenable.

This raised the question, then, where was this electrical activity coming from? By systematic mapping of these potentials in this volume of brain tissue, we found that the primary olfactory (prepyriform) cortex generated an electrical field accounting for them, and that the electromotive forces of the field lay in the molecular layer of the prepyriform cortex (Fig. 4). This was a dipole field, meaning that the surface and base of the cortex were at all times  $180^{\circ}$  out of phase (Freeman, 1959). Such a dipole field existing in a volume conductor has no outside limits. In effect, this field spread throughout the brain and when its amplitude was high enough, or, correspondingly, when the amplitude of electrical activity of other structures was low enough, it could be detected in such distant points as the medulla, cerebellum, and temporal muscles. It was indeed a very powerful electrical field. The iso-potentials shown in Figure 4 continued into the hypothalamus and indicated the existence of current flow from the cortex into this nuclear region. The spread of current is a passive process resulting from the occurrence of a difference in potential in the cortex with spread of currents in all directions, much as there is spread of sound from a source of noise throughout the limits of the confining space. These alternating currents spread outwards in all directions, producing that gradient of potential seen in Figures 1 to 3. Examination of the lesions found to abolish activity recorded in the hypothalamus showed that the effective sections had severely damaged the prepyriform cortex in all cases.

# TEMPERATURE REGULATION "CENTERS"

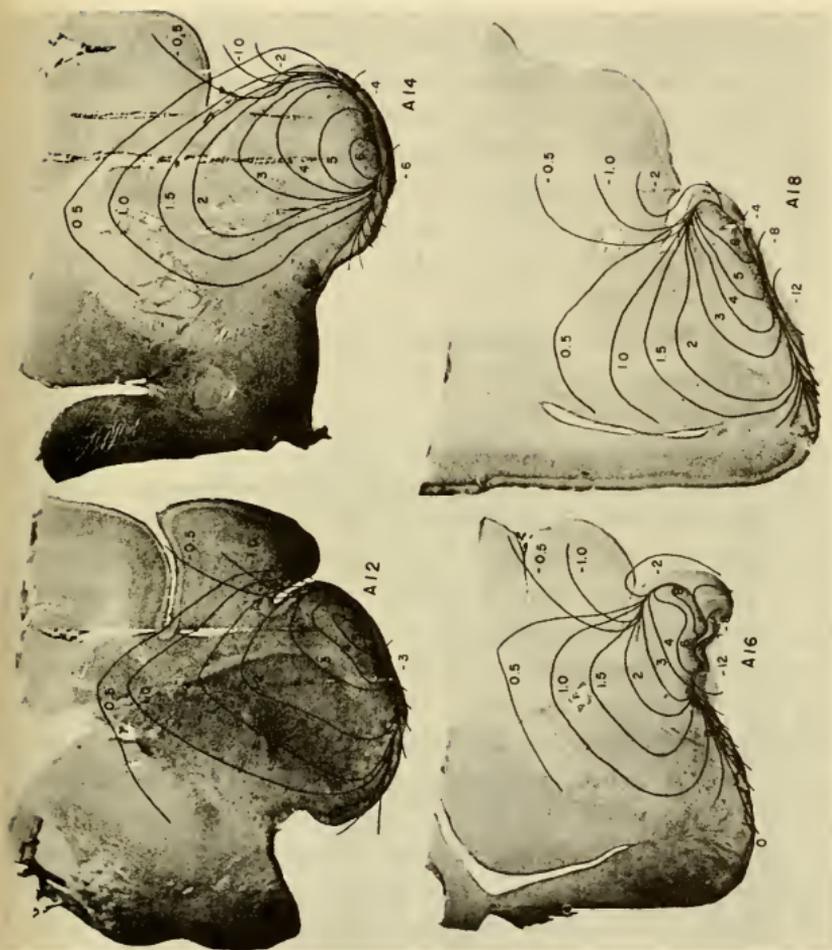


Figure 4. Coronal histological sections of the cat brain are shown at the designated stereotaxic levels. Superimposed on these are the isopotentials in millivolts of the prepyriform evoked field at peak amplitudes independently of time of occurrence.

AN INCONCLUSIVE EXPERIMENT INVOLVING  
STIMULATION

Let us now look at a second experiment which also failed and inquire as to the reason. This experiment was derived from the one preceding, in which the prepyriform electrical field was localized. We became curious as to what its relationship to behavior might be, and we found that there was a variety of correlations with behavior involving sensory stimulation, learning, motivation, and so forth. The particular aspect of interest here is the fact that the amplitude of this electrical activity was correlated with the rate of work done by cats in pursuit of a goal object, in this case, canned milk.

The electrical activity recorded from the structure is shown in Figure 5. It consisted of a series of bursts synchronous with respiration, which is of interest in view of Dr. Kawamura's findings. We determined the frequency and spatial distribution and the amplitude of this signal in order to find out what its parameter of change might be in relation to behavior, and found that the dominant parameter is amplitude, irrespective of the prevailing frequency and spatial distributions. Average amplitude was determined by rectifying and filtering the signal and measuring the surface area under this resulting curve (Fig. 5) graphically, or electronically as a matter of convenience and accuracy. As far as behavior was concerned, the animal waited in a starting box until the door was opened and then approached the milk and started lapping. It was this work period in which we were particularly interested. The work was measured by harnessing the animal after attaching the harness to a rope which pulled on a strain gauge. This rope then passed around a winch which rotated continuously. Whenever the animal was resting, there was no tension on the rope, and there was no rope paid out. As soon as the animal pulled, the rope tightened up on the winch; the winch pulled it through a friction drag and the animal was permitted to pull to reach the goal. It did not have to pull very hard in order to get there at a constant rate (the rate being determined by the winch), but the cats never seemed to learn; they always pulled harder than they needed to, and the hungrier they got, the harder they pulled.

# TEMPERATURE REGULATION "CENTERS"

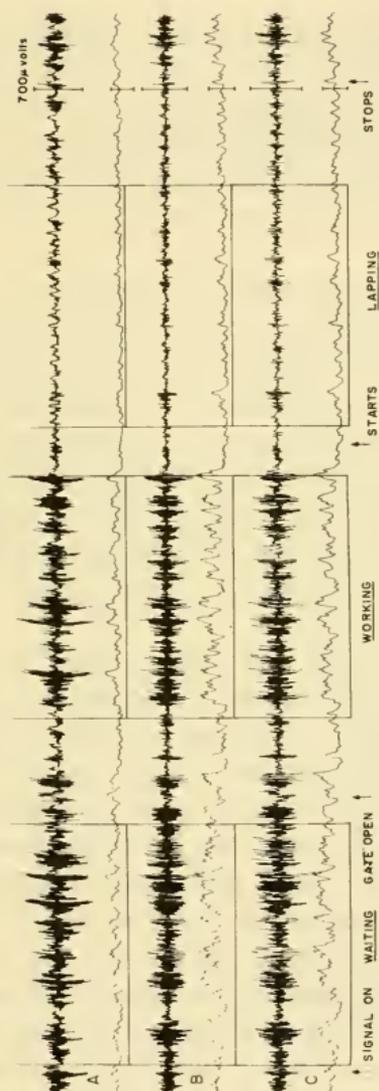


Figure 5. The electrical activity is shown from three adjacent bipolar electrodes straddling the left prepyriform dipole. In both records from each pair the low frequency components were removed. In the lower record from each pair the signal was rectified and filtered. In segments 8 seconds in length the zero baseline for each channel was drawn. The area enclosed by the baseline and tracing in each segment, when corrected with the calibration signal, gave the average amplitude during that segment. The average of the three amplitudes gave the average prepyriform amplitude during that response. The recording period during waiting was the first 8 seconds free of overt anticipatory movement; that during pulling was the last 8 seconds before reaching the goal; that during lapping was the first 8 seconds after a minimal amplitude had been reached (not more than 3 seconds).

This force of pull was integrated, and divided by the duration of pulling to get the average force. We knew velocity of approach; force times velocity gave the power or rate of work which the animal did to reach food. We then correlated this value with the amplitude of electrical activity generated concomitantly by this cortex.

In general, we found a three-to-one ratio such that for every one per cent increase in amplitude there was a three per cent increase in rate of work (Fig. 6). There was a dip in the upper half of the curve which was of considerable theoretical interest, but on the whole, it was apparent that there was a positive relationship between amplitude and the rate of work done by the animal.

It was known from previous work that the amplitude of electrical activity could be increased artificially by direct electrical stimulation of the cortex. Since the amplitude was related to work, one would presume that the increase brought about by stimulation would increase the rate of work done by the animal. We therefore increased the amplitude of electrical activity by direct electrical stimulation and measured the rate of work that the animal did during stimulus periods as compared to alternating non-stimulus runs. We found that there was no increase in rate of work.

Again, something went wrong. We thought about it for a while and decided that our mistake was to equate the increase in amplitude of this electrical activity with an increase in output of the cortex. We went back through our records to find if there were any circumstances under which we could get either positive or negative effects and, in fact, it turned out that this was the case. When we had first started out with our naive animals, there was a positive effect. Stimulation did increase the amount of work, but only for the first four days. Subsequently, this positive effect was averaged out to zero by a negative effect through most of the subsequent three weeks of measurement. In order to get a good measure of these changes, we started off with a fresh series of cats and found that, again, during the first four days of stimulation, as long as we were careful not to stimulate too hard or too often, stimulation would increase the rate of work done by these animals by some five to ten per cent, but that after four or five days, this effect dwindled to zero. We then found rather unexpectedly that we could increase the stimulus

## Prepyriform Electrical Activity vs. Rate of Work

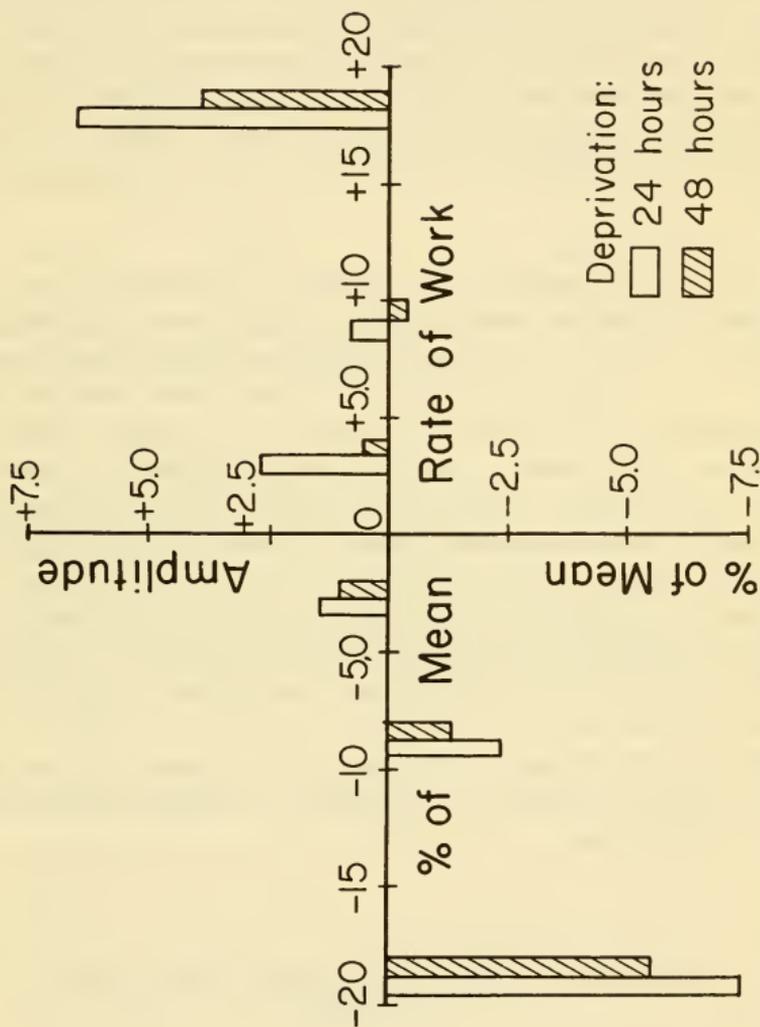


Figure 6. The amplitude of prepyriform electrical activity is shown as a function of concomitant rate of work done by cats to obtain food. Each value represents the average of ten measures from each of three cats.

intensity momentarily to a very high level some ten times threshold and get what is known technically as an "orienting reflex", in which the animal perked up its ears, sniffed the air, and moved its head and eyes as if in search. When this occurred, a rather remarkable change in the electrical activity did also, and thereafter, for at least two days, the positive effect returned. We again found a potentiation of rate of work by stimulation. Subsequently, however, this effect disappeared and in its place there came still a third phase, in which the rate of work was decreased by stimulation below the non-stimulus periods. Something happened that impaired the response; the same stimulus which still doubled the electrical activity and amplitude was associated with a decrease in rate of work.

Still more complicated was the fact that the animal could be trained to perceive this stimulus, so that unless the stimulus was present, it would not pull at all. We could also train it to press a lever to get milk or perform any other type of directed activity. Furthermore, if the stimulus intensity was increased and the effect tested on work, above a certain level the higher the intensity the greater the deficit of work done by the animal, until a point was reached at which the animal stopped completely. If this stimulus was maintained, there developed a behavioral and electrical seizure. So, although the intensity of electrical stimulation was linearly related to the amplitude of electrical activity of the cortex, the behavioral effects of electrical stimulation were much more complicated. The assumption derived from the doctrine of centers, that a correlation could be made between electrical amplitude and cortical function, was not valid, and the experiment that was based on this turned out to be inconclusive.

#### AN INCONCLUSIVE EXPERIMENT INVOLVING ABLATION

I have given examples of two experiments, one involving electrical recording and the other involving electrical stimulation, and would like now to give a third example involving lesion-making. I

## TEMPERATURE REGULATION "CENTERS"

have chosen these three examples because the classical approach to centers involves these three techniques.

This problem involved an extension of Dr. Hemingway's work with Dr. Birzis on electrical recording of unit activity from the brain stem of the cat in association with shivering (Birzis and Hemingway, 1957). You recall seeing yesterday Dr. Kawamura's work on the correspondence between the electromyographic potentials of shivering and inspiration or the onset of pain. The same correspondence was found between the electromyogram (Fig. 7, a, lower line) during a brief painful stimulus and, concomitantly, the interruption of a unit discharge associated with shivering, recorded in the brain stem with a rebound phenomenon occurring before the end of the painful stimulus. In Figure 7, b-d, you see phasic variations in shivering during its onset, when the relationship with respiration was most apparent, the temporal association of the unit spikes to the electromyographic change being quite clear.

These unit discharges were related to shivering in their frequency. When shivering was present, they were present; when it was suppressed by whole body warming, these units stopped firing (Fig. 8). When shivering was re-introduced by cooling the animal again, shivering and the unit potentials returned, with the unit potential coming 5 to 15 seconds after the beginning of shivering. In general, this was a pulse modulated system, meaning that the stronger the shivering, the higher the frequency of the discharge.

The location of these recording sites is shown in Figure 9 and reflects the distribution of a pathway in the nervous system which subserves shivering. Of particular interest was the origin of these unit potentials in the nucleus of the field of Forel. The efferent pathway of this nucleus goes down through the central tegmental fasciculus, turns laterally and, passing dorsal and lateral to the superior olive, goes to or through the inferior medulla. These potentials in general had the same distribution. As Dr. Clark suspects, they were rather widely spread through the brain stem, but they showed a concentration in this pathway. These sites also correspond to the anterior and posterior placement of the lesions that Birzis and Hemingway (1956) found would prevent shivering in anesthetized animals. The suspicion arose that if lesions could be placed bilaterally within the nucleus of Forel or the central tegmental fasciculus,

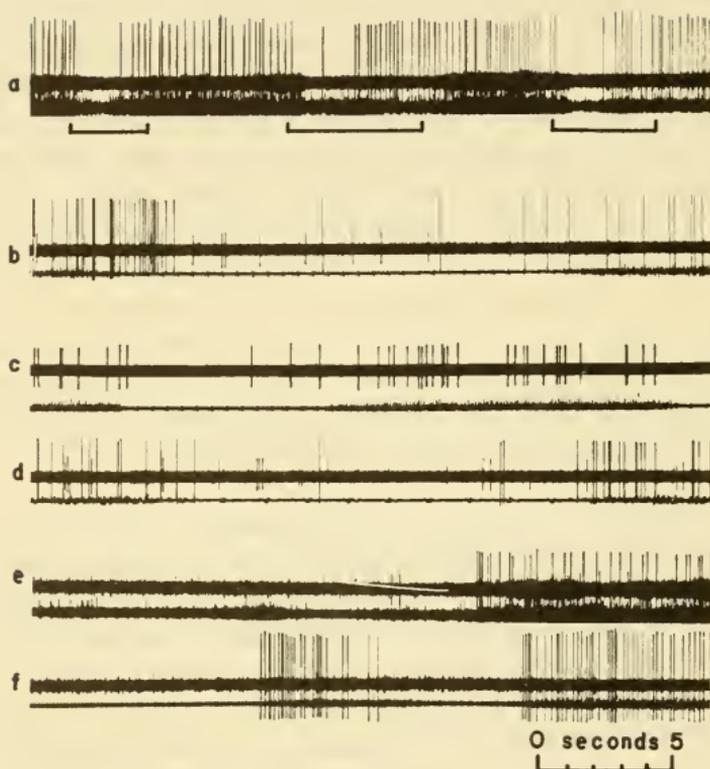


Figure 7. Concomitant changes are shown between electromyograms during shivering (upper trace) and brainstem unit discharge (lower trace); (a) arrest of shivering during nociceptive stimulus (bar); (b-d) phasic variations in synchrony with respiration; (e) onset of unit discharge after start of shivering; (f) onset concomitant with shivering.

## TEMPERATURE REGULATION "CENTERS"

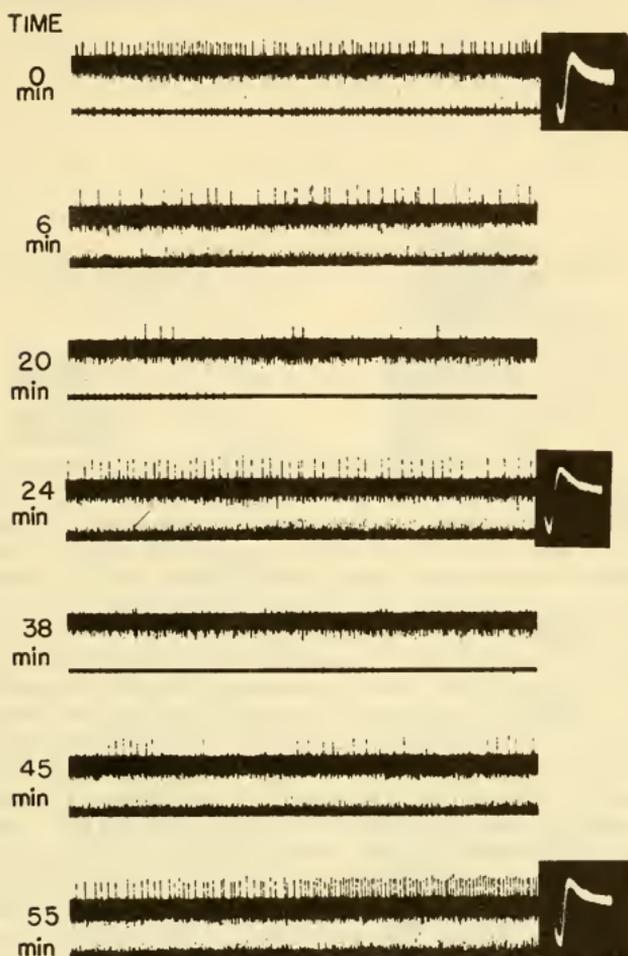
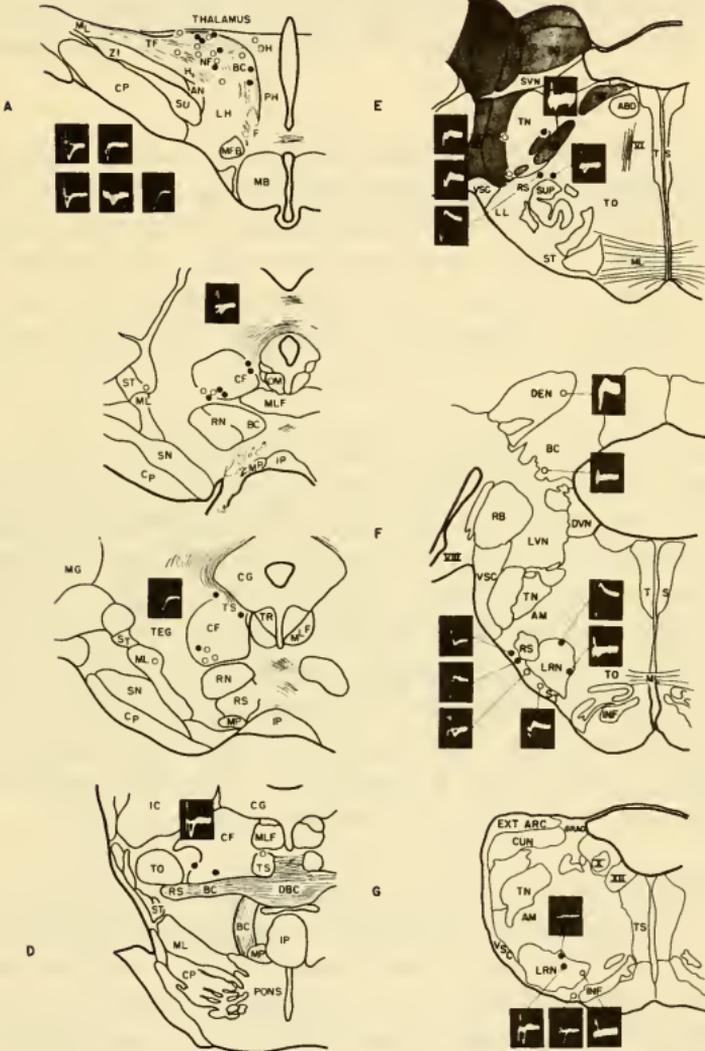


Figure 8. These tracings illustrate the procedures used to establish the association of a unit potential with shivering. The upper tracing of each pair is a continuous record from a microelectrode; the lower tracing is a concomitant electromyogram. At the right are tracings of the unit discharge as observed by triggering the sweep drive on an oscilloscope with the positive phase of the spike (cf. Fig. 3). Only the relatively long-lasting negative wave of the spike was reproducible in the records at the left. At 0 min a unit discharge was located and emptying of the cold water bath was begun. At 6 min the changeover to warm water was complete. At 20 min both shivering and unit were disappearing. Changing the bath to cold water brought an almost immediate reappearance of both the spike and of shivering; re-immersion in warm water again suppressed both. The change to a third cold bath did not produce an immediate effect, but 3 min after complete cold immersion both shivering and the unit reappeared, and thereafter both rapidly increased in intensity. The close similarity of the 3 wave forms at the right indicates that the same unit was re-activated with each cold immersion. Time: left, 1.0 sec; right, 1.0 msec.

Figure 9. These schematic drawings were made from tracings of slides of coronal sections of the brainstem. The dots represent positive points, the circles questionably positive points. The photographic insets show the configuration of representative spikes recorded at the various points. Abbreviations: ABD, n. adducens; AM, ansa lenticularis; BC, brachium conjunctivum; CF, central tegmental fasciculus; CG, central grey; CP, cerebral peduncle; CUN, n. cuneatus; DBC, decussation of brachium conjunctivum; DEN, n. dentatus; DH, dorsal hypothalamus; DVN, dorsal vestibular n.; F, fornix;  $H_2$ , field of Forel; IC, inferior colliculus; INF, inferior olivary n.; IP, n. intrapeduncularis; LH, lateral hypothalamus; LL, lateral lemniscus; LRN, lateral reticular nucleus; LVN, lateral vestibular nucleus; MB, mammillary body; MFB, medial forebrain bundle; MG, medial geniculate; ML, medial lemniscus; MLF, medial longitudinal fasciculus; MP, mammillary peduncle; NF, n. field of Forel; OM, n. oculomotor; PH, posterior hypothalamus; RE, restiform body; RN, red n.; RS, rubrospinal tr.; SN, substantia nigra; ST, spinothalamic tr.; SU, subthalamic n.; SUP, superior olivary n.; SVN, superior vestibular n.; TEG, tegmental reticular formation; TF, thalamic fasciculus; TN, trigeminal n.; TO, tectoolivary tr.; TR, trochlear n.; TS, tectospinal tr.; VSC, ventral spinocerebellar tr.; ZI, zona incerta; V, VI, VII, VIII, X, XII, cranial nerves and nuclei.

# TEMPERATURE REGULATION "CENTERS"



shivering could be abolished with minimal involvement of other activities of the animal. This was a simple logical deduction from our data and from the doctrine of centers. So, then, a series of lesions was made (Fig. 10) in these sites in 34 animals, 29 of which survived for at least three days. Ability to shiver was measured by rectal temperature or by oxygen consumption rate in response to a standard cold stress three, ten, and twenty-one days post-operatively.

In eight cats there was a transient impairment, two of the cats having developed intercurrent respiratory infections (Fig. 10, "deficient"). A similar series of lesions in animals which never showed a deficit are shown on the other side. The location and size of the two sets of lesions was as close as can be expected with the various technical difficulties of placing bilaterally symmetrical lesions.

So, then, this must be regarded as essentially an inconclusive experiment. There was some transient impairment of the ability to shiver in response to cold in a small proportion of the animals, approximately one-quarter of them. In the remainder, there was no deficit and yet these lesions corresponded rather closely to the areas in which it had been predicted they would produce a deficit of shivering. The question must be asked, why did this experiment fail? I do not think that one can blame technical factors. I think, rather, that one must look to the basic hypothesis to the doctrine of centers. I think that we assumed a degree of stability and of localization of function in the brain which does not exist.

In the first place, we have underestimated the number of functions or the degree of functional complexity of this area. This structure must do many other things besides regulate shivering, if, indeed, it does that. This is reflected in the fact that most of our animals during the early post-operative period showed impairment of other functions as well, such as walking, grooming, eating, etc.

I think, secondly, we have overlooked the plasticity of the brain. The basic phenomenon apparent in this set of studies is that the brain recovered the function lost immediately after operation. It

## TEMPERATURE REGULATION "CENTERS"

repaired itself, if you will. The brain apparently has the ability to change its functional organization and so bring about a return of essentially normal output despite the loss of some parts. I have no notion of what this reparative or regenerative process might be. All I can point out is that the doctrine of centers does not take into account this plasticity of the brain in its formulations of the hypothetical function of various centers.

## THE ANALYSIS OF BEHAVIOR INTO ITS ELEMENTS

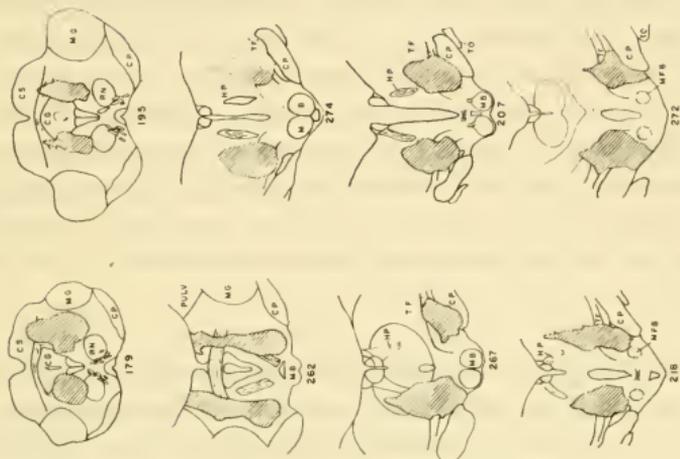
These difficulties I have described so far are largely concerned with manipulative problems of stimulation, ablation, and recording. There are, in addition, some major observational difficulties concerned with how behavior is to be subdivided, and what behavioral elements are to be ascribed to specific sites. The assumptions are, in the doctrine of centers, that each center produces an organized, recognizable entity as its output, that the part of the brain responsible for each response is at a high-energy level, and the others are quiescent. It is a doctrine of mutual exclusion. Consider as an example of these complex assumptions the phenomenon of reflex shivering, which we have already considered at some length. Specifically, is there any one part of the brain which is solely concerned with shivering and with no other reflex phenomenon? What parts of the brain are silent when shivering is going on, but when the animal is otherwise inactive? On the other hand, what parts of the nervous system concerned with shivering are also concerned with other types of behavior, whether thermoregulatory or not?

Beginning with the periphery, it is obvious that cold receptors are not specific for shivering or, for that matter, even for thermoregulatory responses. They can elicit a wide variety of autonomic or somatic responses depending upon previous circumstances, as with our experiment in stimulation of the prepyriform cortex. Nor can there be said to be shivering effectors, since the muscles are used also in a variety of other activities.

Figure 10. Following sacrifice of the cats, the brains were fixed in situ, sectioned serially, and stained for cells (Nissl). By means of a photographic enlarger, the slides showing the lesions were projected onto drawing paper, and tracings were made of the outlines of the brainstem, the nuclear masses, and the lesions. From adjacent intact slides tracings were made of the extent of distribution of the structures from which unit potentials had previously been recorded in association with shivering. The outlines were checked by scrutiny of the histological details of the sections with a microscope. The outlines of the lesions and of the distribution of unit potentials were then superimposed on single tracings made at the level of maximum extent of the lesions. At the right are shown tracings from the 8 cats that were hypothermic or had diminished oxygen consumption rates on at least one cold test. At the left are shown 8 tracings from the remaining 21 cats, which were not hypothermic, but which had lesions corresponding most closely in size and location to those on the right.

# TEMPERATURE REGULATION "CENTERS"

DEFICIENT



NORMAL



10 mm

DISTRIBUTION OF UNIT ACTIVITY

LESION

At the level of the spinal cord, there is a highly complex set of structures concerned with shivering, including the terminal fibers of sensory nerves, the interneurons and their dendritic systems, recurrent collaterals, the afferent fibers from sensory organs in muscle, and so forth. All of these structures comprising the basic apparatus of the segmental spinal reflexes are unquestionably involved in shivering. They are equally unquestionably involved in all other types of directed muscular activity, and yet they are not sufficient for either. The particular contribution of these structures appears to be the adaptation of an overall pattern of body activity to local conditions encountered in the trunk and extremities. Specifically, the frequency of tremor of any given muscle or muscle group is determined at the spinal level. The question of whether or not shivering will occur, and if so, with what severity, is decided elsewhere.

There is a great deal that ought to be known about higher structures in relation to shivering, which we do not yet know. Perhaps Dr. Stuart will tell us something along that line. Proprioceptive activity is associated with the ascending discharges in the spinocerebellar tracts, terminal fibers of which are broadly distributed over the cerebellar cortex. There are indications that cutaneous sensory activity may also reach the cerebellum. The spino-thalamic tracts subserving thermal sensation pass laterally and ventrally through the medulla over the lateral reticular nucleus, and they give off collaterals to it. Virtually the entire efferent discharge of this nucleus is distributed to the cerebellum. It is now known that electrical potentials related to a variety of afferent stimuli including visual, tactile, and auditory stimuli reach the cerebellum, and it seems likely, although the direct evidence is lacking, that thermal stimuli can induce cerebellar responses. In this case, the cerebellum can be regarded as a site for the mixing of cutaneous and proprioceptive discharges to produce a new pattern which is specific for these two types of input. Dr. Kawamura has shown in this symposium that an increase in proprioceptive activity associated with increased muscle tonus is a prelude to shivering. Obviously, cutaneous cooling is an essential element. When proprioceptive and cold receptor activity are mixed, as they may well be in the cerebellum, the groundwork is laid for an appropriate response peculiar to this unique combination of sensory input. Clearly the cerebellum is not specific for shivering, but it plays a significant role, since shivering

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becomes irregular and spasmodic when the cerebellum is removed.

I might also mention the contribution of the reticular formation to shivering, since this is another region which is involved in shivering, but not specific for it; however, time does not permit to go into it in any detail. The anterior hypothalamus is another sensory mechanism, which Dr. Lim and Dr. Hensel have shown to be clearly implicated in the shivering process. It is probably not essential for it to occur, and certainly there are other things that the anterior hypothalamus regulates besides shivering. One might now ask, what about the nucleus of Forel? Is it involved in shivering, as suggested by unit activity, or is it not involved, as the results of the lesions would imply? During the process of shivering there is muscular vasodilation, perhaps active. There is an increase in cardiac output, an increase in rate and depth of respiration, all subserving an increase in oxygen consumption and transport. Does this discharge that we see, which is related to shivering, subserve merely the skeletal muscular contraction, or does it subserve the entire autonomic-somatic pattern associated with shivering?

The nucleus of Forel receives a powerful descending projection from the corpora striata, so that a large proportion of the entire efferent outflow of the basal ganglia passes through this nucleus. It would be rash to assume that other patterns of activity related to other forms of behavior are not partially organized in the nucleus of Forel. Is there a pattern of cellular activity specific for shivering and another pattern specific for each other form of behavior, or is there a common pattern to all these activities? If this structure is stimulated electrically, will it reproduce the pattern for shivering, or will it give something else, some entity which is not related to any observable phenomenon in the nervous system? If stimulation is applied in a situation in which some other rhythmic process is occurring, such as chewing, rutting during sexual behavior, or panting, will shivering occur or some other rhythmic contractile process?

These considerations are summarized in diagrammatic form in Figure 11, showing a sketch of a longitudinal section of the cat brain. It is proposed that each of the structures indicated is active during shivering, and that each contributes some analytical element

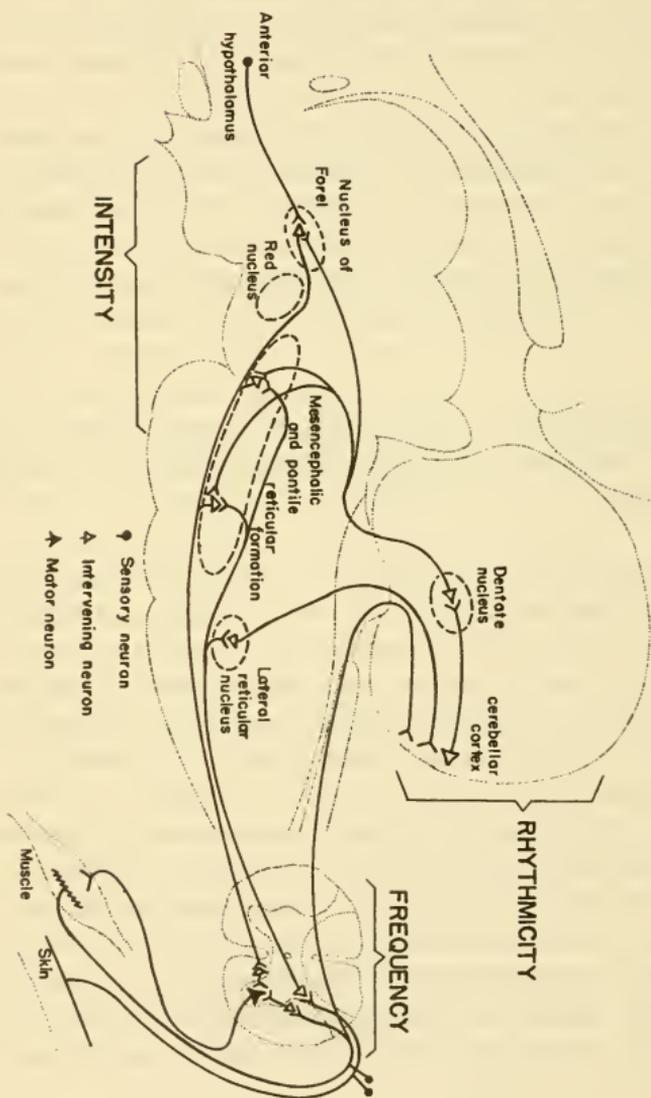


Figure 11. Schematic diagram of some pathways active during shivering.

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to the completed process, e.g. frequency, rhythmicity, and intensity. But it is also proposed that these same structures are active during all other kinds of behavior produced by the intact nervous system. and that the essential nature of the contribution of each would, in some sense, be the same as that during shivering. The precise pattern of output would be determined solely by the previous pattern of input.

## CONCLUSION

It can be said finally that even where the available evidence indicates the existence of a center in the classical sense, such an achievement can no longer be regarded as a satisfactory end point. For, if it be demonstrated that stimulation of a given structure will produce shivering, or, for that matter, feeding, non-feeding, rage, sleep, sexual behavior, etc., it must be recognized that the stimulus evoking this is not normally present in the brain. Where then does it normally come from? What is the nature of the cellular activity that the electrical stimulus has produced; and how does this compare with the normal pattern of electrical or cellular activity? How is this normal pattern brought into being by afferent fibers? Is a transmitter substance involved? Are there chemical gradients of ions moving in response to endogenous electrical fields? What is the nature of the efferent activity? These are all questions which are now within the realm of analysis and I think should constitute the bulk of work in neurophysiology in future decades.

The conclusion of this review is that the various parts of the brain may not be so organized as to subserve particular functions through the increased activity of particular parts, the other parts then remaining quiescent. It is suggested, rather, that during most reflex activities, virtually all parts of the brain are active, that each part of the brain contributes some basic element to all types of reflex activity, and that distinctive spatial-temporal patterns of behavior are determined largely by the pattern of sensory stimulation, which is maintained before and during the activity. In this view

further studies of temperature regulation would require the identification of the functional parts of the brain, of the contribution of each part to behavior as a whole, and finally, of the neuronal mechanism of that contribution. This is the direction to which we must now turn in order to avoid perseverative failures in our experiments.

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### DISCUSSION

DR. STUART: Is it true that the posterior hypothalamus is outside the dipole field generated by the prepyriform cortex?

DR. FREEMAN: Excuse me. It does extend into that area.

DR. STUART: I thought you showed its most posterior aspect as anterior to the posterior hypothalamus.

DR. FREEMAN: That is somewhat different. It is mixed there with another field.

DR. STUART: There is no perceptible disturbance of temperature regulation in cats with the prepyriform cortex ablated. Could it be that the activity you recorded in the hypothalamus with macro-electrodes was masking the unitary activity of small hypothalamic cells whose activity is related to temperature regulation?

DR. FREEMAN: If such activity exists, yes, but one would have to prove that it exists. This is precisely what we were looking for by means of various types of recording. I did not find it. I do not know of anybody else who has. I know several people who looked but were unable to find anything definite. This applies not only to EEG waves, but also to unit activity, which we also made a serious attempt to find, and could not. We could find action potentials, but they came from other structures such as the optic tracts. In other words, they stopped and started with the opening and closing of the eyes, and, therefore, were irrelevant to this area. As far as I could find to date, this structure is electrically silent. I would hope that Dr. Hensel would be able to modify his techniques for recording C fibers to record from small cells in that area, since there are cells there and they can be presumed to generate electrical activity; but before you can say it is being masked, you have to know whether it is there. I have not been able to see it; as far as I am concerned, we cannot yet say that it exists.

DR. RODDIE: Have any intracellular recordings been made around this area?

DR. FREEMAN: These cells are somewhat smaller than red blood cells; the average intracellular electrode is, let us say, one-tenth of one micron in diameter, and its irregular movement due to vibration in this circumstance is too great. The average cell which can be successfully recorded from is some hundred microns in diameter.

DR. RODDIE: Even though it is difficult, until this type of recording is made, I do not think any conclusions can be drawn; the failure of external electrodes to show any independent electrical activity really does not mean very much.

DR. FREEMAN: No, all it means is that the electrical activity cannot be recorded with our presently available technique; and what I am saying is that the electrical activity that can be recorded there is not generated by those cells. It comes from somewhere else, and this is the point that is important in applying doctrinaire thinking to these problems. I started off with the assumption that what I recorded there was generated by cells found there, and this was not so. This is what I would emphasize above all, that which is recorded in a given structure may not come from that structure. In the case of a reticular structure like this, it probably does not. I fully agree that there must be cellular changes there. I think they will be more likely found not with electrical recording, but with other types of recording such as optical density, impedance, or paramagnetic resonance. There are a number of such techniques which are just coming into possibility now, which I think will give far better approachability to this structure. There are obviously changes occurring here which are related to temperature regulation. I do not think electrical recording is the way to analyze them.

DR. STUART: It seems interesting that the unit potentials recorded from the nucleus field of Forel begin fifteen seconds or so after shivering has begun. One wonders whether the units are driving the shivering or whether the shivering is driving the units, particularly since once shivering begins, and a characteristic rhythm is set up in a limb, there is a proprioceptive input to the cerebellum,

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and there are anatomical connections from the cerebellum to the nucleus of the field of Forel. I cannot see how you can conclusively say that the units you recorded are related to the efferent aspect of shivering.

DR. FREEMAN: One can relate them to the shivering process, since they occur in association with it. What you are thinking of is the initiation of shivering. I do not think that they do this, since they usually begin after shivering has started. They are associated with the build-up of shivering, if you will, or the maintenance of the shivering at a level of adequate intensity. This tremor may or may not be shivering. A tremor in response to cold can occur in a decerebrated animal. I would think that the whole mechanism of shivering exists downstream and what this part does is to facilitate this mechanism in response to the combined central-peripheral limbs of the cold receptor system. This means that this discharge is not necessary for the initiation of it, but it may be essential for the maintenance of an adequate degree of intensity.

DR. STUART: It would be interesting to ablate the cerebellum and allow any rostral connection to the cerebellum with this region to degenerate and then see if you can still record these units.

DR. FREEMAN: Well, a rather small proportion of the discharge comes up there in any case. Also, as we have seen, lesions of that area do not abolish shivering. I suspect that there may be other parts of the brain which can do just as well, which also receive afferents from the cerebellum.

DR. STUART: The units that were shown in this work were recorded when animals were shivering under pentobarbital anesthesia, whereas after the lesions were made, the animals were tested in a cold stress in the unanesthetized state. Since this work has been done, I have made similar lesions in six animals in this subthalamic region -- animals that, pre-lesion, could shiver under pentobarbital. After lesions had been made, the unanesthetized animals could still shiver in response to a cold stress, but they did not shiver under pentobarbital anesthesia. That makes me wonder whether or not there is a problem related to the effect of the drug on the response.

DR. FREEMAN: There is undoubtedly a problem related to the effect of the drug. I often suspected that pentobarbital had abnormal potentiating effects on shivering. I have induced shivering in an animal, for example, with a relatively high rectal temperature, and I have seen shivering continue even when the brain temperature has passed  $42^{\circ}\text{C}$  or  $43^{\circ}\text{C}$ . It is an abnormal condition, but if one wishes to study these unit potentials, it is better to have an abnormal condition in which shivering can be obtained than one in which it cannot.

DR. STUART: Still, after the lesions in this region, if the animal is given pentobarbital, it does not shiver at an abnormally high temperature. It is very difficult to get it to shiver even if the animal is cool.

DR. FREEMAN: That is a valuable finding. I agree that the use of anesthesia introduces difficulties, although I would not say that it is to be deplored.

DR. STUART: In the work that you did with unit recording, did you find any units that began before shivering began?

DR. FREEMAN: Yes, we discarded those as sensory.

DR. STUART: What regions were they?

DR. FREEMAN: They were further laterally in the vicinity of the medial lemniscus and spino-thalamic tract. I did not study those to any great length because of limitations of time, but certainly the way in which to approach unit activity of this kind is to study every unit one can find that is correlated with anything. Other types of units we found were those which were initiated or increased in their discharge with this painful stimulus as opposed to the decrease we saw with shivering units. Those also would be of considerable interest.

DR. STUART: Often in neurophysiology we think in terms of recording channels rather than brain activity. When using an oscilloscope we are two-channel thinkers, i.e., the unit and the EMG. When using an EEG machine we are eight-channel thinkers. This imposes a "centristic" approach to the nervous system.

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DR. FREEMAN: I guess if we could afford it, we would be a twenty-five-channel thinker.

DR. CLARK: I have one comment. You brought up the question of plasticity. Now, plasticity to me is a good deal like the spread of current. One may use spread of current to explain why the other man got results different from yours. Plasticity is to me just a recognition of lack of knowledge. For example, if you take out the motor cortex in a cat, and wait about eight months, he behaves quite normally. You do the same thing with a chimpanzee and eight months later he will still have the same paralysis that he began with. If you do it with a spider-monkey, the paralysis remains. Now, if you explain the return of functioning in the cat by invoking the term "plasticity", why does it not occur in these other two species?

DR. FREEMAN: I take it that this is a rhetorical question?

DR. CLARK: It is. And the same is true of the posterior columns. You damage those and the damage is apparently permanent, but as all of you clinicians know, the operation for relief of pain is not uniformly successful. If you invoke plasticity to explain the return of pain, why does function not return in the posterior columns? I think as far as return of shivering in those animals is concerned, there is a question of the probability of hitting a cell or a fiber. Where there is a fair collection of them this is easy, but when they are scattered throughout a large area, the probability of hitting enough of them becomes much less.

DR. FREEMAN: I quite agree. It is a term to describe essentially the recovery process, but it does no more than show that we do not know what it is.

DR. CLARK: It is worse than that, because when you invoke the term plasticity, you assume then that there is no localization, no permanent localization.

DR. FREEMAN: I agree it is a loose term that one could take to mean that, but I would not go that far.

DR. HENSEL: I think that even the results of the acute experiments have a certain significance. Plasticity is no argument against this, because you can get the acute disturbance in one area while in another one, you do not, and this means something, even if there is afterwards a plasticity in a certain recovery.

DR. FREEMAN: It may explain the difference then between the acute experiments and the results of the chronic experiments.

DR. HEMINGWAY: I would just like to point out the need for further work on the unit potentials which occur in the midbrain and are associated with shivering. We still do not know just what part they play in the shivering process. They are there; they come on with shivering and they disappear when shivering stops. They are not quite in phase. I would like to ask if you removed the cerebellum and then looked for them.

DR. FREEMAN: No, I did not do that.

DR. HEMINGWAY: Dr. Stuart suggested that these midbrain unit potentials might have come in from the cerebellum which is a possibility, but experiments should be conducted in which the cerebellum is removed.

DR. FREEMAN: They were seldom encountered in that part of the brain; that is to say, they were not in the brachium conjunctivum.

DR. HEMINGWAY: And remember, if you make a hemisection below where you are recording, they are still there, so they are coming down from above but they might go a round-about way, by way of the cerebellum.

DR. FREEMAN: I think that is a safe conclusion.

DR. HENSEL: I have another question. I was quite interested in your finding of the relationship of arousal of behavioral activity to the potentials of the hypothalamus. We recorded recently the local blood flow in the hypothalamus by means of very thin implanted heated thermocouples in an unanesthetized cat, and we found that there is also very close correlation between the activity or arousal

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of the cat and rate of blood flow. If you show a mouse to the cat, you get an enormous increase in the hypothalamic blood flow by about 100 per cent. When the mouse is gone, then the blood flow drops. And another observation is, if the cat is not able to catch the mouse after some time, say if it were in a glass container, hypothalamic blood flow would drop, which is a sign of resignation.

REFERENCES

1. Birzis, L. and A. Hemingway. Descending brain stem connections controlling shivering in the cat. *J. Neurophysiol.* 19:37-43, 1956.
2. Birzis, L. and A. Hemingway. Efferent brain discharge during shivering. *J. Neurophysiol.* 20:156-166, 1957.
3. Brazier, M. A. B. The historical development of neurophysiology, Chapter I, in the *Handbook of Physiology. Section I: Neurophysiology, Vol. I.* Amer. Physiol. Soc., Washington, D. C., 1959. Ed. J. Field.
4. Darwin, C. *The Expression of the Emotions in Man and Animals.* London, John Murray, 1872. ch. xiv, pp. 374.
5. Freeman, W. J. Oscillating corticonuclear dipole in the basal forebrain of the cat. *Science.* 126:1343-1344. 1957.
6. Freeman, W. J. Distribution in time and space of prepyriform electrical activity. *J. Neurophysiol.* 22:644-665, 1959.
7. Sherrington, C. S. *Man on His Nature.* Doubleday and Co., Garden City, New York, 1953. 2nd ed., ch. xii, p. 316.

# ROLE OF THE PROSENCEPHALON IN SHIVERING

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The experiments reported in this paper were designed to localize control of the production of shivering to a specific region of the hypothalamus and then to study some of the telencephalic influences that by hypothalamic relay could instigate, facilitate, or suppress shivering.

First it was necessary to recognize the results of workers who have claimed that decerebrate preparations can shiver (Barbour, 1939; Dworkin, 1930), even though such results conflict with those of the majority of investigators (Bard, 1961; Bard and Macht, 1958; Bazett and Penfield, 1922; Blair and Keller, 1946; Dusser de Barenne, 1920). If decerebrate preparations can shiver, it means that the primary control of shivering is in the midbrain or pons, since all the above investigators agree that shivering is abolished by transection of the caudal pons.

However, over 60 years of evidence (Ott, 1895, to Keller, 1959) has implicated the hypothalamus as the primary "center" for the production of shivering. Since it was early shown that massive anterior hypothalamic destruction did not affect shivering (Bazett et al., 1922; Clark et al., 1939; Keller and Hare, 1932), it followed that the essential neurons were in the posterior hypothalamus. A more precise anatomical description invites controversy. Some investigators have studied this problem by noting the presence or absence of shivering after destruction of part of the posterior hypothalamus, but their results conflict in localizing the essential neurons to the dorsal posterior hypothalamus (Bazett et al., 1933; Blair and Keller, 1946), the ventro-medial mid hypothalamus (Frazier et al., 1936), the lateral posterior hypothalamus (Clark et al., 1939) and to the ventro-lateral posterior hypothalamus (Birzis and Hemingway, 1956).

Other investigators have studied this problem by stimulating the intact brain to instigate shivering. In three laboratories

(Chatonnet, 1961; Hammel et al., 1960; Kundt et al., 1957), shivering has been evoked by thermal stimulation, but this technique does not permit a precise localization of the effective region. Others have demonstrated the production of shivering during application of an electrical stimulus to the forebrain's septum in anesthetized cats (Akert and Kesselring, 1951) and unanesthetized goats (Andersson, 1957) and to the midbrain and pons in anesthetized cats (Birzis and Hemingway, 1957). In the studies using cats, production of shivering by stimulation of the hypothalamus was mentioned. In each case only one hypothalamic locus was stimulated. In all three reports the investigators' efforts were devoted mainly to regions more rostral or more caudal than the hypothalamus. Since decorticate preparations with the septum destroyed can shiver (Aring, 1935; Bard, 1961; Dusser de Barenne, 1920; Pinkston et al., 1934), it would seem that the most rostral prosencephalic region whose stimulation consistently produces shivering is one whose ablation does not affect shivering. Anatomically the septal region of the forebrain, which is but a vestige in man (septum pellucidum), has been shown to have intimate connections with neocortical and rhinencephalic pathways to and from the thalamus, hypothalamus and midbrain (Fox, 1920; Pribram and Kruger, 1954). Thus, it might well be, but is not proved, that the septum is involved in alterations in temperature regulation evoked by classical Pavlovian conditioning (Bykow, 1957), the production of shivering by hypnotic suggestion (Gessler and Hansen, 1927) and "psychological aspects" to cold tolerance mentioned in recent reports of human adaptation to cold stress (Adams and Covina, 1958; Scholander et al., 1958; and Wyndham and Morrison, 1958).

However, if the septum is involved in the production of shivering, its activity should be but secondary to hypothalamic activity in that it can be ablated without affecting shivering, and all known caudally projecting septal efferents synapse in the hypothalamus to make direct connections with the midbrain (Nauta, 1958; Sprague, 1950). Neither these fibers nor those septal projections to the thalamus could produce shivering, since the thalamus and also the hippocampus, from which the fornical fibers arise, can be ablated without affecting the production of shivering.

Anterior hypothalamic stimulation either thermally (Eliasson and Ström, 1950; Freeman and Davis, 1959; Hemingway et al., 1940;

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Magoun et al., 1938) or electrically (Andersson et al., 1957; Andersson and Persson, 1957; Andersson et al., 1960; Hemingway et al., 1954) is known to suppress shivering. There are septal projections to both anterior and posterior hypothalamic regions. Therefore, if septal stimulation can evoke shivering, it should also be capable of suppressing it. Such suppression has been reported during septal stimulation (Hemingway et al., 1954) and during stimulation of more rostral telencephalic structures, the orbito-frontal gyrus (Kaada, 1951) and the amygdala (McLean and Delgado, 1953). It is not known if the neurons activated to suppress shivering during stimulation of the orbito-frontal gyrus and the amygdala traverse the septum or relay within it.

Some investigators have shown that on exposure to cold shivering appears sooner and is more intense after decortication (Aring 1935; Bard, 1961; and Pinkston et al., 1934) and on this basis have claimed that the cerebral cortex is inhibitory with respect to shivering. However, evidence that the telencephalon can activate as well as suppress shivering is just as valid and suggests that the effects of decortication on shivering should be re-examined. From the above mentioned literature the following questions emerge:

1. Can decerebrate preparations shiver?
2. Is the shivering intensity of decorticate preparations equal to, greater than, or less than that of unoperated animals?
3. Is the septum or the posterior hypothalamus primarily involved in the production of shivering?
4. Can septal stimulation suppress shivering and if so, how is this related to septal activation of shivering and to anterior hypothalamic suppression of shivering?

On the basis of both anatomical and physiological studies, it appeared that septal production and suppression of shivering should be secondary to hypothalamic production and suppression of shivering. Secondly, if septal and midbrain electrical stimulation could produce shivering, so should electrical stimulation of the hypothalamus. It was felt that the use of electrical stimulation would

permit a localization of that region of the hypothalamus responsible for the production of shivering. Thirdly, it seemed that the net effect of decortication on shivering could be one of depression, facilitation, or nil, depending on the relative tonic preponderance of facilitating versus suppressive telencephalic influences on the critical hypothalamic region in the intact brain.

In defense of these hypotheses the following experiments have been undertaken in Dr. Allan Hemingway's laboratory in the past two years:

1. Re-examination of the decerebrate cat's response to a cold stress.
2. Re-examination of the decorticate cat's response to a cold stress.
3. Localization of the hypothalamic region which when activated produces, and when destroyed abolishes, shivering.
4. Comparison of somatic effects evoked during stimulation of such a region and the septum.
5. Comparison of relative suppression evoked by septal, anterior and posterior hypothalamic stimulation during shivering.
6. Effects of septal lesions on shivering.

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## EXPERIMENTS

### EFFECTS OF DECEREBRATION ON SHIVERING

#### Methods

Aseptic decerebration surgery was performed on seven cats under pentobarbital sodium anesthesia (35mg/kg I. P.). Care was taken to preserve the blood vessels on the ventral surface of the brain. Figure 1 shows the gross aspects of such surgery and illustrates the fact that the only connection between the prosencephalon and the lower brain is by virtue of the meninges. By preserving the ventral diencephalon, the hypothalamic-hypophyseal system can function relatively effectively, as evidenced by the preparations' lack of polyurea after surgery.

After surgery the preparations were poikilothermic, and body temperatures were maintained artificially at 36° C to 38° C by appropriate alterations of environmental temperature. For the first three days after surgery, the preparations were given intramuscular injections of a mixture of streptomycin, dihydrostreptomycin, and sodium and procain penicillin (0.5 cc I. M., Dicrysticin Fortis, E. P. Squibb and Sons, New York, N. Y.). They were daily fed by stomach tube, 150 cc of a homogenized mixture of meat and milk, were kept dry and clean and by frequent alteration of their relatively immobile postures, their "bed sores" were kept in check.

One to nine days post surgery, the animals' oxygen consumption rates ( $\dot{V}O_2$ 's) were determined over 20-minute periods with rectal



DORSAL VIEW



PARASAGITTAL VIEW

Cms

1	2	3	4	5	6	7	8

Figure 1. Gross views of decerebrate cat brain No. 7.

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temperatures maintained near  $38^{\circ}\text{C}$ . The body temperatures were then lowered  $0.5^{\circ}\text{C}$  to  $9^{\circ}\text{C}$  by immersing the cats in cool water for 10 minutes. Ten minutes after completion of this cooling stress the oxygen consumption rates ( $\dot{V}\text{O}_2$ ) were redetermined over a 20-minute period. During the cooling stress and second determination of  $\dot{V}\text{O}_2$ , the somatic responses of each animal were checked by independent observation. Somatic responses included all forms of skeletal muscular activity and patterns of movement that were apparent on visual inspection. By independent observation it is meant that more than one investigator visually inspected each preparation and after such inspection the somatic responses were discussed.

Comparisons were made of the somatic responses during such rapid cooling and during slower cooling (exposure to  $25^{\circ}\text{C}$  environmental temperature), rapid rewarming (immersion in  $50^{\circ}\text{C}$  water) and slower rewarming (immersion in  $40^{\circ}\text{C}$  water). After these tests an attempt was made to keep the animals alive for further tests at one month post surgery, but this met with failure. Of the 22 cats decerebrate surgery was performed on, 20 lived one day or more, 13 two days or more, 9 three days or more and five 5 days or more post surgery.

After these tests the animals were sacrificed and their brains fixed in formalin for gross and sometimes histological inspection.

### Results

Somatic observations. Table I summarizes the metabolic and somatic responses of seven decerebrate cats subjected to a rapid cooling test one to nine days after surgery. All the animals made somatic responses to the rapid cooling stress of immersion in cold water. Movements consisted of intermittent spasmodic twitches, jerks and large amplitude kicks and running movements of the somatic musculature. These somatic responses were accompanied by an increase in respiratory rate and depth. The violence and frequency of these intermittent movements were greater in the animals

## Oxygen Consumption Rates and Temperature Measurements

Cat No.	Weight Before Surgery	Days After Surgery	Before Cold Stress			During Cold Stress			After Cold Stress			Independent Observations of Somatic Responses	
			$\dot{V}O_2$	R. T.	E. T.	$\Delta R. T./10'$ imm.	W. T.	$\dot{V}O_2$	%Dev.	$\Delta R. T./20'$	E. T.	During Cold Stress	After Cold Stress
5	3.75	3.70	6.0	37.5	30	-2.5	10	6.2	+3	-3.5	30	Intermittent twitching	Quiet
6	2.01	2.00	8.0	38.0	30	-3.4	10	8.0	0	-3.1	30	As above	As above
7	3.36	2.98	5.0	36.0	30	-3.5	10	6.6	+32	-3.0	30	Gross kicking Intermitt. slow kicking and tremor-Hypervent.	Less frequent kicking and twitching
8	2.7	2.5	7.2	38.0	30	-0.5	20	7.9	+10	-5.0	30	Faster tremor-No gross movements	Tremor maintained
10	2.7	2.35	7.4	36.2	30	-9.2	0	4.3	-42	+0.6	31	Violent intermitt. kicking & running	Hypotonic
17	3.45	3.09	3.8	35.2	32	-2.0	10	3.1	-18	-0.8	32	As above	As above
22	3.5	2.93	3.7	38.0	35	-6.0	5	3.4	-9	0	35	As above	As above

Table I. Oxygen consumption rates of decerebrate cats before and after rapid body cooling. Oxygen consumption rates ( $\dot{V}O_2$ ) expressed in ml $\dot{O}_2$  STPD/kg/min, rectal temperature (R. T.), environmental and water temperature (E. T. and W. T.) expressed in degrees Centigrade. Weight expressed in Kg's.  $\dot{V}O_2$  based on a 20 min. determination in a closed circuit system immediately before and after animal immersion in cool water.  $\Delta R. T./20'$  is the change in rectal temperature during the  $\dot{V}O_2$  determination after immersion.  $\Delta R. T./10'$  imm. is the change in rectal temperature during immersion in cool water.

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tested five and nine days after surgery than in those tested one and three days after surgery. Cat No. 7 gave evidence of a slow tremor interspersed between grosser arrhythmic twitches, and Cat No. 8 had a faster tremor that, by palpation, resembled shivering. If the body temperature of the preparations were slowly lowered simply by decreasing the environmental temperature to  $25^{\circ}\text{C}$ , no somatic responses to cooling were evident even when the body temperatures fell to the same levels as those following immersion in cold water. When the animals were rewarmed by immersion in warm water ( $40^{\circ}\text{C}$ ), the movements disappeared when the body temperatures reached  $36^{\circ}\text{C}$  to  $38^{\circ}\text{C}$ . If the rewarming was rapid (immersion in  $50^{\circ}\text{C}$  water), the animal's somatic responses were similar to those seen during rapid cooling. This suggests that the response the decerebrate animal makes to rapid cooling and rewarming is a non-specific avoidance response to a nociceptive stimulus. This concept is supported by the fact that similar somatic responses of briefer duration were evoked by other "unpleasant" stimuli such as rectal thermometer insertion, pinching the hindlimb or fast rotation of the animals.

Metabolic and rectal temperature determinations. As shown in Table 1, the oxygen consumption rate before cooling for Cats 5, 6, 7, 8, and 10 lies within the normal range for unoperated cats of weight range 2 to 4 kg. Cats 17 and 22 had lower oxygen consumption rates in keeping with their enfeebled condition. There was little variation between the animals in somatic responses during cooling. However, the variation in somatic movements during the second  $\dot{V}\text{O}_2$  determinations was quite marked, Cats 5 and 6 making few somatic responses, Cat 7 making intermittent gross kicks, Cat 8 maintaining the tremor evoked by the cooling stress, and Cats 10, 17, and 22 becoming quite hypotonic after cooling stresses, although making violent movements during such stresses. The variations in oxygen consumption rate of the animals after cold exposure paralleled the variations in their somatic responses. During the oxygen consumption rate measurements after cold exposure, the cat had cold wet skin and the rectal temperatures of Cats 5, 6, 7, and 8 continued to fall during the 20-minute period of the determinations. This was not the case with Cats 10, 17 and 22. The rectal temperature of Cat 10 rose  $0.6^{\circ}\text{C}$  during the post-cold  $\dot{V}\text{O}_2$  determination, but the rectal temperature of this cat was only  $27^{\circ}\text{C}$  at the beginning

of this determination. Cats 17 and 22 had rectal temperatures of  $33.2^{\circ}\text{C}$  and  $32^{\circ}\text{C}$  respectively at the beginning of this post-cold stress determination, similar to the beginning rectal temperature of  $32.5^{\circ}\text{C}$  of Cat 7. However, Cat 7 had a decline in rectal temperature of  $3.0^{\circ}\text{C}$  during the 20-minute post-cold stress  $\dot{V}\text{O}_2$  determination but an elevation of  $\dot{V}\text{O}_2$  of +32% over the pre-cooling stress level, in keeping with its intermittent somatic activity during this period. In contrast, Cats 17 and 22 were quite hypotonic after cold exposure, and their oxygen consumption rate determinations were less than 50 percent of that of Cat 7; yet the rectal temperature of Cat 17 fell only  $0.8^{\circ}\text{C}$  and that of Cat 22 remained unaltered during this period.

### Comments

Shivering was defined above as cold-induced rhythmic muscular activity resulting in a two to four-fold increase in oxygen consumption rate and limb tremor frequencies of 9 to 11 cycles/sec. On the basis of this definition none of these decerebrate animals shivered in response to cooling. Even Cat 8, who displayed a fast tremor that appeared on cooling, disappeared on warming and by palpation and independent observation resembled shivering, could not be said capable of shivering in that there was no appreciable oxygen consumption elevation during the period of tremor. Additionally, Cat 8 and all the other cats displayed similar somatic responses during rapid cooling and rapid warming and no responses during slow cooling and slow warming. Thus, these limited observations suggest that the decerebrate cat is capable of making similar somatic responses to rapid cooling, warming, and other nociceptive stimuli and also has the neurological "substrate" that if activated produces tremulous motions that are not related to temperature regulation. This latter concept is based on the fact that tremulous activity was seen in two of the seven cats (No.'s 7 and 8). This may be explained by the results of Jenkner and Ward (1953), Folkert and Spiegel (1953) and Wycis, Szekely and Spiegel (1957), who produced tremulous activity in anesthetized monkeys and cats by electrical stimulation of the reticular formation over a wide region of the midbrain, pons

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and bulb. Although the production of tremulous activity probably involves a reticular formation activation from a more rostral structure than the midbrain (Carpenter, 1958), it is conceivable that in the decerebrate animal, there could be a nociceptive stimulation of reticular neurons capable of producing tremor. This suggestion awaits experimental confirmation.

The results listed in Table I confirm the work of Dusser de Barenne (1920), Bazett and Penfield (1922), Bazett, Alpers, and Erb (1933), Keller (1959), and Bard and Macht (1958). Bard and Macht kept animals alive for many months after decerebration and reported that several weeks after surgery there was a return of cold-induced fine rapid tremors in decerebrate cats that resembled shivering. However, in a later report, Bard (1961) stated that although such cold-induced muscular activity increased in frequency and vigor during extreme falls in environmental and body temperature, it did not affect the rate of body temperature decline. It would seem that Bard and Macht's results support the above-mentioned concept of shivering being replaced after decerebration by somatic activity alternatively and intermittently rhythmic and arrhythmic and deficient in heat productive capacity.

Unfortunately, all the above work refutes, yet cannot explain, Dworkin's (1930) report of shivering returning in chilled rabbits from 5 to 230 minutes after brainstem transection as low as the caudal pons. Moreover, the body temperatures of these preparations rose while "shivering." Barbour (1939) reported the return of shivering in two cats one and two days after decerebration, but his account seems too fragmentary to support Dworkin and refute all previous and subsequent work. Although the majority of past and present evidence supports the concept of shivering production involving a more rostral neural structure than the midbrain, there is no satisfactory explanation in the literature of Dworkin's diverse results. However, on the basis of the metabolic data presented and the observations of Bard and Macht on animals more carefully nursed for longer periods of time after surgery, the evidence seems to favour a lack of true shivering in decerebrate preparations.

## EFFECTS OF DECORTICATION ON SHIVERING

Methods. Removal of the cerebral cortex by aseptic surgery was performed on 21 cats all under pentobarbital sodium anesthesia (35 mg/kg I. P.). On the first three post-operative days these animals were given injections of Dicrystin Fortis and were maintained in a 25° C environment.

Figure 2 is a film positive of buffered thionine sections at various frontal levels of a decorticate cat brain. It demonstrates that in preserving the medial aspects of the anterior heads of the caudate nuclei, the septum is preserved, even though the corpus callosum is removed (Fig. 2A). Additionally, although the fornices were removed, direct paleocortical-diencephalic connections still existed by virtue of the integrity of the right amygdaloid nucleus (Fig. 2B). The thalamus, hypothalamus and midbrain are undamaged by this surgery (Fig. 2C and 2D).

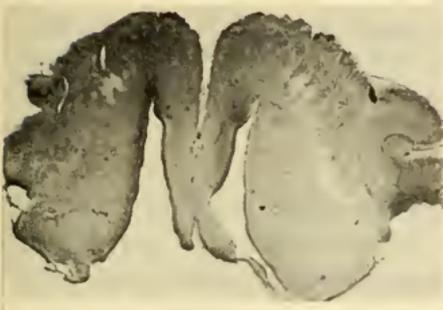
Immediately prior to and three days after surgery, the resting and shivering oxygen consumption rates were determined. One cat was tested at 3, 28 and 470 days after surgery. A mild cooling stress induced active and continuous shivering at a rectal temperature of 36° C to 37° C. This stress consisted of immersing each animal in 10° C water for two minutes and 40° C water for one minute. This was repeated once and finally the animal was immersed in 10° C water for one minute. The rectal temperature of each cat was monitored during the determination of  $\dot{V}O_2$ .

At the conclusion of these tests an attempt was made to keep the animals alive for 28 days, but, with the exception of one animal, this met with failure. Of the 21 cats on which the decortication was performed, 10 lived three days or longer, 5 lived one week or longer, 2 lived two weeks or longer, and one animal was sacrificed 570 days after surgery. The most frequent cause of death was aspiration of vomitus. This was probably caused by undue traumatization of the vagus nerve during temporary clamping of the common carotid artery. If such traumatization permanently damages afferent fibers

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A. Forebrain Level

B. Preoptic-Supraoptic Level



C. Tuberal Hypothalamic Level

D. P. Hypothalamic-Midbrain Level

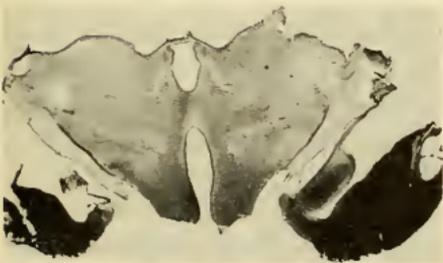


Figure 2. Frontal sections of decorticate cat brain No. 14.

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involved in vomiting reflexes, it could account for the animal's inability to vomit effectively. When the animals died their brains were fixed in formalin for gross and sometimes histological examination.

The animals were not fed between surgery and the days of testing three days after surgery. Three intact cats were therefore tested in similar fashion before and after a three-day fast.

Results. Tables II and III summarize the results for 10 cats tested before and after decortication, one cat further tested 28 and 570 days after decortication, and one hemidecorticate cat tested 42 days after surgery.

Three days after decortication all the tested animals shivered in response to a mild cooling stress. It was evident, by independent observation, that the shivering of these animals lacked continuity as the tremor frequently ceased in the various somatic muscles. This observation was supported by  $\dot{V}O_2$  determinations indicating a decreased  $\dot{V}O_2$  associated with shivering after decortication. The resting oxygen consumption rates of the animals before and after decortication lay within the same range (Table III), but whereas the mean elevation in  $\dot{V}O_2$  during shivering was X2.58 before decortication, the mean elevation during shivering after decortication was X1.6. The range of  $\dot{V}O_2$  elevations during shivering was X2.1 to X3.8 when the animals were intact, but after decortication this range was more restricted, being X1.4 to X1.7. The standard deviation of the ratio for the intact animals (mean value X2.58) was 0.48 while that for decorticate animals (mean value X1.6) was 0.12.

When tested after decortication, the animals were hyperactive, with sham or undirected rage easily induced by such nociceptive stimuli as pinching the pinna, rectal thermometer insertion or rapid body rotation. They tended to hyperventilate at intervals, to have violent fits of gross somatic activity (leaping, running) followed by periods of complete physical quiescence. They defecated, urinated, and vomited excessively in a disorganized manner with adoption of faulty postures for these expulsions. The one animal tested 28 and 570 days post surgery became more subdued in the second week after decortication, assumed a crouched posture and moved slowly

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Cat No.	Before Surgery				3 Days After Surgery				
	Weight	$\dot{V}O_2R$	$\dot{V}O_2S$	$\dot{V}O_2S/R$	Weight	% Weight Loss	$\dot{V}O_2R$	$\dot{V}O_2S$	$\dot{V}O_2S/R$
2	4.59	5.3	20.0	3.8	4.23	8	8.8	12.9	1.5
3	2.77	9.5	25.0	2.6	2.41	13	7.6	10.5	1.4
8	2.98	8.1	18.5	2.3	2.53	15	7.9	12.2	1.5
10	2.29	9.1	19.2	2.1	1.95	15	8.4	14.9	1.8
14*	2.08	9.0	19.6	2.2	1.84	12	7.2	12.2	1.7
15	3.02	13.0	30.4	2.4	2.63	13	8.7	14.4	1.7
18*	2.91	8.4	22.8	2.7	2.81	4	7.0	11.6	1.7
19	3.04	9.1	21.6	2.4	2.60	15	7.5	11.7	1.6
20	4.09	9.7	24.3	2.5	3.66	10	7.0	11.0	1.6
21	2.57	7.1	20.7	2.9	2.23	13	7.6	13.0	1.7

\* 28 days post decortication  $\overline{\dot{V}O_2R} = 7.8$ ,  $\overline{\dot{V}O_2S} = 20.2$ ,  $\overline{\dot{V}O_2S/R} = 2.6$

\*470 days post decortication  $\overline{\dot{V}O_2R} = 7.9$ ,  $\overline{\dot{V}O_2S} = 18.6$ ,  $\overline{\dot{V}O_2S/R} = 2.3$

One hemidecorticate preparation tested 42 days post surgery  $\overline{\dot{V}O_2R} = 9.00$ ,  $\overline{\dot{V}O_2S} = 19.50$ ,  $\overline{\dot{V}O_2S/R} = 2.2$

Table II. Resting (R) and shivering (S) oxygen consumption rates before and after decortication. Oxygen consumption rates ( $\dot{V}O_2$ ) expressed in mls  $O_2$  S. T. P. D. /kg/min and based on closed circuit determinations. Weight expressed in kilograms.

Before Surgery			3 Days After Surgery		
	$\dot{V}O_2R$	$\dot{V}O_2S$	$\dot{V}O_2R$	$\dot{V}O_2S$	
Mean	8.82	22.20	7.77	12.43	
S. D.	1.94	3.41	1.99	1.35	
	Ratio $\dot{V}O_2S/R$		Ratio $\dot{V}O_2S/R$		
Mean	2.58		1.60		
S. D.	.48		.12		
28 Days After Surgery			470 Days After Surgery		
	$\dot{V}O_2R$	$\dot{V}O_2S$	$\dot{V}O_2R$	$\dot{V}O_2S$	
Mean	7.72	20.18	7.94	18.55	
	Ratio $\dot{V}O_2S/R$		Ratio $\dot{V}O_2S/R$		
Mean	2.60		2.33		

Table III. Mean shivering (S) and non-shivering (R) oxygen consumption rates ( $\dot{V}O_2$ ) of 10 cats before and after decortication.  $\dot{V}O_2$  expressed in mls  $\dot{V}O_2$  STPD/kg/min.

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in response to nociceptive stimuli. The resting and shivering oxygen consumption rates 28 and 570 days after surgery were similar to those measurements made before decortication. Continuous shivering in response to cooling was observed.

The resting and shivering oxygen consumption rates of the one hemidecorticate animal tested 42 days after surgery lay within the normal range, although great difficulty was experienced in measuring resting  $\dot{V}O_2$ . This animal with a left-side decortication continually circled to the left after surgery and tended to be hyperactive. Shivering appeared to be of equal intensity and duration on both sides of the body.

The range in body weight of the animals three days after surgery was from 8 to 15 per cent of the weights before surgery. As shown in Table IV, the range in body weight of three intact cats after a three-day fast was from 6 to 15 percent that of before-fast weights. However, these three cats shivered just as effectively after as before fasting.

All animals, during all tests before and after decortication and fasting, assumed a huddled posture while shivering.

Comments. These results would suggest that in a chronic decorticate cat the intensity of shivering is normal, but in the acutely decorticate stage, shivering is diminished in intensity even though such a preparation is displaying overt visceral activity symptomatic of hyperactive hypothalamic function. This conflicts with Bard's (1961), Pinkston, Bard, and Rioch's (1934), and Aring's (1935) observations of cold-induced shivering appearing with more vigor and shorter latency after decortication. My chronic observations involve but one cat, whereas the above investigators studied more cats for longer periods of time after surgery. On the other hand, they do not have the support of metabolic data similar to that presented in Table II. If Pinkston, Bard, and Rioch's observations of a tendency to chronic peripheral vasodilatation after decortication is valid, it is conceivable that after decortication, shivering would appear with less latency on exposure to cold since the blood temperature should drop more rapidly. Conversely, if shivering is instigated more by a change in skin rather than blood temperature (as suggested first by Liebermeister in 1860, and more recently by

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Cat No.	Control Weight	$\dot{V}O_2$ Before Fast		
		R	S	S/R
A	2.93	7.2	25.2	3.5
B	2.16	5.3	26.0	4.9
C	2.36	5.4	25.2	4.7

Cat No.	Weight	$\dot{V}O_2$ After 3 Day Fast %Weight Loss	$\dot{V}O_2$ After 3 Day Fast		
			R	S	S/R
A	2.77	6	4.6	22.1	4.8
B	1.95	10	7.4	20.3	2.7
C	2.00	15	5.6	19.0	3.4

Table IV. Resting (R) and shivering (S) oxygen consumption rates before and after a 3 day fast. Oxygen consumption rates ( $\dot{V}O_2$ ) expended in mls  $O_2$  STPD/kg/min and based on a 20 minute closed circuit determination.

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Benzinger in 1960, but denied by many other workers from Richet in 1892 to Hammel, Hardy, and Fusco in 1960), then shivering would have a longer latent period after decortication since the skin would be warmer due to vasodilation. It would appear that there has been insufficient experimentation to solve the problem of the degree and latency of shivering in decorticate cats. Possibly the application of techniques of measuring brain and peripheral temperatures, and hypothalamic and skin blood flow (perfected by Hensel and his co-workers in 1961) to chronic decorticate cats would solve this pertinent problem.

The word pertinent is used because the results of Bard, Pinkston, Rioch, and Aring suggested to them that the telencephalon exerted a tonically inhibitory influence on shivering, whereas my single chronic decorticate experiment would suggest that shivering is normal in intensity after decortication. It is known that shivering can be suppressed by electrical stimulation of the cortex as reported by Kaada in 1951. McLean and Delgado in 1953 reported similar suppression of the amygdala and globus pallidus. Hemingway, Forgrave, and Birzis (1954) have reported the suppression of shivering by septal stimulation, and such stimulation has been shown to evoke it by Akert and Kesselring (1951) and Andersson (1957). Additionally, Gessler and Hansen (1927) have reported the production of human shivering by hypnotic suggestion. Thus the question is not whether the telencephalon is inhibitory or facilitory with respect to shivering, since both have been shown, but rather which telencephalic influence dominates in the intact brain. It is doubtful that any of the above mentioned work has solved this problem.

The shivering response of decorticate cats three days after surgery is, as shown in Tables II and III, of some moment. These preparations shivered feebly even though they were hyperactive autonomically (i.e., excessive vomiting, urinating, defecating, "sham rage," etc.). However, they shivered with a more consistent intensity after than before decortication in that the standard deviation of shivering/resting  $\dot{V}O_2$  was four times less after than before decortication. One might speculate that decortication had thereby removed both tonic facility and inhibitory influences which, in the intact animals, varied in their relative effects. In order to justify such a speculation it would be necessary to make more  $\dot{V}O_2$  deter-

minations on the same and several animals before, three days after, and 28 days after decortication.

LOCALIZATION OF THE HYPOTHALAMIC REGION  
ESSENTIAL FOR THE PRODUCTION OF  
SHIVERING

Electrical Stimulation Studies

Methods. An attempt was made to produce shivering by electrical stimulation of the hypothalamus of anesthetized cats with histological confirmation of the loci of stimulation which produced or failed to produce shivering.

The cats were anesthetized either with alpha chloralose (40-60 mg/kg I. P.) or pentobarbital sodium (35 mg/kg I. P.). Each preparation's brain was stimulated with a stainless steel concentric bipolar electrode insulated but for 0.5 mm of each tip. The outer cylinder of each electrode had a diameter of 0.4 mm and a thickness of 0.15 mm. The insulated inner wire was 0.1 mm in diameter. The resistance of each electrode was 30 to 50 megohms in 0.9 per cent saline. The electrode could be connected either to an electroencephalographic machine (Grass Instrument Co., Model IID) or, by way of a current monitor oscilloscope (The Heath Co., Model OL-1) and stimulus isolation unit (Grass Instrument Co., Model SIV-4A), to a stimulator producing square wave stimulating currents of which the frequency duration and voltage could be regulated (Grass Instrument Co., Stimulator Model S 4C). To detect shivering and other somatic responses, electromyograms of fore and hind limbs were recorded on the electroencephalographic machine. Muscle electrodes consisted of either stainless steel electrodes (diameter 0.7 mm) inserted into muscles 10 mm apart, or at the same distance apart, insulated stainless steel wires (outer diameter 0.25 mm) were wrapped around a portion of a muscle and a 2 mm length of insulation was removed from each wire on the inner surface of the muscle.

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Respiration was recorded by a strain gauge (Statham Laboratory, Model P23B) transducer from a rubber chest tambour. Fronto-occipital EEG waves were recorded from stainless steel electrodes that pierced the calvarium to lie on the dura above the medial edge of the sigmoid gyrus and the posterior margin of the suprasylvian gyrus.

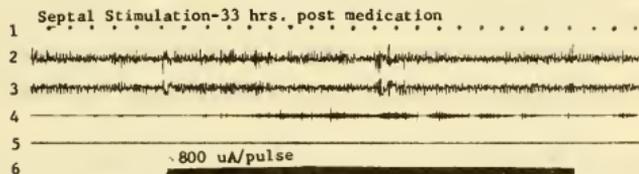
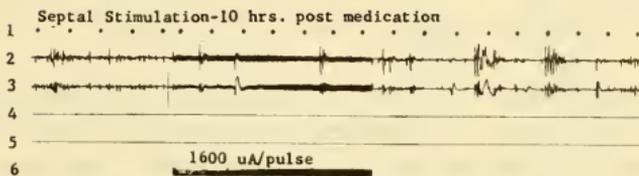
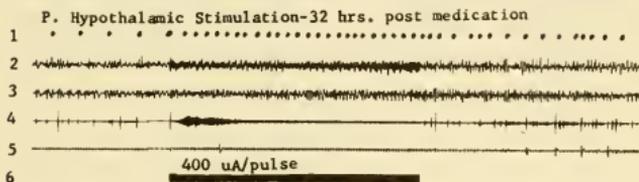
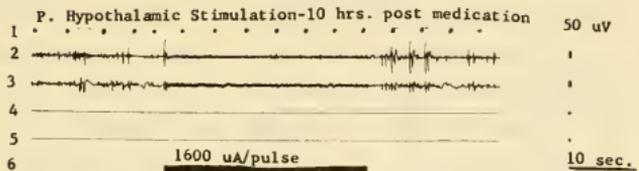
The head of each preparation was mounted in the stereotaxic frame (Labtronics, Inc., stereotaxic instrument Model No. 4), the scalp skin reflected after midline skin incision, and the temporal muscles retracted from these origins and sufficient calvarium removed to expose the dorsal aspect of the marginal gyrus. The stimulating electrode was stereotaxically inserted into the hypothalamus, and at each point of insertion, the dura was minutely cut to permit passage of the electrode into neural tissue. The hypothalamus was unilaterally stimulated in planes 0.5, 1.5, 2.5, and 3.5 mm from the midline and EEG, respiration, somatic, and visceral changes recorded and/or noted by independent observation. In each given experiment the locus of any stimulated site was 1 mm dorsal or ventral and/or 1 mm medial or lateral to any other stimulated site. Throughout these experiments an attempt was made to maintain the animal's rectal temperature at  $38.5^{\circ}\text{C}$  to  $37.5^{\circ}\text{C}$  by appropriate adjustments of environmental temperature. At the conclusion of each experiment the brain was fixed in formalin, sectioned every  $80\mu$  in the plane of the electrode tracts and each alternate section stained with buffered thionine. In this way all stimulated sites could be confirmed histologically. The schemata of brain electrode tracts in subsequent figures are based on such histology. Table V is a key to the abbreviations of nomenclature used in these schematics.

Results. In detailed mapping of the hypothalamus for a shivering response to electrical stimulation, the animals were stimulated 9 to 24 hours after injection of 40 to 60 mg/kg alpha chloralose. Figure 3 illustrates the necessity for the long delay between induction of anesthesia and initial stimulation. In this particular experiment, the effects of septal and posterior hypothalamic stimulation responses were compared on the ipsilateral side of the brain in which stimuli were applied 10, 23 to 24, and 32 to 33 hours after beginning anesthesia. As shown in Figure 3 neither posterior hypothalamic stimulation nor septal stimulation produced a somatic response nor a change in respiration rate 10 hours after alpha

AC	Anterior Commissure
CC	Corpus Callosum
Cd	Caudate Nucleus
CI	Internal Capsule
En	Entopeduncular Nucleus
Fx	Fornix
GL	Lateral Geniculate Body
GP	Globus Pallidus
Hp	Posterior Hypothalamic Nucleus
LPO	Left Preoptic Region
MFB	Medial Forebrain Bundle
MI	Massa Intermedia
Mm	Mamillary Body
OC	Optic Chiasm
OT	Optic Tract
PC	Posterior Commissure
Ped	Cerebral Peduncle
PO	Preoptic Region
R	Reticular Nucleus
RE	Reuniens Nucleus
RPD	Right Preoptic Region
S	Stria Medullaris
Sn	Substantia Nigra
Spt	Septum
Su	Subthalamic Nucleus
TMT	Mammillo-thalamic Tract
VPL	Ventropostero lateral Nucleus of Thalamus
VPM	Ventropostero medial Nucleus of Thalamus

Table V. Nomenclature: Key to abbreviations

1. Respiration Rate
2. EEG - R. Cortex
3. EEG - L. Cortex
4. EMG - R. Forelimb
5. EMG - R. Hindlimb
6. Stimulus Duration



Septum

P. Hypothalamus

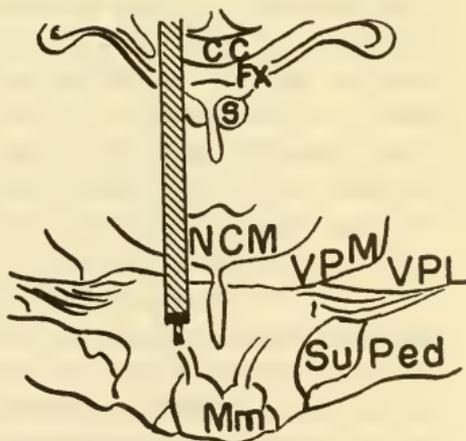
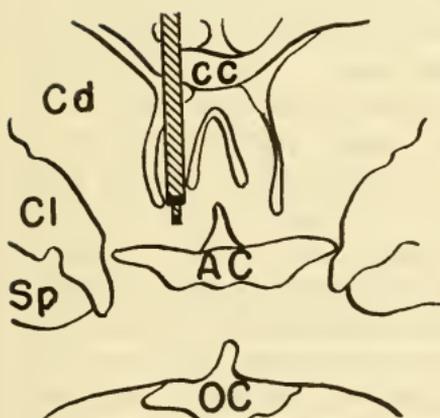


Figure 3. Somatic response evoked by septal and posterior hypothalamic stimulation at various times post alpha chloralose medication (Cat No. ST, 17).

chloralose medication. The posterior hypothalamic stimulation did, however, abolish bilateral EEG spindle bursts, whereas the spindling persisted to a lesser degree during the septal stimulation. Thirty-two hours after chloralose medication, stimulation of the posterior hypothalamic locus evoked an immediate "burst" of shivering followed by subsequent milder bursts after the cessation of the stimulus. This response was evoked with a stimulus intensity of  $400 \mu\text{A}/\text{pulse}$ . However, a stimulus intensity of  $800 \mu\text{A}/\text{pulse}$  was necessary to evoke less intense but more continuous shivering during septal stimulation 33 hours after beginning anesthesia. When this intensity of  $800 \mu\text{A}/\text{pulse}$  was used in stimulating the contralateral posterior hypothalamus 10 hours earlier than this last septal stimulation, more intense and continuous shivering was maintained for the duration of the stimulus, as shown later in Figure 14.

As shown later in Table VIII, shivering could be produced both by septal and posterior hypothalamic stimulation from 9 to 24 hours after induction of alpha chloralose anesthesia. Shivering could also be produced during stimulation of these structures in cats anesthetized with pentobarbital sodium. This indicates that the response was not solely a characteristic of alpha chloralose anesthesia.

Figure 4 illustrates the somatic responses evoked by stimulation of a variety of hypothalamic loci in 6 cats. In 13 other cats not listed, stimulation of one or more of these intermediate loci evoked responses similar to those presented. The schemata of stimulated loci are based on reconstruction of electrode tracts from the buffered thionine sections of the appropriate brains. Plane A is a frontal section 10 mm anterior to the interauricular line and Plane B, 9 mm anterior to this line. Loci 1, 2, and 3, and 10, 11 and 12 are 2.5 mm from the midline, loci 4, 5, and 6 and 13, 14 and 15 are 1.5 mm from the midline while loci 7, 8, and 9 and 16, 17 and 18 are 0.5 mm from the midline. Loci 1 and 7 and 10 and 16 are 10 mm dorsal to the interauricular line and loci 4 and 13, 9 mm dorsal to this line. Each locus shown is 2 mm ventral to any other locus in the same vertical plane. As previously mentioned, loci were stimulated at 1 mm depth intervals. These loci stimulation responses are not shown or discussed for the sake of clarity and in recognition of the accuracy limitations involved in comparing the specific loci stimulated in any one brain to those of another brain. The plane of brain section varies from one experiment to another, as does the

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CAT NO.	LOCUS																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
ST. 7				TW	TW		O	SH	O					†				
ST. 9	O	TR	TO	TR	TO	O	O	SH	TW	TO	TR	TO	SH	TO	O	TO	TO	O
ST. 10	TO	TW		SH	SH		O	SH	O	TR	TR	TO	SH	SH	O	TO	SH	TO
ST. 11	TO	TO		TW	TW	O	O	SH	O	TO	TO	TO	SH	SH	O	O	SH	O
ST. 13										TO	TO	O	O	SH	O	O	SH	
ST. 17												TO	TO	SH	O	O	SH	O

TO - Increase in muscle tone

TW - Muscle twitching

TR - Alternating tremor

SH - Shivering

O - No somatic response

\* - Stimulation produced shivering in cats

No. ST. 5, 15, and 20.

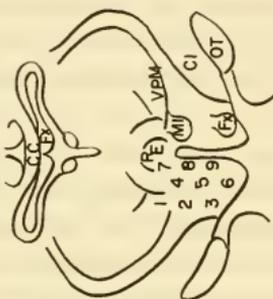
† - Stimulation produced shivering in cats

No. ST. 14, 18, 21, 23, 24, 31<sup>a</sup>, 32<sup>a</sup>,

33<sup>a</sup>, 33<sup>b</sup>, and 38.

### SCHEMA OF LOCI

Plane A



Plane B

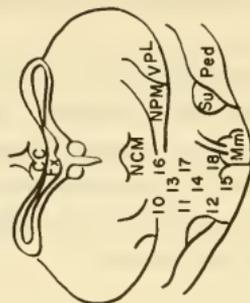


Figure 4. Somatic responses evoked by posterior hypothalamic stimulation.

alteration in brain volume and the alteration in brain size caused by formalin perfusion in brain fixation.

Locus 14 in Figure 4 does, however, include responses evoked by stimulation of a locus 1 mm dorsal to it. Such loci stimulation responses were included under locus 14 rather than 13 because stimulation of a site 1 mm dorsal to the latter locus never evoked responses similar to those seen during stimulation of locus 13 and the intermediate locus.

In Figure 4 the somatic responses presented are a generalized increase in muscle tone, or more precisely an increase in fore and hind limb rigidity, arrhythmic muscle twitching, alternating tremor and shivering. Alternating tremor is a 4 to 7 cycle/sec limb tremor in which agonists relax when antagonists contract. In shivering the rate of tremor is faster (9 to 11 cycles/sec) and the muscles contract synergistically. Additionally, shivering characteristically waxes and wanes in intensity. Differences between these two tremors were observed both visually and electromyographically. Alpha cholralose anesthesia customarily evokes muscle twitching as the animal enters and emerges from the anesthetic state, but no stimuli were applied at such stages. All stimulation responses of the presented loci were repeatable in the same preparation.

The table in Figure 4 demonstrates that shivering was best and consistently produced by stimulation of a diencephalic region bounded dorsally by a plane 9 mm dorsal to the interauricular line, ventrally by a plane 7 mm dorsal to the interauricular line, laterally by a plane 1.5 to 2.0 mm lateral to the midline and medially by the midline. Anatomically the region is bordered by ventral thalamic, dorsal hypothalamic, and medial subthalamic structures. Systematic exploration of a plane 1 mm rostral to Plane A was performed in 5 cats (No.'s ST 9, 10, 11, 13, and 17). Shivering was never evoked by stimulation of any such loci, but alternating tremor was evoked by stimulating loci 1 mm rostral to loci 1 and 2. Shivering was evoked by stimulation of loci 1 mm caudal to loci 14 and 17 but not in any other loci of this plane in Cats No. ST 9 and 11. Loci 3.5 mm lateral to the midline in frontal planes corresponding to A and B were stimulated in Cats No. ST 14 and ST 33<sup>b</sup>, but shivering was not evoked by any such stimulation.

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Within the region thus localized, it was not possible to demonstrate stimulation of a specific part as being more effective in producing shivering than any other part when the responses of one cat were compared to another. For example, Figure 5 illustrates the production of well defined shivering by stimulation of a locus 1.5 mm from the midline (arrow B) in Cat No. ST 10. In the same animal, stimulation of a locus 0.5 mm from the midline (arrow F) produced a much less defined shivering response. Stimulation of a locus 2.5 mm from the midline (arrow A) produced a larger and slower limb oscillation response that could not, by independent observation, be termed "shivering." In contrast, in other cats (e.g., ST 9) there was a better production of shivering by stimulation of a locus 0.5 mm from the midline with a more discontinuous production of less well defined shivering produced by stimulation of a locus 1.5 mm lateral to the midline.

The parameters of stimulation were similar in each given experiment, but the intensity of stimulation necessary to evoke shivering varied from animal to animal, ranging from 200  $\mu$ A/pulse to 1600  $\mu$ A/pulse. The frequency of stimulation utilized ranged from 25 to 100 pulses/sec. In some experiments 25 pulses/sec seemed more effective in evoking shivering than 50 to 100 pulses/sec, and in others 25 and 50 pulses/sec seemed more effective than 100 pulses/sec. With the exception of two experiments (Cat No. ST 17 and Cat No. ST 33<sup>b</sup>) no attempt was made to explore systematically the frequency-intensity combination that would evoke shivering when repeatedly stimulating the same locus. Figure 6 illustrates an experiment in Cat No. ST 33<sup>b</sup> in which the minimum intensities necessary to evoke shivering at stimulus frequencies of 10, 25, 50, and 100 and 200 pulses/sec were determined. In all cases the stimulus pulse duration was 1 msec, the period of stimulation 30 seconds, and the locus of stimulation the same. An attempt was made to clarify the results by gauging shivering response as being "strong," "mild," or "dubious." This classification was based on a combination of independent observations and the pattern of recorded EMG's. This is shown schematically at the top of Figure 6. A response was classified as "strong" and coded as a filled-in circle if the electromyogram of at least one limb muscle recorded shivering for the duration of the stimulus. A response was classified as "mild" and coded with an open circle when visible shivering either began when the stimulus began but terminated before the

Upper Record - EMG - L. Hindlimb  
 Lower Record - Stimulus Duration  
 Stimulus Frequency - 100 pulses/sec  
 Pulse Duration - 3 msec  
 Stimulus Intensity - 400  $\mu$ A/pulse

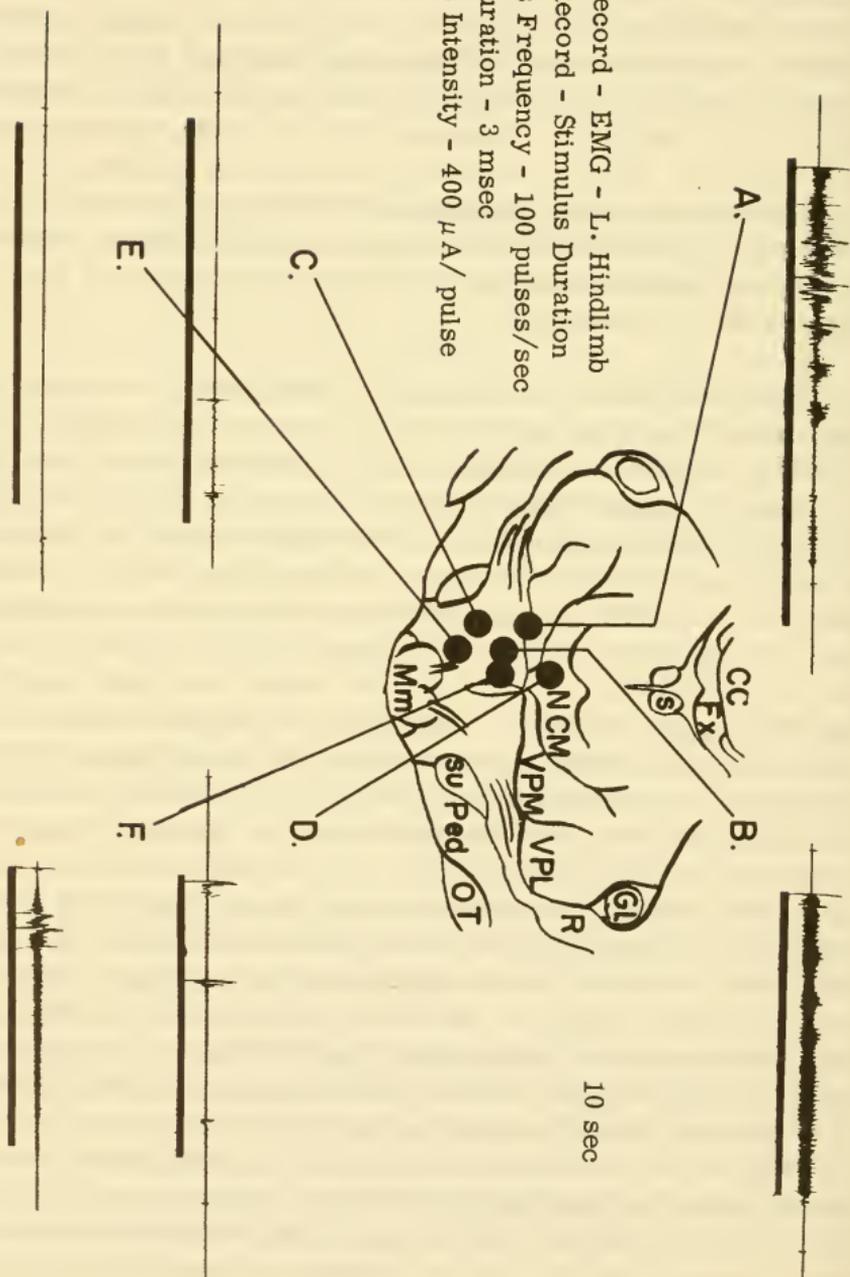


Figure 5. Somatic responses evoked by electrical stimulation of the posterior hypothalamus (Cat No. ST. 10).

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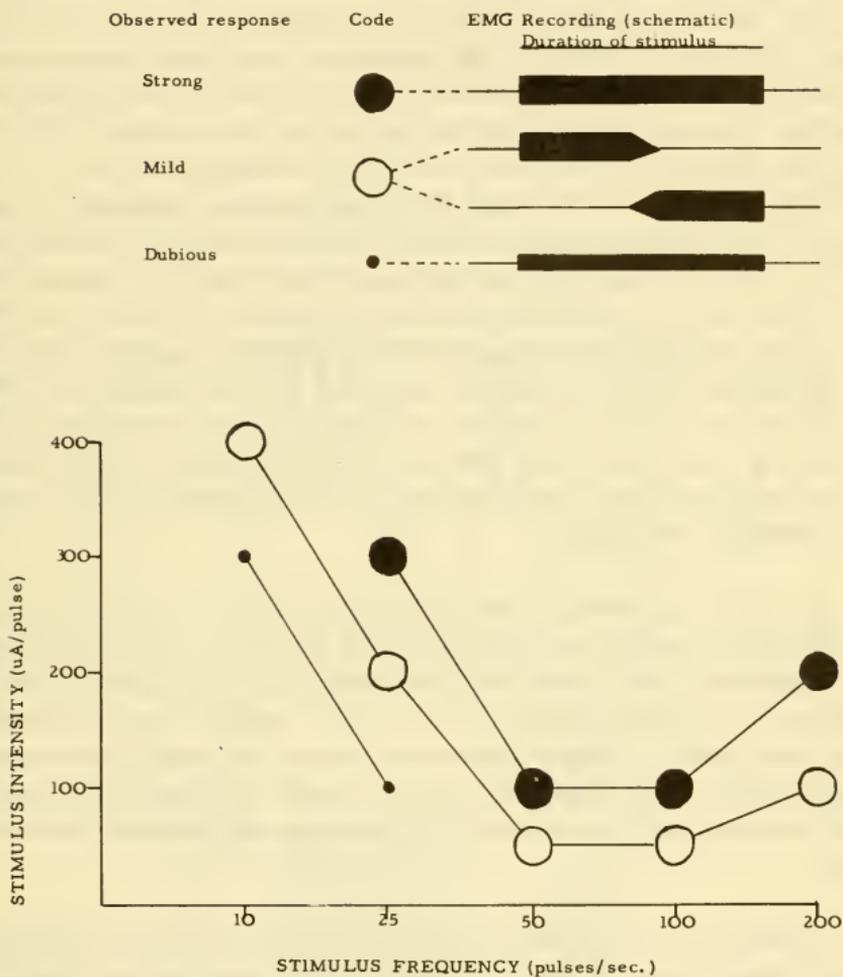


Figure 6. Frequency dependent graded instigative responses.

cessation of stimulation or when visible shivering began at some latent period after the beginning of stimulation but ceased when the stimulus was terminated. A response was coded as "dubious" and coded with a small filled-in circle when neither visual inspection nor the pattern of EMG recording indicated whether or not the muscle activity evoked by the stimulus was truly shivering or merely an increase in muscle tone. Stimuli of 50 and 100 pulses/sec required less intensity to evoke shivering than stimuli of 10, 25 and 100 pulses/sec. The best shivering response evoked by a 10 pulse/sec stimulus was mild shivering lacking continuity. Conversely, the best response evoked by stimulation at 200 pulses/sec was a tremor in which background muscle tone appeared excessive. In Cat No. ST 17, shivering could not be evoked by stimuli of 1600  $\mu$ A/pulse intensity even though well defined shivering was evoked at 25 pulses/sec of 400  $\mu$ A/pulse intensity. In this experiment 200 pulses/sec stimuli were not applied, but less intense stimuli were necessary at 25 pulses/sec than at 100 pulses/sec. In both experiments 50 pulses/sec stimuli evoked well defined shivering at minimal stimulus intensities.

In early experiments (Cats No. ST 5 to ST 17) a stimulus pulse duration of 3 msec was utilized. In Cat No. ST 17, using a variety of frequencies, less intense stimuli were necessary to evoke shivering with a pulse duration of 1 msec than with 3 msec. Following this experiment, a pulse duration of 1 msec was used, but no systematic study was attempted of the intensity of stimulation needed to evoke shivering at a variety of pulse duration-frequency combinations.

Comments. The dorsomedial region of the posterior hypothalamus, which, when stimulated electrically, induces shivering, is dorsal and medial to the shivering pathway described by Birzis and Hemingway (1956, 1957). These investigators abolished shivering by ventrolateral posterior hypothalamic destruction in anesthetized cats. In our laboratory it is now the contention that there is a conflict in interpretation but not experimental results. For example, Figure 7 illustrates an experiment in which bipolar electrodes were inserted into bilateral ventrolateral posterior hypothalamic loci (the center of the lesions noted with insert A and B) and into the dorsomedial posterior hypothalamus (tip of electrode noted C). With the brain intact, 30-second stimulation of locus A

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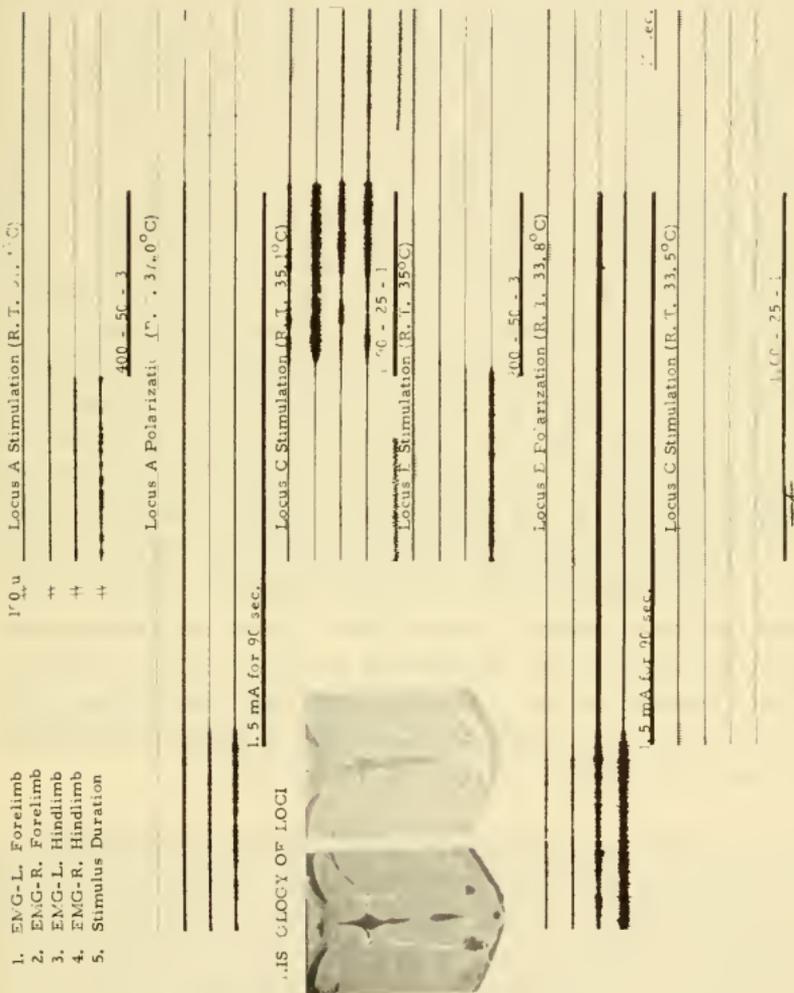


Figure 7. Stimulation and polarization of the ventrolateral posterior hypothalamus of a shivering cat (No. ST. 38).

with 400  $\mu$ A/pulse, 50 pulses/sec and 3 msec pulse duration suppressed shivering in the cat anesthetized with pentobarbital sodium (35 mg/kg I. P.). Shivering returned after 10 minutes and was again suppressed in the process of destroying tissue at locus A electrolytically. Shivering was depressed for 10 minutes but was reproduced by stimulating locus C at 1600  $\mu$ A/pulse with 25 1 msec/pulse/sec. Following locus C stimulation, spontaneous shivering returned on the right hindlimb, but was suppressed by locus B stimulation with a 30-second stimulus of 200  $\mu$ A/pulse and 50 3 msec pulses/sec. Shivering was then reproduced by stimulation of locus C (not shown in Figure 7) but suppressed by electrolytic destruction of locus B. Following bilateral ventrolateral posterior hypothalamic destruction, shivering did not reoccur while the animal was anesthetized, but thirty-one days after surgery it was immediately apparent on exposure of the cat to cold, the  $\dot{V}O_2$  shivering/resting being 3.2. The failure of shivering to occur immediately after bilateral ventrolateral posterior hypothalamic destruction may have been due to an unmeasured cardio-vascular depression, in that Fuster and Weinberg (1960) have shown that stimulation of the regions destroyed in this particular experiment increases myocardial contractility. The main aspect of this experiment is the demonstration of Birzis and Hemingway's result in an experiment that also illustrates seemingly conflicting results. That is to say, shivering can be evoked by dorsomedial posterior hypothalamic stimulation and suppressed by ventrolateral posterior hypothalamic stimulation. It can also be suppressed by ventrolateral posterior hypothalamic destruction in an acutely observed anesthetized preparation. Following such destruction shivering does return in the unanesthetized, chronically maintained preparation.

This does not mean that all Birzis and Hemingway's acute lesion experiments are subject to question. They have hitherto unreported confirmation of the validity of this shivering pathway in the midbrain, pons, and bulb in that they have demonstrated the lack of shivering in chronic animals with bilateral lesions in the region in which the tissue destroyed is similar to that destroyed in the acute experiments. Perhaps the reason for their diverse hypothalamic result is that the majority of their efforts were directed to the descending paths, rather than the central origin of impulses related to the production of shivering.

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It is not here the purpose to claim that the dorsomedial region of the posterior hypothalamus is an exclusive "center" for shivering. Figures 3, 14, and 26, and Table VIII illustrate EEG, heart and respiratory changes during stimulation of this region. Rather it is to suggest that activation of certain neurons within this region produces shivering along with other ergotropic effects.

Shivering limbs have a tremor frequency of 9 to 11 cycles/sec. This frequency was not effective in producing shivering when applied to an electrical stimulus to the hypothalamus. Stimuli of frequency 25 to 100 pulses/sec were much more effective. This suggests that the rhythm of shivering is controlled peripherally, but shivering itself is instigated centrally. This concept will be elaborated at a later symposium. It helps to explain the paucity of information from Hess's laboratory (Akert and Kesselring, 1951, Hess, 1957) concerning the production of shivering during electrical stimulation of the prosencephalon. That is to say, when the brains of over 350 anesthetized and unanesthetized cats were stimulated at about 7,000 prosencephalic loci, shivering was observed but 11 times in 8 cats. The stimulus used in this laboratory consisted of a variable direct current that could be mechanically interrupted but 4 to 15 times/sec. If Hess had had the advantage of modern electronic stimulators permitting higher stimulation frequencies, he undoubtedly would have unmasked even more physiology of the diencephalon.

### Electrolytic Lesion Studies

Methods. In these experiments bilateral electrolytic lesions were made in various hypothalamic regions of 29 cats. Each cat was anesthetized with pentobarbital sodium (35 mg/kg I. P.) and the head mounted in a stereotaxic frame. The scalp skin was reflected on appropriate holes burred through the calvarium to permit insertion of a stereotaxically oriented insulated monopolar electrode. Each electrode was 0.7 mm in diameter and without insulation approximately 1 mm from the tip. An electrolytic lesion was made by cathodal polarization of the electrode with a current of 1.5 to 2.5 mA passed for 1 to 2 minutes. A remote anodal connection was provided on the tongue. The scalp skin was repositioned with wound

clips. Great attention was directed to the postoperative care of each animal. The rectal temperature was kept at  $36^{\circ}\text{C}$  to  $38^{\circ}\text{C}$  by appropriate alterations in environmental temperature. For the first 2 to 3 weeks after surgery each animal was tube fed with frequent testing for the recovery of licking and swallowing reflexes. Care was taken to keep each animal clean and dry and given daily periods of exercise.

Twenty-one animals recovered from the above procedure, and once they had regained their pre-operative weight by spontaneous eating, their responses to cooling were studied. One animal died at 12 hours, one at 5 days, one at 8 days and one at 10 days after surgery. Three animals died during the course of heat stress tests administered 4 days after surgery. The resting oxygen consumption rate of 18 of the 21 cats which recovered was determined 13 to 132 days after surgery at an environmental temperature of  $20^{\circ}\text{C}$  to  $25^{\circ}\text{C}$ . They were then exposed to an environment of  $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  temperature, and 15 minutes after such exposure their oxygen consumption rates were determined for a further twenty minutes of exposure. Rectal temperature was maintained throughout these determinations.

Control experiments consisted of measuring oxygen consumption rates and rectal temperatures of unoperated cats in the warm ( $25^{\circ}\text{C}$ ) and cold ( $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$ ) environment.

If the animals with hypothalamic lesions had oxygen consumption rates and rectal temperature responses that fell within the unoperated cat range of responses, they were sacrificed immediately after the test, their brains fixed in formalin and sectioned every 80 microns, and alternate sections stained with buffered thionine. If any of the animals did not have control unoperated responses they were tested at least twice more at varying lengths of time after the first test before being sacrificed.

In subsequent figures illustrating the extent of various brain lesions, a schematic midsagittal diagram will show the rostrocaudal extents on each side of the brain. Such diagrams are based on reconstruction of the extent of the lesions from the buffered thionine slides. Additionally two to three film negatives of buffered thionine slides are presented to illustrate the dorsoventral and medial lateral extents of tissue destruction.

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Results. Table VI lists the oxygen consumption rates and rectal temperatures of 9 intact cats while exposed to a temperature of 24.5° C to 29° C air and while shivering in a temperature of 0° C to 5° C air. The mean  $\dot{V}O_2$  shivering/resting ratio was 2.7, range 2.1 to 3.8 and standard deviation 0.5. The mean drop in rectal temperature during the 20-minute determination of  $\dot{V}O_2$  in 0° C to 5° C was 0.8° C, range 0.2° C to 1.3° C, and standard deviation 0.4° C. Expressed in other terms, the mean rate of rectal temperature drop per unit time was 0.04° C/min, range 0.02° C to 0.07° C, and standard deviation 0.02° C/min. Table VI shows that on successive days the ratio of  $\dot{V}O_2$  shivering/resting was 2.4 and 2.6 for Cat No. 1 and 3.2 and 2.1 for Cat No. 2. In the former case the rectal temperature drops were 0.2° C and 1.3° C and in the latter case 0.6° C and 0.8° C. These figures would indicate that the increase associated with shivering could vary from a two to fourfold increase in both the same or a sequence of cats. Additionally, the range in rectal temperature drops that accompanied the period of shivering oxygen consumption rates determination could vary by over 1° C in the same cat and a sequence of cats and that this variance was not necessarily correlated with the  $\dot{V}O_2$ . It was not considered necessary to run additional tests on the other 7 cats to illustrate this point. This was because, in a previous study, the oxygen consumption rates of 7 cats were determined on successive days while they were shivering for the duration of time necessary to elevate their rectal temperatures from 33° C to 37° C. The determined ratios were as follows:

- Cat A: 4.1, 2.4, 4.4 and 2.1
- Cat B: 2.2, 2.8, and 2.5
- Cat C: 3.1, 2.9, 2.2 and 2.8
- Cat D: 2.1, 2.4, and 2.2
- Cat E: Pre midbrain lesion: 2.8 and 3.1  
Post midbrain lesion: 2.0 and 2.4
- Cat F: Pre midbrain lesion: 2.0 and 2.3  
Post midbrain lesion: 2.6 and 3.8
- Cat G: Pre midbrain lesion: 2.1 and 2.5  
Post midbrain lesion: 2.4 and 2.7

In the above determination there was no significant correlation between the ratio and the time taken by the cats to elevate their rectal temperatures from 33° C to 37° C. On the basis of this, and

	Before Cold Stress				During Cold Stress				VO <sub>2</sub> shivering resting		
	VO <sub>2</sub>	Rectal Temperature			VO <sub>2</sub>	Rectal Temperature					
		B	E	Δ		B	E	Δ			
1	7.2	37.0	39.0	0.0	24.5	17.1	39.0	38.8	-0.2	3.0	2.4
	9.0	38.0	38.3	-0.3	26.5	23.8	38.3	37.0	-1.3	4.0	2.6
2	5.5	37.7	38.0	-0.3	26.0	17.5	38.0	37.4	-0.6	1.0	3.2
	7.5	38.0	38.0	0.0	27.0	15.8	38.0	37.2	-0.8	3.0	2.1
3	6.2	38.4	38.4	0.0	26.5	17.3	38.4	37.3	-1.1	1.0	2.8
4	7.7	38.5	38.8	-0.3	26.5	25.5	38.0	37.0	-1.0	5.0	3.3
5	8.6	37.5	38.2	-0.7	29.0	25.3	38.2	37.0	-1.2	0.0	3.0
6	7.0	38.1	37.6	-0.5	25.5	15.1	38.0	37.9	-0.1	4.0	2.2
7	6.3	38.0	38.0	0.0	25.5	19.1	38.0	37.0	-1.0	5.0	3.0
8	9.7	37.8	37.8	0.0	26.5	20.1	37.8	37.0	-0.8	2.0	2.1
9	6.4	38.0	38.4	0.0	29.0	24.3	38.0	37.5	-0.5	5.0	3.8
Mean:	7.4						20.1		-0.8		2.7
Range:	5.5-9.7						15.1-25.5		-0.2-1.3		2.1-3.8
S. D.:	1.0						3.0		-0.4		0.5

Table VI. Oxygen consumption rates and rectal temperatures of nine intact cats before and during a cold stress.

VO<sub>2</sub> - Oxygen consumption rate in ml/s O<sub>2</sub> S. T. F. D. /kg/min based on a 20 minute determination in a closed circuit system.  
 B - Rectal temperature in °C at beginning of VO<sub>2</sub> determination.  
 E - Rectal temperature in °C at end of VO<sub>2</sub> determination.  
 Env. Temp. (T) - Temperature in °C of closed circuit in which VO<sub>2</sub> is being determined.  
 Δ - The change in rectal temperature / 20 minutes during the VO<sub>2</sub> determination in 0.5° C air.

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the data in Table VI, it was concluded that both the intensity of heat production (shivering) and the heat retention capacity could vary in intact cats over rather wide ranges and independently of each other. It was therefore decided to compare the ratio of shivering/resting  $\dot{V}O_2$  and rectal temperature variations in  $0.5^\circ\text{C}$  air of the animals with hypothalamic lesions to the mean and range of data presented in Table VI rather than to data collected on each animal prior to surgery. This was done because it was felt that declines in shivering capacity and heat retention capacity would only be significant if they resulted in a ratio of  $\dot{V}O_2$  shivering/resting below  $2.0$  and in a decline of rectal temperature/unit time in  $0^\circ\text{C}$  to  $5^\circ\text{C}$  air above  $0.07^\circ\text{C}$  min, i.e., below the two lower limits of the ranges listed in Table VI.

Five animals typify the results and the extent of neural tissue destruction in these cats is illustrated in Figures 8-11. In Table VII the various metabolic determinations and somatic observations are listed for cats No.  $H_1$ ,  $H_2$ ,  $H_3$  and  $H_{14}$ ,  $F_8$  and  $F_{10}$ , ST 24, ST 25. Additionally the table shows the animals with similar lesions and similar metabolic responses to the cold stresses. Cats No.  $H_1$ ,  $H_2$ ,  $H_3$ ,  $H_4$  and  $H_9$ ,  $F_1$ ,  $F_2$ ,  $F_5$ ,  $F_7$ ,  $F_8$ , ST 19 and ST 38 shivered in response to the cold stresses and the  $\dot{V}O_2$  ratio shivering/resting ranged for these animals from 2.1 to 2.6. The lesions in these various cats would embrace all anterior and posterior hypothalamic tissue except the dorsomedial region of the posterior hypothalamus. In Cat No.  $F_{10}$  the lesion extended somewhat into this region (Fig. 8), and in this cat shivering was present but somewhat feeble, the ratio of shivering/resting  $\dot{V}O_2$  being 1.9. In Cat No. ST 25 there is even greater encroachment of the lesion into this region (Fig. 10), but shivering was present, if somewhat more feeble. In this cat the ratio of  $\dot{V}O_2$  shivering/resting was 1.7, 1.7, and 1.8 on successive days tested. In Cat No.  $H_{13}$ , the dorsomedial region of the posterior hypothalamus was destroyed to a far greater extent (Figure 11), and this cat did not shiver during the cold stress, the ratio of  $\dot{V}O_2$  cold stress/resting being 1.2 and 1.0 on successive days tested. This cat was subjected to a third day of testing in order to take moving pictures of the animal's ability to piloerect and assume a huddled posture while at a low, non-shivering rectal temperature. On this day it was obvious that this cat could make appropriate behavioral responses to low body temperature in that at the conclusion of each

Cat No.	Lesion	Days Post Surgery	Cold Test	Shivering Resting $\dot{V}O_2$	Rectal Temperature Measurements			Observations		Animals with Similar Lesions and Cold Stress Responses	
					At Room Temp.	Begin. of $\dot{V}O_2$ Deter.	End of $\dot{V}O_2$ Deter.	$\Delta^{\circ}RT$	Shivering		Heat Retention
H <sub>1</sub>	A. Hypothalamus (Lateral)	48	B	2.1	37.6	37.4	37.6	+0.01	Normal	Normal	H <sub>2</sub> and 3
F <sub>10</sub>	P. Hypothalamus (Lateral)	46	B	1.9	39.2	39.0	36.5	-0.13	Feeble	Diminished	F <sub>7</sub> and H <sub>9</sub>
H <sub>4</sub>	P. Hypothalamus (Ventrolateral)	132	B	2.4	39.6	39.4	39.2	-0.01	Normal	Normal	F <sub>1</sub> , 2, 5, ST19, 38
F <sub>8</sub>	P. Hypothalamus (Dorsolateral)	46	B	2.6	39.2	36.6	34.0	-0.13	Normal	Diminished	
ST25 P.	Hypothalamus (Dorsomedial)	7	A	1.7	39.0	32.1	31.0	-	Feeble	-	
I <sub>2</sub>	A	12	A	1.7	39.0	32.1	31.9	-	Feeble	-	
H <sub>13</sub>	P. Hypothalamus (Dorsomedial)	33	A	1.8	39.0	34.0	33.0	-	Feeble	-	
H <sub>14</sub>	P. Hypothalamus (All Bar Dorsomedial)	20	A	1.2	39.1	34.2	32.6	-	None	-	
		21	B	1.0	39.4	38.0	36.4	-0.11	None	Normal?	
H <sub>14</sub>	P. Hypothalamus (All Bar Dorsomedial)	34	B	2.1	37.4	35.0	29.5	-0.33	Normal	Diminished	
ST24 P.	Hypothalamus (Ipsilateral Dorsomedial)	8	A	3.2	39.0	33.5	34.2	-	Normal	-	H <sub>12</sub>

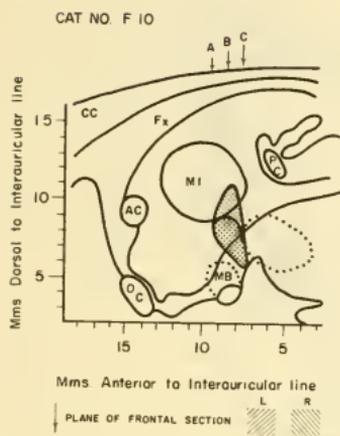
Table VII. The effects of hypothalamic lesions on the ratio of shivering to resting  $\dot{V}O_2$ .

Cold Test A: Closed circuit determination of  $\dot{V}O_2$  and rectal temperature ( $^{\circ}C$ ) for a 15-30 minute period in 20 $^{\circ}C$  to 25 $^{\circ}C$  air after lowering the body temperature 5 $^{\circ}C$  to 7 $^{\circ}C$ .

Cold Test B: Closed circuit determination of  $\dot{V}O_2$  and rectal temperature for a 15-30 minute period in 0 $^{\circ}C$  to 5 $^{\circ}C$  air, 15 minutes after exposure to this temperature.

$\Delta^{\circ}RT$  : The change in rectal temperature per unit time during the  $\dot{V}O_2$  determination in 0 $^{\circ}C$  to 5 $^{\circ}C$  air. Expressed in  $^{\circ}C$ /minute.

# ROLE OF THE PROSENCEPHALON IN SHIVERING



B

C



Figure 8. Extent of neural tissue destruction in Cat No. F 10.

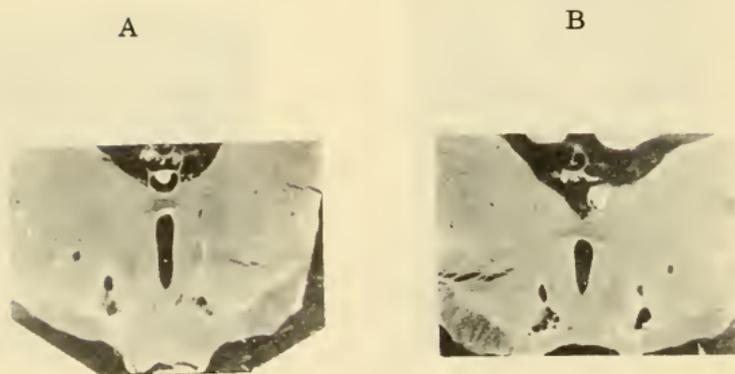
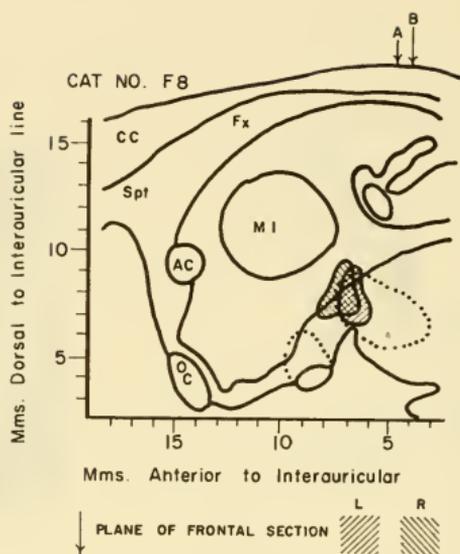
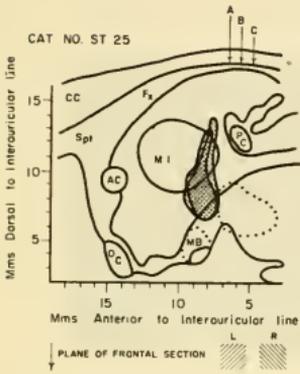


Figure 9. Extent of neural tissue destruction in Cat No. F 8.

# ROLE OF THE PROSENCEPHALON IN SHIVERING



A



B



C



Figure 10. Extent of neural tissue destruction in Cat No. ST. 25.

Cat No. H 13 - A



Cat No. H 13 - B



Cat No. H 13 - C



Cat No. H 14 - A



Cat No. H 14 - B



Figure 11. Extent of neural tissue destruction in Cats No. H 13 and H 14.

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cold test it sought a warm pad and heating lamp when they were moved around the laboratory. On the third day of testing, 40 days post surgery, the animal was placed in a cage with another larger cat renowned for aggressiveness. After a typical display of aggression by the second cat, H<sub>13</sub> promptly escaped from the cage when the door was opened. During the cold test the warm pad and heating lamp were placed in the cage with the aggressive cat and at the conclusion of the cold test H<sub>13</sub>, with a rectal temperature of 33° C and still not shivering, entered this cage to stand on the warm pad despite the aggressive cat's auditory and somatic objections.

Although the impairment of shivering in Cats No. F<sub>10</sub>, ST 25 and H<sub>13</sub>, is such as to implicate the integrity of the dorsomedial posterior hypothalamus in the production of shivering, the above results do not indicate how little of this tissue can remain in order to permit effective shivering. In Cat No. H<sub>14</sub> an attempt was made to destroy all of the tissue of the posterior hypothalamus except the dorsomedial region. As Figure 11 shows, this attempt was only partially successful. At the tuberal level of the posterior hypothalamus in this cat, most of the dorsolateral right side posterior hypothalamus was destroyed but the dorsomedial tissue was preserved on the left side. However, on the left side most of the dorsal tissue was destroyed at the posterior hypothalamic level (Fig. 11-Cat No. H<sub>14</sub> B), but the dorsomedial region was preserved on the right side. Since this cat could shiver effectively, this would suggest the ipsilateral preservation of the dorsomedial posterior hypothalamus tissue was sufficient to permit effective shivering. This point is further illustrated in Cat No. ST 24, in which the posterior hypothalamic lesions were bilateral but only overlapped for a distance of 0.75 mm approximately. However, at the level or region of overlap there was widespread dorsomedial posterior hypothalamic destruction except in that the ventral tissue within this region was still intact. This animal could shiver quite effectively. Similarly, Cat No. H<sub>12</sub> could shiver quite effectively with all the dorsomedial posterior hypothalamic region destroyed on the right and partially on the left. Again the more ventral tissue within these boundaries was intact on both sides.

In summary, these limited observations on 18 cats would suggest that ipsilateral preservation of the dorsomedial posterior

hypothalamus is sufficient for an animal to shiver effectively in the cold. However, it is not possible on the basis of these experiments to designate a more precise or limited region as being responsible for the production of shivering.

In Table VII cold test A was only used when the mechanical breakdown of the cold test B refrigerator system occurred. In such tests it was not possible to gain an indirect picture of an animal's heat retention capacity. However, in cold test B, by measuring both oxygen consumption and rectal temperature while exposed to  $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  air, this was possible. As shown in Table VI, the range of rectal temperature drop/unit time in  $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  air was  $0.02^{\circ}\text{C}$  to  $0.07^{\circ}\text{C}/\text{min}$  for intact cats. Table VII shows this figure was  $.13^{\circ}\text{C}/\text{min}$  for Cat No. F<sub>10</sub>,  $.13^{\circ}\text{C}/\text{min}$  for Cat No. F<sub>8</sub>, and  $.33^{\circ}\text{C}/\text{min}$  for Cat No. H<sub>4</sub>. Additionally, Cats No. F<sub>7</sub> and H<sub>9</sub> had figures of over  $.13^{\circ}\text{C}/\text{min}$  and Cats No. F<sub>1</sub>, F<sub>2</sub> and F<sub>5</sub>, ST 19 and ST 38 figures of less than  $0.07^{\circ}\text{C}/\text{min}$ . Since Cats No. F<sub>7</sub> and F<sub>10</sub> and H<sub>9</sub> and H<sub>14</sub> had bilateral lesions that effectively destroyed the lateral tuberal and posterior hypothalamic regions and Cats No. H<sub>4</sub>, F<sub>1</sub>, F<sub>2</sub> and F<sub>5</sub>, ST 19 and ST 38 had lesions that destroyed only the ventrolateral tuberal and posterior hypothalamic tissue, it would appear that the effective retention of heat is a function of the dorso-lateral tuberal and hypothalamic tissues. Such a conclusion is further supported by destruction of this tissue being evident in Cat No. F<sub>8</sub> (Fig. 9). It would appear that the dorsolateral anterior hypothalamus is not involved in heat retention in that in Cat No. H<sub>1</sub> the dorsolateral anterior hypothalamic tissue was destroyed yet the animal both shivered effectively and had a rectal temperature rise/unit time in  $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  air of  $.01^{\circ}\text{C}/\text{min}$ .

Although the animals with lateral and dorso-lateral hypothalamic lesions appeared to have a diminution in heat retention capacity in  $0^{\circ}\text{C}$  to  $5^{\circ}\text{C}$  air, by indirect determination, this was not obvious in  $25^{\circ}\text{C}$  air. That is to say, these animals had, at this higher temperature, rectal temperatures and resting oxygen consumption rates within the normal range.

No systematic attempt was made to study temperature regulation disturbances in the immediate postoperative period. Table VIII lists the responses of three cats to heat and cold stresses 4 to 46 days after surgery. Four days after surgery the three animals had

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Cat No.	R. T. after 8 hours of 25° E. T.	Observations	R. T. after 3 hours of 45° E. T.	Observations
4 Days After Surgery				
F <sub>8</sub>	35.8	No shivering	41.0	No panting Languid posture
F <sub>9</sub>	35.0	No shivering	43.0	No panting Languid posture -Death-
F <sub>10</sub>	35.8	No shivering	41.0	No panting Languid posture
46 Days After Surgery				
F <sub>8</sub>	39.2	Shivering X2.6 elev. $\dot{V}O_2$	41.0	Panting Languid posture
F <sub>10</sub>	39.2	Feeble shivering X1.9 elev. in $\dot{V}O_2$	41.0	Panting Languid posture

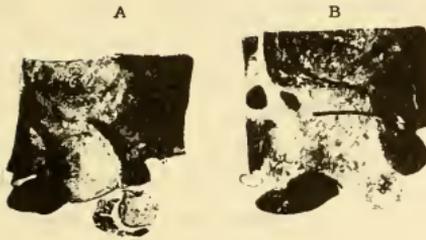
Table VIII. The responses of 3 cats with hypothalamic lesions to heat and cold stresses. R. T. - rectal temperature in degrees Centigrade. E. T. - environmental temperature in degrees Centigrade.  $\dot{V}O_2$  - oxygen consumption rates.

low body temperatures in a 25° C environmental temperature but could not shiver. When exposed to a 45° C environmental temperature, the animals' rectal temperature rose to 41° C to 43° C, this rise being accompanied by assumption of a languid posture that would permit maximal conductive heat loss. However, panting was not evident. Thus at four days after surgery, these animals verged on poikilothermy rather than homeothermy. Forty-nine days after surgery the two animals that survived the initial tests had normal rectal temperatures in the 25° C environmental temperature, could shiver in response to cold stresses and pant in response to heat stresses. Two other animals, H<sub>10</sub> and H<sub>11</sub>, with massive hypothalamic lesions, demonstrated similar results when tested five days after surgery. Both these animals expired during the heat stress tests, without assuming languid postures and without panting.

These results are listed to illustrate the author's reluctance to expose animals with massive hypothalamic lesions to heating and cooling tests in the early postoperative period of recovery. In this somewhat enfeebled condition death often results and the somatic responses to both high and low body temperatures are usually impaired above and beyond the impairment present after the animals have recovered relatively fully from the surgery.

Comments. The results support the electrical stimulation data in implicating the dorsomedial posterior hypothalamus in the production of shivering. If it is also accepted that cutaneous vasoconstriction is activated by the dorsolateral posterior hypothalamic neurons, then some of the seemingly diverse results of other investigators can be explained in rather simple terms. For example, Figure 12 shows typical lesions produced by three sets of investigators whose results have been widely quoted. First, Isenschmid's work with Krehl (1912) and Schnitzler (1914) implicated the lateral hypothalamus in temperature regulation (Figure 12 - Isenschmid D) but not the medial hypothalamus (Figure 12 - Isenschmid C). However, in this work, the animals' rectal temperatures were taken over a range of environmental temperatures, and at very low environmental temperatures the body temperature of the animal with lesion C began to fall. If it is assumed that all these animals were in a debilitated condition and that, at least in terms of functional and nonfunctional nervous tissue, "C" could not shiver but could vasoconstrict, then it is feasible that its body temperature would

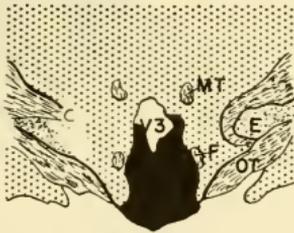
# ROLE OF THE PROSENCEPHALON IN SHIVERING



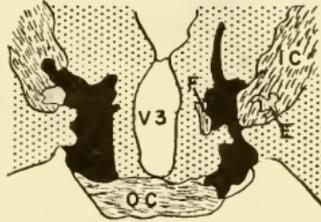
KELLER (DOGS)

These two dogs had subnormal temps. for several days but subsequently could maintain normal body temp. in an environmental temp. range of 5-35°C.

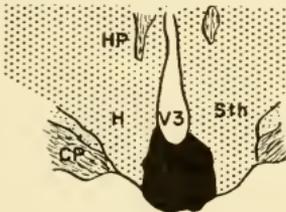
A. Undisturbed Temp.



B. Heat Loss Deficit



C. Undisturbed Temp.

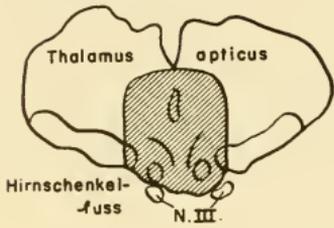


D. Heat Product. Deficit

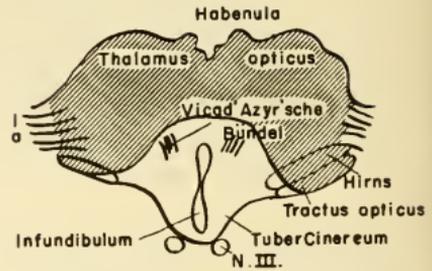


CLARK, MAGOUN, & RANSON (CATS)

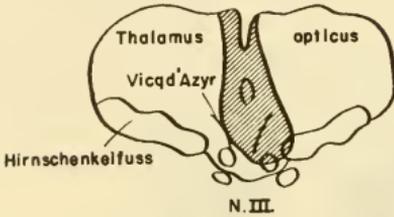
A. Disturbed Temp. Reg.



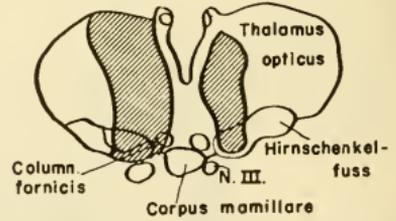
B. Undisturbed Temp. Reg.



C. Undisturbed Temp. Reg.



D. Disturbed Temp. Reg.



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ISENSCHMID (RABBITS)

Figure 12. Lesions produced by various investigators that failed to disturb and did disturb body temperature regulation.

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be relatively normal until the environmental temperature plummeted. Conversely, if the rabbit with lesion "D" could shiver but not vasoconstrict cutaneously, then it is conceivable that in an enfeebled condition its body temperature would fall despite the neural "drive" to produce heat by muscular shivering. That their animals, studied but for five days post-surgery, were enfeebled seems evident from their statement (1914) that "we have never observed that an originally disturbed heat regulation later became normal, but we have often witnessed the reverse." This completely contradicts the latter-day findings, exemplified by the work of Hess (1957), that functional deficits produced by hypothalamic lesions become attenuated the longer the preparation lives after surgery.

Figure 12 secondly shows schema of four lesion preparations that were considered by Clark, Magoun, and Ranson to implicate the anterolateral hypothalamus in body temperature regulation against heat stress and the posterolateral hypothalamus in regulation against cold stress. Admittedly in a later review Ranson and Magoun (1939) stated that their observations on shivering were fragmentary, but this work (which essentially confirms the work of Isenschmid and his co-workers but had the advantage of being based on observation of animals fully recovered from surgical trauma) is still widely quoted with respect to the neurogenesis of shivering. Their work does not conflict with our results if it is accepted that their lesion "C" does not include the dorsomedial posterior hypothalamus and their lesion "D" affects both dorsomedial and dorsolateral hypothalamic tissue as well as the more pronounced ventrolateral destruction.

Thirdly, two lesions from one of Keller's (1959) investigations are shown in Figure 12. Their dogs, maintained for long periods after surgery, could shiver and maintain normal body temperature even when placed in a 5<sup>o</sup> C environmental temperature for several hours. The hypothalamic lesions spare only the dorsal posterior hypothalamus, thus suggesting that shivering involves the dorsomedial neurons and vasoconstriction the dorsolateral neurons.

Time does not permit a more detailed comparison of our results with divergent results in the literature. If it is accepted that shivering will not return in the early post-operative period after any hypothalamic lesion, and that cutaneous vasoconstriction

involves the dorsolateral posterior hypothalamus and will return in the early postoperative period after any hypothalamic lesion that spares this region, then many seemingly divergent results can be explained.

## COMPARISON OF SOMATIC EFFECTS EVOKED DURING SEPTAL AND POSTERIOR HYPOTHALAMIC STIMULATION

### Anesthetized Preparation Studies

Methods. In 7 experiments on cats anesthetized with either alpha chloralose (40 to 60 mg/kg I. P.) or pentobarbital sodium (35 mg/kg I. P.), the septum was systematically explored for sites which when stimulated evoked somatic responses. In each experiment the intensity of stimulation needed to evoke shivering by stimulation of a dorsomedial posterior hypothalamic site was noted. In some of these experiments comparisons were also made of alterations in heart rates and respiration rates during septal and posterior hypothalamic stimulation. In these experiments an attempt was made to maintain the rectal temperature of each cat between 37° C and 38° C by appropriate alterations of environmental temperature.

The surgical, electronic, brain fixing, sectioning, staining, and electrode tract location techniques were similar to those described above.

Results. In five experiments (Cats No. ST 5, ST 13, ST 14, ST 15 and ST 17) the septal region was systematically explored for loci which when stimulated produced either an increase in muscle tone or shivering. The strongest somatic response evoked by stimulation of any given septal locus was compared with the shivering response to posterior hypothalamic stimulation in the same cat. Comparisons were made of the latency and intensity of the response and the stimulus intensity necessary to evoke it. Additionally, in some

## ROLE OF THE PROSENCEPHALON IN SHIVERING

experiments a comparison was made of the alterations in respiration and heart rate produced by such stimulation. In two of these five experiments (Cats No. ST 13 and 17) limited posterior hypothalamic mapping was also undertaken. In two further experiments (Cats No. ST 18 and 24) the comparisons were not undertaken after extensive septal mapping, but rather the electrodes were oriented to septal loci when stimulation had produced somatic responses in previous experiments.

Figure 13 lists the somatic responses evoked by septal stimulation in five cats. Planes A and B are schemata of typical cat brain frontal sections 16 mm (midseptum) and 14 mm (posterior septum) anterior to the interauricular line respectively. Loci 1, 2, 3 and 4 and 9, 10, 11 and 12 are 1.5 mm from the midline while loci 5, 6, 7 and 8 and 13, 14, 15 and 16 are 0.5 mm from the midline. Loci 1 and 9 are 15 mm dorsal to the interauricular line, and loci 5 and 13, 16 mm dorsal to this line. Loci ventral to these are at 2 mm depth intervals. As with the posterior hypothalamus, loci were stimulated at 1 mm depth intervals, but responses to stimulation of these loci are not listed for the previously mentioned reasons. Extensive mapping was undertaken at a frontal plane 15 mm rostral to the interauricular line, but responses to stimulation of these loci are not listed, since the responses at this plane were similar to those seen at Plane A.

Only two somatic responses are listed, an increase in muscle tone and shivering. The table in Figure 13 indicates that shivering was observed in three of the five cats. The response was best evoked by stimulation of midseptal loci 1.5 mm lateral to the midline and from 13 mm to 9 mm dorsal to the interauricular line. Stimulation of loci 1 mm rostral to this region evoked an increase in muscle tone but not shivering. When shivering was observed it seemed of equal intensity and duration in limbs both ipsi and contralateral to the stimulated site. In these experiments this latter finding was based on both visual observation and EMG recordings.

Table IX lists comparison of somatic, heart and respiration rate responses during stimulation of the most "active" septal loci and a posterior hypothalamic locus within the previously determined region whose activation produces shivering. In the four cats (No.'s ST 5, 13, 18 and 24) in which shivering was not observed

CAT NO.	LOCUS															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ST. 5	TO	TO	TO	TO	O	O	O	O	O							
ST. 13									TO	O	O	TO	TO	O	O	O
ST. 14	TO	SH	TO	SH	O	TO	O	O	TO	TO	TO	TO	O	O	O	O
ST. 15	O	O	O	SH	O	O	O	O	O	O	O	O	O	O	O	O
ST. 17	TO	SH	SH	SH	O	O	O	O	O	O	O	SH	O	O	O	O

SCHEMA OF LOCI  
Plane A                      Plane B

TO - Increase in Muscle Tone  
 SH - Shivering  
 O - No Somatic Response

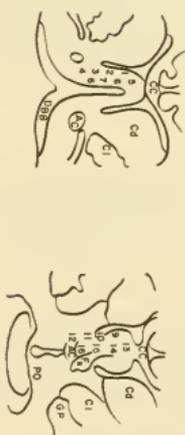


Figure 13. Somatic responses evoked by septal stimulation.

# ROLE OF THE PROSENCEPHALON IN SHIVERING

Cat No.	I. P. Dose of Alpha Chloralose in mg/kg	Site Stimulated	Time in Hours Post I. P. Injection	Rectal Temp. in°C	Environ. Temp. in°C	STIMULUS PARAMETERS				RESPIRATION RATE IN BREATHS/MIN.				HEART RATE IN BEATS/MIN.				Observation on Limb Musculature
						Intensity in $\mu$ A/Pulse	Pulse Duration in msec	Pulse Freq. in Pulses/sec	Stimulus Duration in sec	Pre Stimul.	During Stimul.	$\Delta$ Stimul.	Pre Stimul.	During Stimul.	$\Delta$ Stimul.	Pre Stimul.	During Stimul.	
ST5	65	Septum P. Hypothalamus	3.5 9.0	37.9 38.6	27.8 29.0	1600 1600	3 3	100 100	30 90	24 28	26 34	+2 +6	210 216	210 246	+0 +30	0 Shivering after 25 sec lat.		
ST13	95	Septum P. Hypothalamus	24.0 25.0 25.1	36.8 37.0 37.0	29.5 29.5 29.5	1600 800 1600	3 3 3	100 100 100	30 30 30	16 14 14	18 17 48	+2 +3 +30	-- No Data --	-- No Data --	--	Increase in hind limb twitching Increase in muscle tone Continuous shivering		
ST14	50	Septum P. Hypothalamus	16.3 17.1	38.6 38.4	28.8 28.2	1600 800	3 3	100 100	36 23	12 24	22 50	+10 +26	-- No Data --	-- No Data --	--	Mild shivering Shivering		
ST15	63	Septum P. Hypothalamus	20.0 20.3	37.6 37.6	29.2 29.2	1600 1600	3 3	100 100	35 30	36 33	40 60	+14 +30	168 172	168 216	+0 +44	Mild shivering Continuous shivering		
ST17	60	Septum----- P. Hypothal.--	23.5 23.6 22.3 24.5	37.8 37.8 37.8 38.8	28.0 28.0 28.0 28.0	1600 1600 800 800	3 3 3 3	50 50 50 50	30 60 30 60	12 14 16 28	12 14 40 28	0 +2 +30 +14	114 114 96 164	102 120 156 192	-12 +6 +60 +28	Mild shivering 45 secs after stimulation Mild shivering Continuous shivering Continuous shivering		
ST18	50	Septum P. Hypothalamus	24.5 25.0	36.2 36.0	28.0 28.0	1600 800	3 3	50 50	30 30	18 20	18 36	0 +18	-- No Data -- 174	-- No Data -- 174	--	Two muscle twitches Mild shivering post stimulation		
ST24	35 mg/kg (P. B.)	Septum P. Hypothalamus	6.0 6.0	32.5 32.5	28.0 38.0	1600 1600	1 1	50 50	60 60	26 26	18 18	-6 -6	-- No Data -- 154	-- No Data -- 156	+2	No response Shivering - continuous		

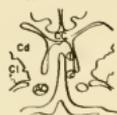
Table IX. Comparison of effects of septal and posterior hypothalamic stimulation on respiration rate, heart rate, and limb musculature.

during septal stimulation, it was observed during posterior hypothalamic stimulation. In the three cats (No.'s ST 14, 15 and 17) in which shivering was observed during septal stimulation, a more intense and less latent shivering was produced by the same or less intense stimulation. In Cat No. ST 5, the comparison is hardly valid in that the septum was stimulated 3.5 hours after induction of alpha chloralose anesthesia and the posterior hypothalamus was stimulated 9 hours post medication. That is to say, the preparation may have been at too deep a level of anesthesia to shiver during septal stimulation. However, in all other cats the stimuli were applied to the two loci within a short period of time of each other. Figure 14 illustrates the comparisons for Cat No. ST 17. In this figure there are schemata of septal loci labelled 1 and 2, 2 being 2 mm ventral to 1. The posterior hypothalamic loci 1 and 2 are within the previously determined dorsomedial region whose stimulation evokes shivering. The hypothalamic locus denoted 2 is 1 mm lateral and 1 mm ventral to the locus marked 1. Loci posterior hypothalamus 2 and septum 1 were stimulated for 30 seconds at 50 pulses/sec with a pulse duration of 3 msec. In both cases shivering was produced, but the stimulus intensity necessary at the hypothalamic locus was only half that necessary at the septal locus (800  $\mu$ A/pulses vs. 1600  $\mu$ A/pulse). Additionally, as shown in records No. 4 and 5 for the loci in Figure 14, shivering was more intense and appeared with less latency during hypothalamic than during septal stimulation. Loci posterior hypothalamus 1 and septum 2 were stimulated for 60 seconds using the same frequency and pulse duration. As shown in records 4 and 5 for these loci, shivering was less intense during the septal stimulation and required a stimulus intensity double that used during hypothalamic stimulation. These loci were stimulated in the order posterior hypothalamus 2, septum 1, septum 2 and posterior hypothalamus 1 at 22.3, 23.5, 23.6, and 24.5 hours after induction of alpha chloralose anesthesia (60 mg/kg I. P.). The rectal temperature during stimulation of these loci was 37.8° C, 37.8° C and 38.8° C respectively. In all these cases the environmental temperature was 28° C. These results indicate that shivering can be induced by electrical stimulation of sensitive loci in both the hypothalamus and the septum, but the sensitivity of the hypothalamic loci is considerably greater than that of the septal loci as revealed by the necessary intensity of stimulating current and the EMG response. The EMG of the hind-

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1. Resp. Rate
2. EEG - L. Cortex
3. EEG - R. Cortex
4. EMG - L. Forelimb
5. EMG - L. Hindlimb

SEPTUM



P. HYPOTHALAMUS



Black line - Stimulus Duration  
 All Stimuli 50 pulses/sec.  
 Pulse Duration 3 msec.

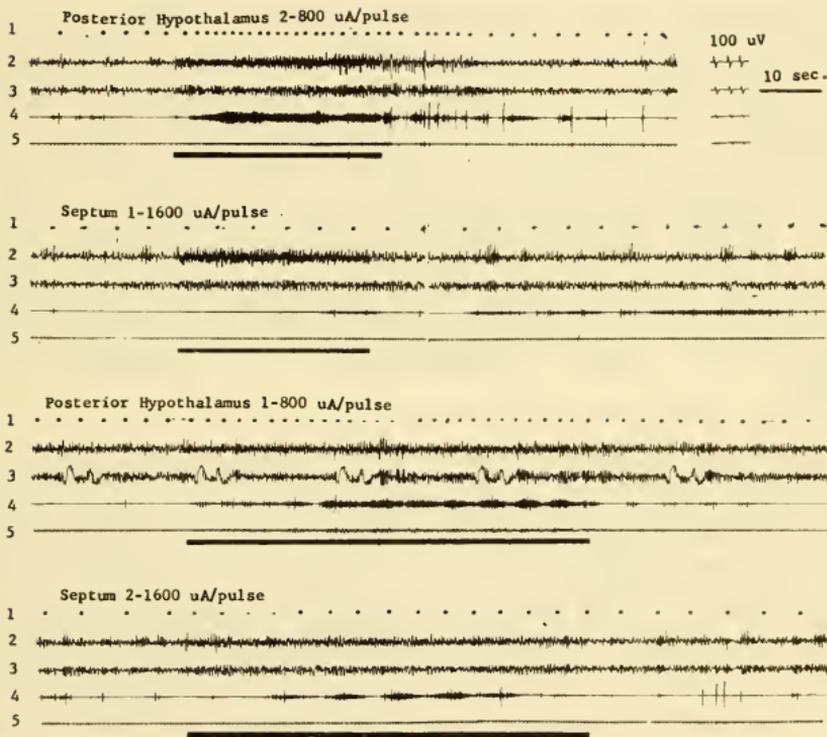


Figure 14. Comparison of somatic effects produced by septal and posterior hypothalamic stimulation (Cat No. ST. 17).

limbs (record 5) for each stimulated locus was similar to that of the forelimbs (record 4) but weaker in intensity of response.

As well as the production of greater somatic activity during posterior hypothalamic stimulation than during septal stimulation, respiration and heart rate increases were of greater magnitude in the former than in the latter case. The appropriate figures are listed in Table IX, but it must be pointed out that no systematic attempt has been made in this study to compare the alterations in these rates during stimulation of septal or posterior hypothalamic stimulation loci.

Comments. These results tend to confirm neuroanatomical data that septal projections to the midbrain first relay in the hypothalamus. It is not possible on the basis of the presented data to deduce the number of relays involved between septum and hypothalamus, but this was not the purpose of these experiments. Rather, it was to show that shivering can be induced during electrical stimulation with a greater stimulus intensity during septal stimulation. This suggests the possibility that the main control for the production of shivering is in the posterior hypothalamus and that facilitating influences can reach the hypothalamus via or originating in the septum.

Akert and Kesselring (1951) first reported the production of shivering by stimulation of 10 septal loci and only one hypothalamic locus in 8 cats. Based on this work, they suggested that the septum was primarily implicated in the production of shivering, since Hess's results, from which their report was gleaned, contained but this one isolated example of hypothalamic stimulation producing shivering. However, as mentioned above, this was due more to the parameters of stimulus than of the locus of stimulation. Similarly, Andersson (1957), in reporting the consistent and repeatable evocation of shivering during septal stimulation in 3 unanesthetized goats, speculated that "it might be possible that an integrative action of all mechanisms concerned with heat conservation is exerted from this part of the forebrain." Possibly he would not have so speculated had he compared the shivering response during both septal and hypothalamic stimulation. Certainly the fact that shivering occurs in animals with transection separation of the anterior from the posterior hypothalamus, first reported by Bazett, Alpers

## ROLE OF THE PROSENCEPHALON IN SHIVERING

and Erb (1933), would indicate that structures more rostral than the posterior hypothalamus could play but a secondary role in the production of shivering.

The data listed in Figure 13 and those later to be discussed in Figure 21 indicate that the ventrolateral midseptum is facilitating and the ventromedial midseptum inhibitory with respect to shivering. Jacobson, Craig and Squires (1960) found that electrolytic destruction of the ventromedial midseptum suppresses the shivering of lightly anesthetized cats. This implied that the ventromedial midseptum was involved in the production of shivering, and as such conflicts with our concept. An experiment was then performed to illustrate that the results from the two laboratories do not conflict, only the interpretation. In this experiment, shown in Figure 15, bipolar electrodes were inserted bilaterally into the center of the lesion shown in the top lefthand corner of Figure 13, i.e., the photograph of a frontal section through the septal region. The tracts of the electrode do not appear because the brain was sectioned at a different angle to the paths of the electrode tracts. When these electrodes were inserted, the brain was intact; the lesions were produced later in the experiment. A bipolar electrode was also inserted into the posterior hypothalamus as indicated by the white stain in the lower photograph. The locus stimulated by this electrode was the lowermost tip of the white stain. (Unfortunately this electrode slipped medially several days after the experiment when it was being removed from the living cat. Hence the white stain shows a vertical and a slanted angle to the electrode tract.) This cat was anesthetized with pentobarbital sodium (35 mg/kg I. P.), and once spontaneous shivering began, the following sequence of stimuli was applied, as shown in the figure in which the upper record is the electromyogram of the forelimb and the lower record the duration of the stimulus:

1. 1600 $\mu$ A/pulse stimulation of the right ventromedial midseptum to suppress shivering for the 30-second duration of stimulus.
2. 800 $\mu$ A/pulse stimulation of the posterior hypothalamus to augment shivering for the 30-second duration of stimulus.
3. Right ventromedial midseptum destruction by cathodal

Septal Pre-optic Lesion

1. R. Septal Stimulation-1600 uA/pulse



2. L. P. Hypothalamic Stimulation-800 uA/pulse



3. R. Septal Polarization-1 mA for 90 sec.



4. L. P. Hypothalamic Stimulation-1600 uA/pulse  
(Post Bilateral Fornical Destruction)



All Stimuli 50 pulses/sec., 1 msec. pulse duration  
Upper Record-EMG-R. Hindlimb  
Lower Record-Duration of Stimulus

10 sec.

P. Hypothalamus

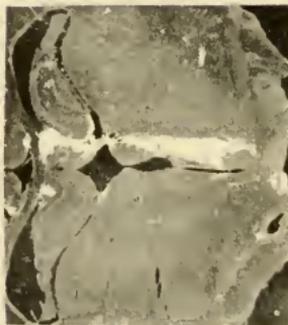


Figure 15. Shivering suppression evoked by stimulation and polarization of the septal-preoptic region (Cat No. ST. 23).

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polarization of the electrode to suppress shivering for the 90-second duration of stimulus.

3<sup>b</sup>. (Not shown). The same destruction on the left side to produce a lesion the extent of which is shown in the upper photograph of Figure 15 and which suppressed shivering completely.

4. Reproduction of shivering by 1600  $\mu$ A/pulse stimulation of the posterior hypothalamus for the 60-second duration of stimulus.

The above stimuli were applied to the animal in the anesthetized state. After bilateral ventromedial midseptal destruction the animal only shivered when the posterior hypothalamus was electrically stimulated. However, four days later, in the unanesthetized state, the animal shivered vigorously on exposure to cold, the ratio of  $\dot{V}O_2$  shivering/resting being 3.7.

This experiment illustrates the suppression of shivering during stimulation of the ventromedial midseptum and during electrolytic destruction of the same region. Since shivering returned four days after surgery, it suggests that the immediate suppressive effects of electrolytic destruction of this region in the anesthetized cat masked the real role of this region in shivering, which is suppression.

### Unanesthetized Preparation Studies

Methods. In six cats, electrodes were stereotaxically implanted in central nervous tissue sites permitting observation and recording of animal responses to either hypothalamic or septal electrical stimulation, in the unanesthetized and unrestrained state.

Each preparation was first anesthetized (pentobarbital sodium, 35 mg/kg), its head mounted in the stereotaxic frame, scalp skin incised and reflected, temporal muscles retracted, and calvarium exposed. Bipolar stimulating electrodes similar to those already described were stereotaxically placed at various subcortical sites by drilling appropriate holes in the calvarium. The electrodes were

so designed that their tops protruded by 1 mm from the calvarium. The electrodes were permanently fixed by a cement (NuWeld, L. D. Caulk Co.) to the calvarium, the lead-off electrode wires being soldered to a female plug (Winchester Electronics, Inc., Monobloc M 95), cement-attached to the skull also. Various muscles of the fore and hindlimbs were also implanted with electrodes using the previously described wire wrapping technique. The lead-off wires from the muscles were also soldered to the female plug via subcutaneous route. With this technique it was possible to implant a total of 8 bipolar brain and/or muscle electrodes, 4 electrodes and a ground electrode to each 9 pin receptacle (Monobloc M9P) which could be inserted into each female plug attached to the preparation's skull. The cables were so suspended that the animal could move freely within the confines of the Faraday cage. Electrical stimuli could be applied through any given electrode and recordings made from the other electrodes, all with apparatus previously described for acute stimulation studies.

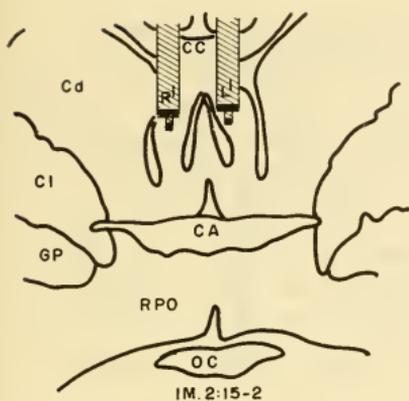
After consistent patterns of responses were obtained to stimulation via the various electrodes the animals were sacrificed, their brains fixed in formalin, sectioned every  $80\ \mu$ , and alternate sections stained with buffered thionine to permit localization of electrode tracts.

In Figures 16 and 17 the positions of the various electrodes in two such cats are shown schematically. In such sketches each electrode is numbered and drawn to brain scale. At the bottom of each sketch of a frontal plane of the brain a second number appears that is a code for the particular stained section of nervous tissue on which the sketch is based.

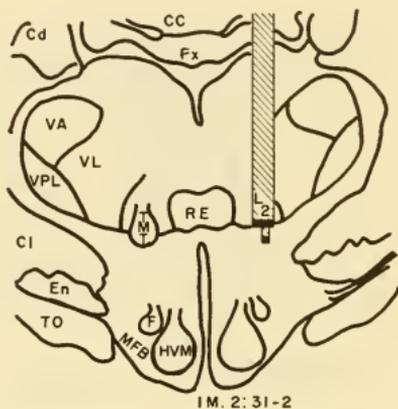
Results and Comments. The responses of cats No. IM 2 and IM 6 typify the results and Figures 16 and 17 show the loci activated by electrical stimulation. In Cat No. IM 2 (Figure 16), shivering was produced during stimulation via electrode No.  $L_1^1$ , which, as shown in the upper lefthand sketch, would activate a dorsal mid-septal region. It was not produced during stimulation of electrode  $R_1^1$ , which was in a dorsal midseptal region but somewhat more lateral than electrode  $L_1^1$ . In this cat, shivering was also produced during stimulation of the posterior hypothalamic locus around

# ROLE OF THE PROSENCEPHALON IN SHIVERING

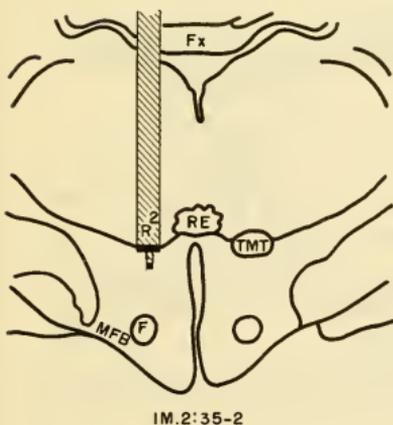
Midseptal Level



Tuberal Hypothalamic Level



P. Hypothalamic Level



P. Hypothalamic-Midbrain Level

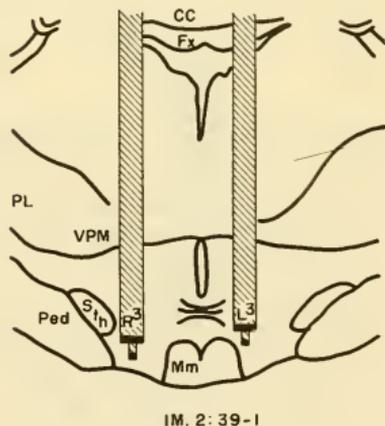
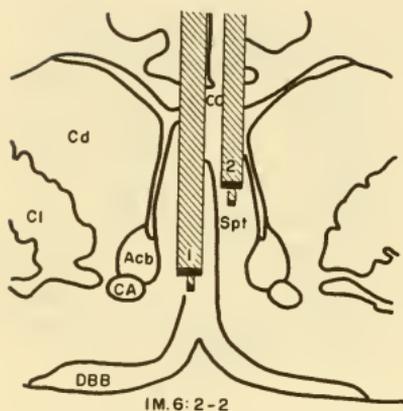
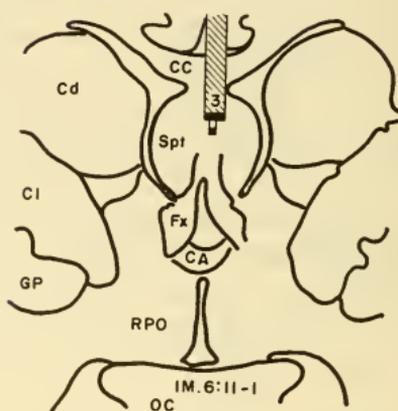


Figure 16. Schematic frontal representations of electrode tracts in Cat No. IM. 2.

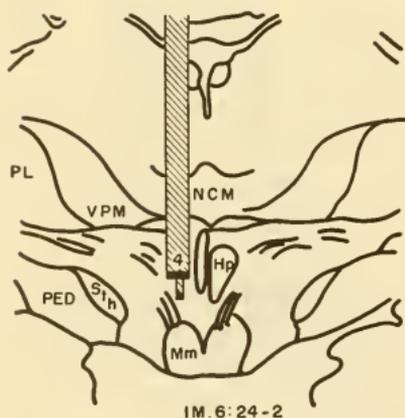
Midseptal Level



Posterior Septal Level



P. Hypothalamic Level



Rostral Midbrain Level

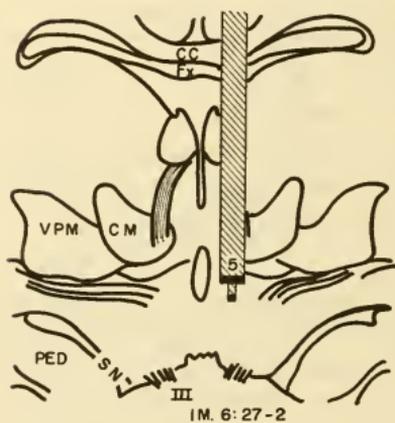


Figure 17. Schematic frontal representations of electrode tracts in Cat No. IM. 6.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

electrode R<sup>2</sup>, shown in the lower lefthand sketch of Figure 16. This region is the most rostral aspect of the dorsomedial region of the posterior hypothalamus. Activation of a contralateral<sup>2</sup> region about 1 mm more rostral during stimulation via electrode L<sup>2</sup> never produced shivering. Stimulation of two ventrolateral posterior hypothalamic regions shown in the lower righthand sketch never produced shivering.

In Cat No. IM 6, activation of the dorsal midseptal region, indicated by electrode 2 in the top lefthand figure, produced shivering. At this midseptal level, shivering was not produced by stimulation of a ventromedial region (electrode 1, top lefthand sketch), and at the posterior septal level, shivering was not produced by stimulation of a dorsomedial locus (electrode 3 in the top righthand sketch). At the posterior hypothalamic level, shivering was produced by stimulation of the dorsomedial region (electrode 4 in the bottom lefthand sketch), and in the rostral midbrain it was produced by dorsomedial activation (electrode 5 in the bottom righthand sketch).

These results for unanesthetized preparations confirm the results for anesthetized preparations with respect to the localization of regions whose activation produces shivering. Such confirmation was considered a necessary part of this study in order to negate the possibility that the shivering responses seen during the anesthetized preparation studies were not peculiar to the use of alpha chloralose or pentobarbital sodium.

On the other hand, the results add no information regarding the relative sensitivity of septal and posterior hypothalamic loci with respect to the production of shivering. In all cases shivering was produced in the unanesthetized cats with stimuli of intensity 800  $\mu$ A/pulse and not produced with stimuli of intensity 400  $\mu$ A/pulse. However, stimuli of interim intensity were not delivered. Secondly, nothing is known of the latency of the response because the presence or absence of shivering was noted by visual inspection and by palpation. At the moment the stimuli were applied, the door of the Faraday cage was closed. It was only opened after the investigator was reasonably sure it was safe to palpate the cat.

During stimulation of these loci, many sympathetically and parasympathetically mediated responses were observed. They

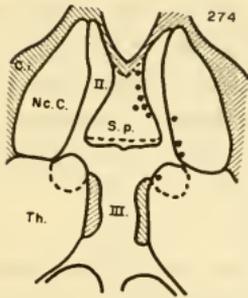
included salivation, lacrimation, urination, defecation, pupillary dilation and constriction, piloerection, and sham rage. With the investigator's attention focused mainly on the presence or absence of shivering, it was difficult to make detailed observations of these responses. However, it was obvious that both parasympathetic and sympathetic responses could be evoked during stimulation of septal loci. Sometimes stimulation of the same locus evoked both sympathetic and parasympathetic responses.

Figure 18 illustrates the septal loci stimulated by Akert and Kesselring (A) and Andersson (B) shown in schematic horizontal sections. The former schema are more dorsal than the latter. Figure 18C is a photograph of a frontal section of a cat brain from our laboratory in which a septal electrode passage is shown. The electrode tract in this photograph is through the lateral septum immediately adjacent to the ventricle. When the electrode was used to stimulate the animal, the animal shivered. Data from three laboratories is assembled on a figure to illustrate that Andersson's septal loci were medial, whereas Akert and Kesselring's and our own loci were lateral. In our case this was true in both anesthetized and unanesthetized preparations. As will be shown in the next section of this paper, stimulation of loci similar to those of Andersson evoked a suppression, not activation of shivering.

#### SUPPRESSION OF SHIVERING DURING SEPTAL, ANTERIOR, AND POSTERIOR HYPOTHALAMIC STIMULATION

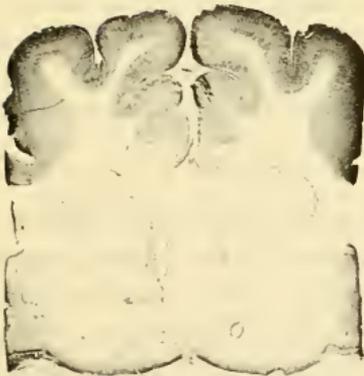
Methods. In 8 experiments on animals anesthetized with either alpha chloralose (40 to 60 mg/kg I. P.) or pentobarbital sodium (35 mg/kg I. P.), the septum was explored systematically for sites which when stimulated suppressed shivering. Shivering occurred spontaneously in such preparations in the waning stages of anesthesia because the rectal temperature of each animal was maintained at 33° C to 36° C by appropriate alterations of environmental temperature. During these experiments a stimulus was not applied to any

ROLE OF THE PROSENCEPHALON IN SHIVERING



A - Akert and Kesselring  
(Anesthetized Cats)

B - Andersson  
(Unanesthetized Goats)



C - Stuart, Kawamura  
and Hemingway  
(Anesthetized and  
Unanesthetized Cats)

Figure 18. The production of shivering by septal stimulation.

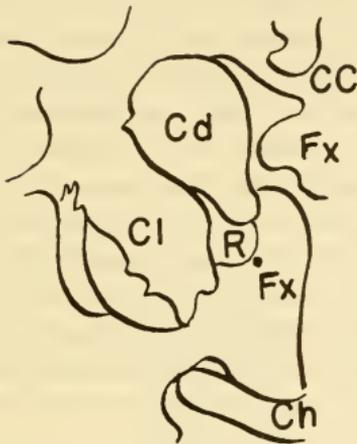
given region until shivering had been continuous in at least one limb for a period of 5 minutes. In two of these experiments the fornices had been sectioned at a more caudal level one week prior to experimentation. In six additional experiments the intensities of stimulation needed to suppress shivering during septal, anterior, and posterior hypothalamic stimulation were compared. In two of these experiments the relative inhibitory effects of various stimuli frequencies and pulse durations were noted.

The surgical, electronic, brain fixing, sectioning, staining, and electrode tract reconstruction techniques were similar to those described above.

Results. In order to explore systematically the septum and posterior hypothalamus for loci whose stimulation suppressed shivering, it was considered advisable to use cats anesthetized with pentobarbital sodium. This was done because continuous shivering occurs spontaneously in the waning stages of such anesthesia. If the intensity of stimulation necessary to suppress shivering is kept constant in each mapping experiment, it is important that such an experiment be conducted in as short a time as possible so that the preparation can be stimulated at a relatively constant level of anesthesia. Since it was arbitrarily decided that no locus would be stimulated until shivering had been active and continuous for the preceding 5 minutes, it was necessary to utilize a stimulus intensity that would clearly produce a suppression of shivering when applied to an "active" locus without a concomitant long post-stimulation period of suppressed shivering.

Figure 19 illustrates this point. In this experiment on Cat No. ST 22, continuous shivering was occurring in the waning stages of pentobarbital sodium anesthesia. Stimulation of a dorsal supraoptic locus evoked a short and mild suppression of shivering 5 seconds after the cessation of stimulation. The intensity of stimulation was  $200 \mu\text{A}/\text{pulse}$ . Five minutes later a stimulus intensity of  $300 \mu\text{A}/\text{pulse}$  applied to the same locus evoked a suppression of shivering in the latter half of the 30-second stimulation period. Shivering resumed immediately post-stimulation. Five minutes later stimulation of the same locus with a stimulus intensity of  $400 \mu\text{A}/\text{pulse}$  evoked immediate suppression of shivering, and shivering did not

# ROLE OF THE PROSENCEPHALON IN SHIVERING



Schema of Locus

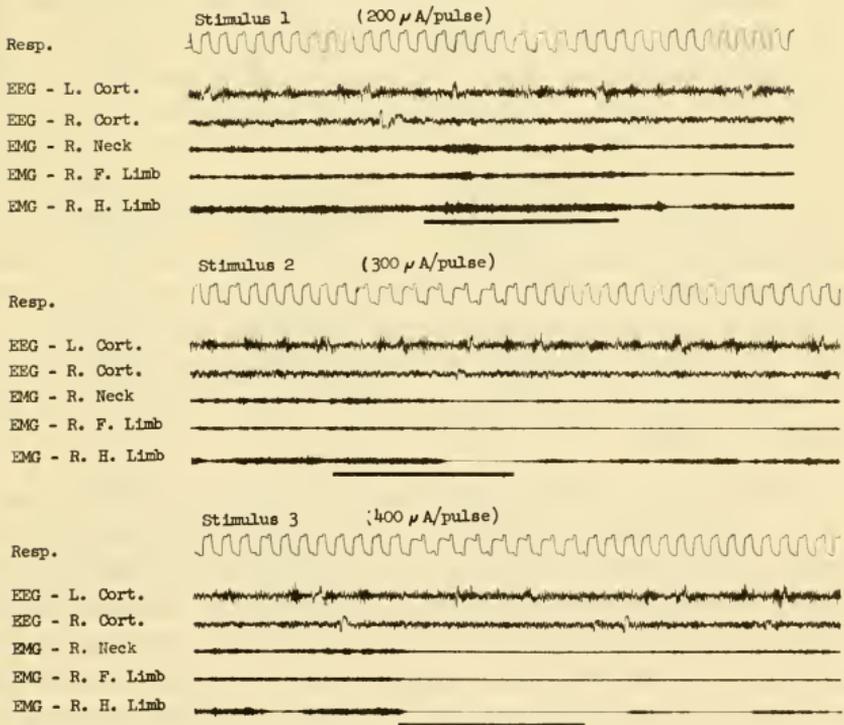


Figure 19. Graded suppression of shivering (Cat No. ST. 22)

become active and continuous until 10 minutes post the cessation of stimulation. In all cases the stimuli had a frequency of 25 pulses/sec and a pulse duration of 1 msec. On the basis of such observations, it was arbitrarily decided to use a stimulus intensity that would evoke the second, rather than the third, suppressive response. Figure 20 illustrates a typical experiment in which spontaneous shivering was suppressed by electrical stimulation. In this experiment on Cat No. ST 22, the stimulus frequency was 25 pulses/sec, the pulse duration 1 msec, and the stimulus intensity  $800 \mu\text{A/pulse}$ . Each fifth minute, a locus was stimulated in the order A, B, C, D, E, and F. As shown, shivering was not suppressed during stimulation of locus A. It was mildly suppressed during stimulation of loci B, D, and E, and strongly suppressed during stimulation of loci C and F.

Figure 21 summarizes the results for 8 cats in which the septum was systematically explored for loci whose activation suppressed shivering. The schemata of Planes A and B and the loci numbers have been described previously. An intermediate frontal plane was systematically explored, but the results are not listed. Similarly, loci were stimulated at 1 mm depths, but the results are not listed for these intermediate loci. In Cats No. ST 19 and ST 31, both the left and right sides of the septum were stimulated. Cat No. ST 19 was under alpha chloralose medication. In Cat No. ST 31, an attempt was made to destroy the right side fornix at a more caudal level one week prior to experimentation to permit degeneration of pre-commissural fornical fibers. In Cats No. ST 27 and ST 29, an attempt was made one week prior to experimentation to destroy the fornix bilaterally at a more caudal level. By "mild suppression" it was meant that shivering stopped for part of the stimulus duration, while in "strong suppression" the activity was suppressed for the entire stimulus duration.

The results indicated that stimulation of ventromedial (loci 7, 8, and 16) and ventrolateral (loci 4 and 12) midseptal and posterior septal regions consistently evoked a suppression of shivering. Stimulation of extreme dorsal regions (loci 1, 5, 9, and 13) tended not to suppress shivering, but some variability of response existed. Stimulation of intermediate regions (loci 2, 3, and 6) suppressed shivering in some cats and not in others. Stimulation of locus 11 never suppressed shivering although stimulation of locus 10 sometimes and locus 12 always suppressed shivering. In every experiment the responses listed were reproducible.

Schema of Loci

1. EEG - L. Cortex
2. EEG - R. Cortex
3. EMG - L. Forelimb
4. EMG - R. Forelimb
5. EMG - L. Hindlimb
6. Stimulus Duration



50  $\mu$ v  
 10 sec.

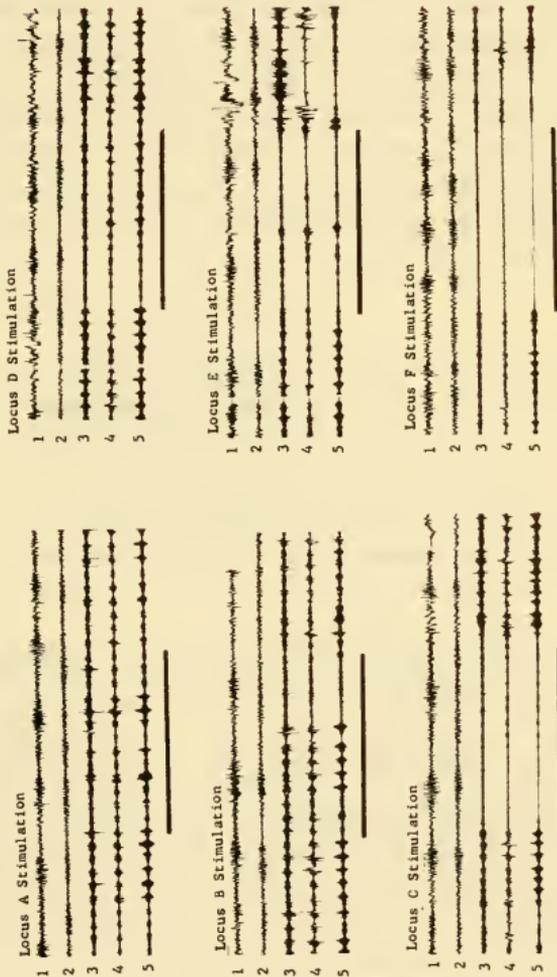


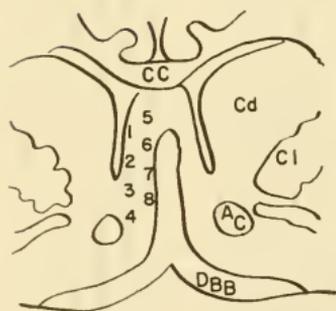
Figure 20. Suppression of shivering during stimulation of various septal loci (Cat No. ST. 22).

CAT NO.	LOCUS															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ST. 12							+	++				++				+
ST. 18	O	++	++	++	O	++	++	++	O	+	O	+	O	+	+	++
ST. 19	L		O	O	O	O	O	+	+	O	+	O	+	O	+	++
	R		O	O	++		O	+	+	O	+	O	++	O	O	O
ST. 20		O	+	++		O	+	++								
ST. 22	O		O	+	O		++	++	O	O	O	++	+	+	+	O
ST. 27*	+	+	++		+	+	+	+								
ST. 29*	O	F	F			+	+	++	O	+	O	++	O	+	O	++
ST. 31†	L	O		+		+		++		O		+		+		++
	R	+		++		O		++		+		++		O		++

O - No suppression  
 + - Mild suppression  
 ++ - Strong suppression  
 F - Facilitation  
 L - Left side stimulation  
 R - Right side stimulation  
 \* - Bilateral fornical destruction  
 † - Right fornix destruction

Schema of Loci

Plane A



Plane B

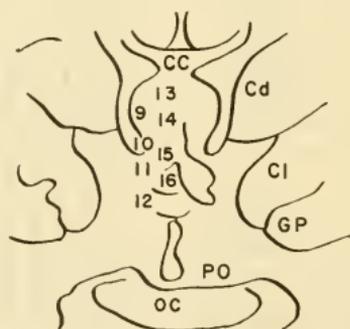


Figure 21. Suppression of shivering during septal stimulation.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

The responses evoked after bilateral fornical destruction were relatively similar to those evoked in cats which the precommissural fornical fibers were intact. Similarly the responses evoked in Cat No. ST 31 were relatively similar for both sides of the brain, even though the right side septum contained degenerated precommissural fornical fibers. Figures 22 and 23 illustrate these facts.

Figure 22 illustrates an experiment on Cat No. ST 29<sup>a</sup>. In this cat an attempt was made to destroy the fornix one week prior to experimentation. The upper right-hand corner photographs illustrate partial left fornix destruction at a slightly more rostral level than more complete right fornix destruction. Loci were stimulated each fifth minute in the order A, B, C, D, and E with stimuli of frequency 25 pulses/sec, 1 msec pulse duration and 300  $\mu$ A/pulse. As shown, shivering was not suppressed by stimulation of loci D and E, mildly suppressed by stimulation of loci A and B, and strongly suppressed by stimulation of locus C.

Figure 23 illustrates partial right fornical destruction in Cat No. ST 31. As shown, stimulation of locus A evoked mild suppression of shivering during left side but not right side stimulation. Stimulation of the more ventrally situated locus B evoked suppression of shivering during both right and left side stimulation. The parameters of stimulation for these responses were a frequency of 25 pulse/sec or pulse duration of 1 msec and a stimulus intensity of 800  $\mu$ A/pulse.

In the above-mentioned experiments the frequency of stimulation ranges from 25 to 100 pulses/sec and the pulse duration from 1 to 3 msec. In four experiments the minimum of stimulus intensities necessary to evoke both strong and mild suppression of shivering at a variety of frequencies and pulse durations were noted. Figure 24 is a schematic representation of the effects of alterations in pulse duration on the intensity of stimulation necessary to suppress shivering in Cats No. ST 32<sup>a</sup> and 34. The stimulus frequency was maintained at 25 pulses/sec. Less intense stimuli were necessary to evoke suppression of shivering at pulse durations of 3 and 5 msec than at 0.5, 1, and 7 msec in both cats. In Cat No. ST 34 this appeared true for both septal and anterior hypothalamic suppression of shivering, although not so detailed observations were made during septal stimulation. However, the intensity of stimulation necessary

Septal Loci

1. EMG - L. Forelimb
2. EMG - R. Forelimb
3. EMG - L. Hindlimb
4. EMG - R. Hindlimb
5. Stimulus Duration

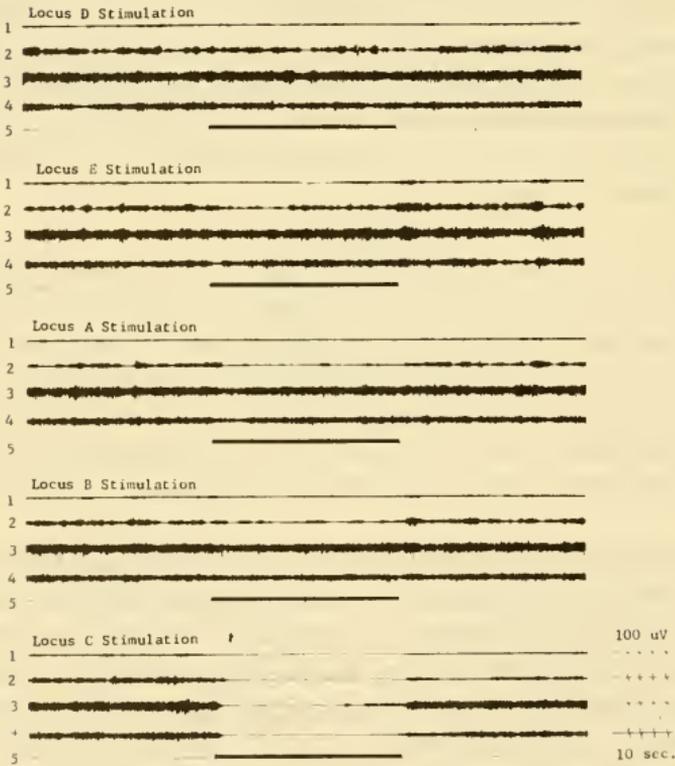
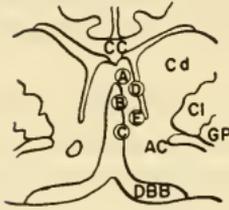
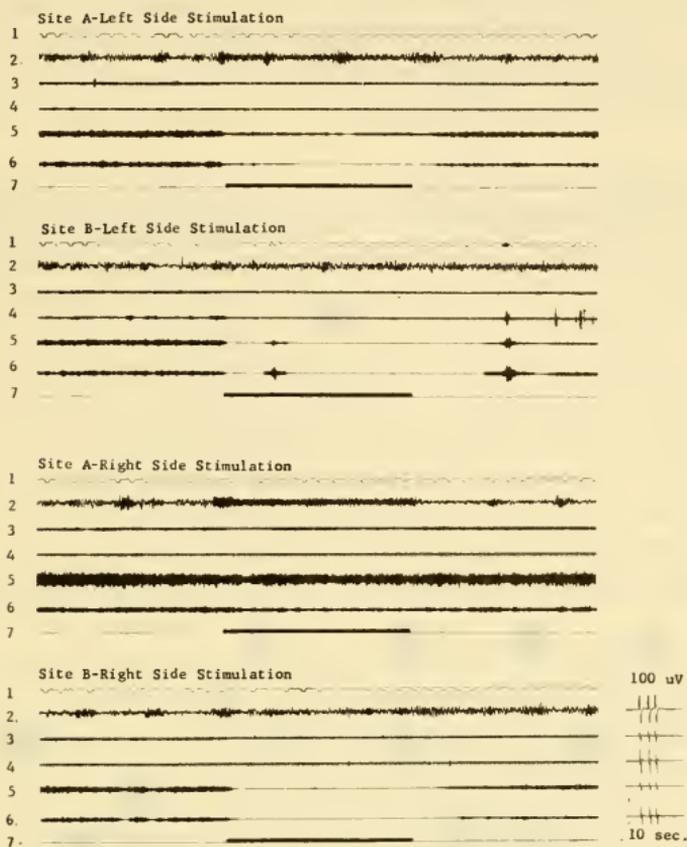


Figure 22. Suppression of shivering during septal stimulation after bilateral fornical destruction (Cat No. ST. 29<sup>a</sup>). Stimuli 25 pulses/sec., 800  $\mu$ A/pulse, 1 msec. pulse duration.

# ROLE OF THE PROSENCEPHALON IN SHIVERING



1. Resp. Rate **367** Schema of Loci  
 2. EEG - R. Cortex  
 3. EMG - R. Forelimb  
 4. EMG - R. Forelimb  
 5. EMG - L. Hindlimb  
 6. EMG - R. Hindlimb  
 7. Stimulus Duration

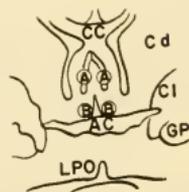


Figure 23. Suppression of shivering during septal stimulation after ipsilateral fornical destruction (Cat No. ST. 31).

All stimuli 25 pulses/sec., 400  $\mu$ A/pulse, 1 msec. pulse duration.

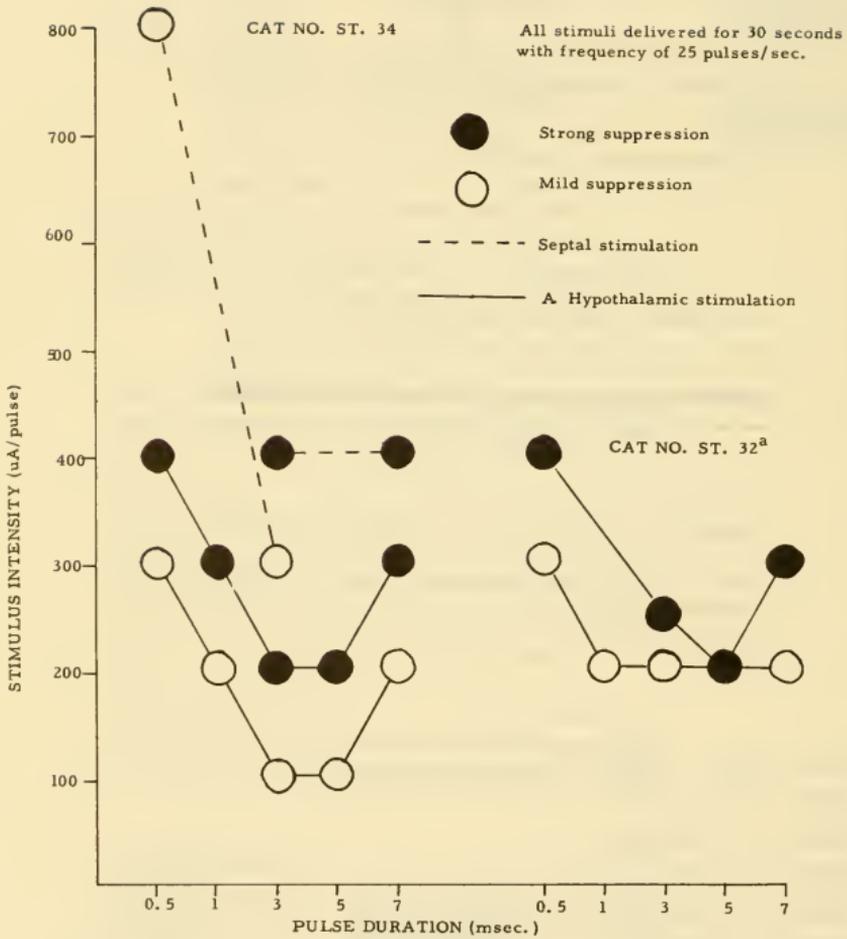


Figure 24. Pulse duration dependent graded suppressive responses.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

to suppress shivering was greater during septal than anterior hypothalamic stimulation. The anterior hypothalamic locus stimulated was within the region found to be most effective in inhibiting shivering (Andersson, 1957; Dworkin, 1930). The septal locus of stimulation was within the ventromedial region of the midseptum.

Figure 25 is a schematic representation of the effects of alterations in stimulus frequency on the intensity of stimulation necessary to suppress shivering. The pulse duration was maintained at 3 msec and the septal and hypothalamic locus stimulated within the previously described regions. In the three cats (ST 32<sup>2</sup>, 33<sup>a</sup>, and 34) less intense stimuli were necessary to suppress shivering at stimulus frequencies of 25, 50, and 100 pulses/sec than at 10 and 200 pulses/sec. In two of the three experiments, stimuli of 100 pulses/sec were less effective than 50 and 25 pulses/sec frequencies. In Cat No. ST 33<sup>a</sup> both septal and anterior hypothalamic loci were stimulated with less intense stimuli needed to suppress shivering during anterior hypothalamic than during septal stimulation.

During experiments on the inhibition of shivering the dorso-medial portion of the posterior hypothalamus was routinely stimulated to illustrate an augmented response. It was observed that ventrolateral posterior hypothalamic stimulation suppressed shivering. Two experiments on Cat No. ST 36 and 37 were conducted to compare the relative stimulus intensities necessary to suppress shivering during anterior and posterior hypothalamic stimulation to the relative stimulus intensities necessary to suppress shivering during septal and anterior hypothalamic stimulation of Cats No. ST 33<sup>a</sup> and ST 34. In Cat No. ST 34 stimulation of a ventromedial mid septal locus suppressed shivering at a stimulus intensity of 400  $\mu$ A/pulse. Stimulation of a supraoptic locus suppressed it at a stimulus intensity of 200  $\mu$ A/pulse, but stimulation of a dorsomedial posterior hypothalamic locus augmented shivering. In all cases loci were stimulated at 5-minute intervals and the frequency of stimulation of 25 pulses/sec with a 3-msec pulse duration.

Figure 26 illustrates the experiment on Cat No. ST 37 that confirmed the results for the experiment on Cat No. ST 36. That is to say, stimulation of anterior and ventrolateral posterior hypothalamic loci suppressed shivering with stimulus intensities of 200 and 150  $\mu$ A/pulse respectively, while stimulation of the dorsomedial

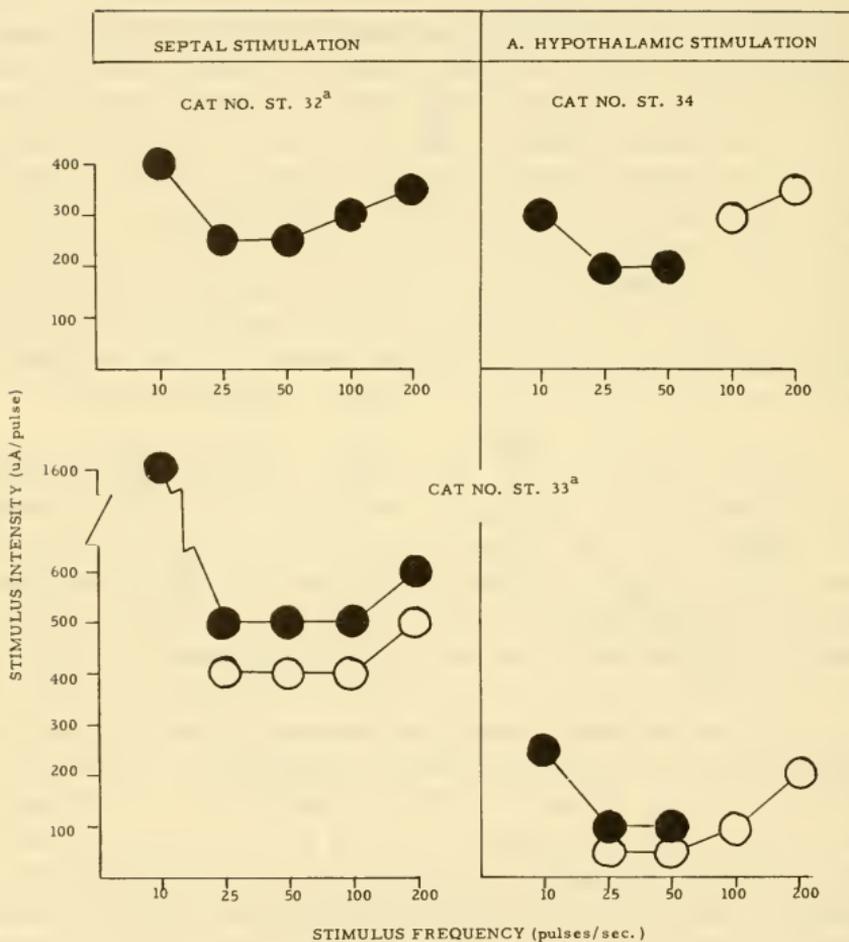


Figure 25. Frequency and locus dependent graded suppressive responses.

# ROLE OF THE PROSENCEPHALON IN SHIVERING

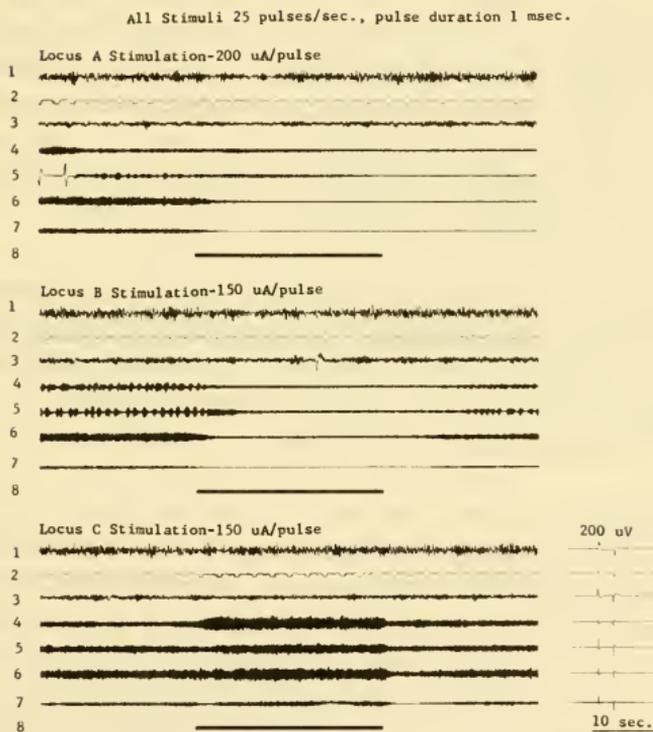
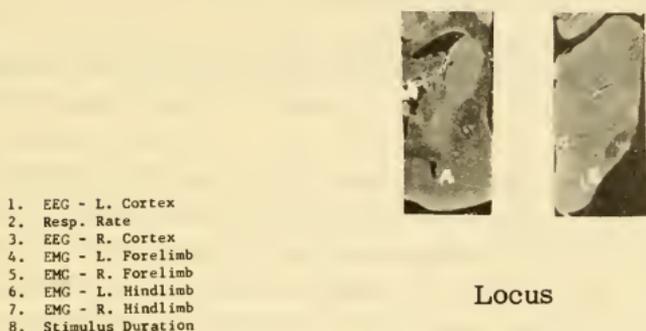


Figure 26. Anterior and posterior hypothalamic stimulation of an anesthetized shivering cat (No. ST. 37).

posterior hypothalamus augmented shivering. Similar results were obtained by stimulating contralateral loci.

The ratio of septal locus stimulus intensity for the suppression of shivering to anterior hypothalamic intensity was 5.0 in Cat No. ST 33<sup>a</sup> and 2.0 in Cat No. ST 34. A similar intensity ratio for ventrolateral posterior hypothalamus to anterior hypothalamus was 1.7 in Cat No. ST 36, 1.0 in Cat No. ST 37 for right side stimulation and 1.5 for left side stimulation. In all experiments in which shivering was suppressed by ventrolateral posterior hypothalamic stimulation, it could be evoked by dorsomedial posterior hypothalamic stimulation.

As with the production of shivering, bilateral suppression of shivering was evoked by ipsilateral stimulation. Variability existed as to the extent to which right and left fore and hindlimb shivering was suppressed either strongly or mildly. No consistent pattern emerged from these experiments. Similarly, some variability existed as to the extent of forelimb vs. hindlimb shivering suppression, but no consistent pattern was evident.

In the above experiments the inhibition of shivering was generally accompanied by a slowing of respiration and heart rate. Alterations in fronto-occipital EEG wave patterns were not obvious during such stimulation, but none of these parameters was systematically studied in the course of these investigations.

Comments. It was previously shown that a higher intensity of stimulation is needed to evoke shivering during septal stimulation than during posterior hypothalamic stimulation. The results on shivering suppression are similar, a higher intensity of stimulus being used to suppress shivering during septal stimulation than during anterior hypothalamic stimulation. Such results are additional physiological confirmation of the known anatomy of caudal septal projections.

The experiments on Cats No. ST 27, 29, and 31, with fornices cut and efferent projections denervated, would suggest that the shivering suppression produced by medial septal stimulation was not due to stimulating fornical fibers passing through the septum to either the hypothalamus or midbrain. However, it is known from

## ROLE OF THE PROSENCEPHALON IN SHIVERING

Kaada's report (1951) that fornical activation can suppress shivering, but it is not known if direct fornical or hippocampal stimulation can facilitate shivering. Thus the relation of septal suppression and facilitation of shivering to the more rostral hippocampal activity is still obscure.

Secondly, the relation of the septum's role in shivering to that of the amygdala is obscure. McLean and Delgarda (1953) suppressed shivering by stimulation of the junction of the rostral amygdala and globus pallidus, and by stimulation of the amygdala's basomedial complex. Koikegami, Hiroshi, and Kimoto (1952) have reported an inhibition of gastric motility when stimulating this complex, but an elevation of body temperature when stimulating the amygdala's lateral complex. Thus it might well be that stimulation of separate amygdaloid structures can either facilitate or suppress shivering. Such impulses could be carried by the direct diffuse amygdaloid connections with the hypothalamus, first described by Fox (1920) or the suppressive impulses could be carried by the stria terminalis to the hypothalamus which Fox (1943) has shown to be efferent from the amygdala and which Ban and Omakai (1959) and Hall (1960) have shown to receive medial, not lateral, amygdaloid projections. It is not known if amygdaloid activity related to shivering influences the septum by way of the diagonal band of Broca. Earlier anatomists considered this band to form two way connections between the amygdala and medial midseptum, but recent work of Lauer (1945), Ban and Omakai (1959), and Hall (1960) would suggest that this tract is afferent to, not efferent from, the amygdala.

Thirdly, our experiments have not separated septal neuron stimulation from stimulation of neocortical projections to the hypothalamus that traverse the septum. Obviously there is a need for further studies on the facilitation and suppression of shivering during septal stimulation in animals in which various single and combined telencephalic structures have been ablated at a time sufficiently before stimulation to permit degeneration of projections to and through the septum. Such experiments, with the exception of the three fornical destruction experiments, were considered beyond the scope of this present study. It has, however, clearly demonstrated instigation, augmentation and suppression of shivering by stimulation of the telencephalon's septum and as such might well

lay the groundwork for an eventual neurological explanation of Gessler and Hansen's (1927) report of the activation and suppression of shivering by hypnotic suggestion and the Russian work, recently reviewed by Bykov (1957), that has illustrated classical Pavlovian conditioning of temperature regulatory responses.

The suppression of shivering by ventrolateral posterior hypothalamic stimulation is in agreement with the previous work from our laboratory reported by Hemingway, Forgrave, and Birzis (1954). (See their Table I and Figure 2.) This locus is within the medial forebrain bundle's projection to and from the midbrain. It seems that stimulation of this locus evokes suppression of shivering, not via the anterior hypothalamus but via a level more caudal than the hypothalamus. This is because the intensity of stimulus necessary to suppress shivering during stimulation of this locus is not greater than that needed during anterior hypothalamic stimulation. Additionally, there are no known connections in the posterior hypothalamus between the ventrolateral and dorsomedial regions that by activation of the suppressive locus could result in attenuation or activity of dorsomedial neurons presumed on the basis of our experiments to be active during shivering.

We have evidence of a second system of suppressive neurons that perhaps originate in the anterior hypothalamus and terminate in the posterior hypothalamus after dorsal periventricular passage. Stimulation of the most medial dorsal posterior hypothalamus suppresses shivering with stimulus intensities greater than those necessary to stimulate the ventrolateral posterior hypothalamus. Since this dorsal region is within that whose activation produces shivering, there was a possibility that the stimulus was disrupting activity related to the production of shivering (Wedensky inhibition). This proved not to be the case in that stimulation of loci 0.25 mm to 0.5 mm more lateral than the third ventricle augmented rather than suppressed shivering. Additionally, shivering could be suppressed at all loci within the dorsomedial posterior hypothalamus with 200 pulses/sec stimuli. Conversely, stimuli of 25 to 100 pulses/sec augmented shivering at all dorsomedial loci except those immediately adjacent to the third ventricle.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

This suggests that the anterior hypothalamus might suppress shivering and depress the posterior hypothalamic neurons which activate the tremor by separate neural pathways. However, we will need additional experimental evidence in order to defend this concept.

In a previous paper from our laboratory, Birz is and Hemingway (1957) reported that shivering was best produced with stimuli of 25 pulses/sec and best suppressed with stimuli of 200 pulses/sec. They cited no experimental results and their concept is in conflict with the results shown in Figures 6 and 25 and the discussion following a recent paper by McLean (1959), all of which suggest the optimal stimulus frequency to be about 50 pulses/sec for septal effector mechanisms.

Time does not permit an adequate recognition of the work of Heath (1953) and McLean (1959), who have illustrated the variety of vegetative and psychological phenomena influenced by the septum. The experiments reported here are but an isolated aspect of septal modulation of hypothalamus functions.

## THE EFFECTS OF SEPTAL LESIONS ON SHIVERING

Methods. Bilateral septal lesions were made in 14 cats. The surgical and postoperative nursing techniques involved were similar to those outlined above.

One animal died 6 days, one 9 days, one 10 days and one 34 days after operation. This last animal appeared normal in all respects except for his refusal to eat spontaneously and his habit of vomiting all force-fed feed. At the time of death, his weight was only 58 percent of the pre-surgery level.

The remaining ten animals were given cold stress tests, sacrificed, and their brains fixed, sectioned, and stained as described above.

Results. In two animals electrodes were inserted into the septum but no current was passed. These animals recovered within a week but were not subjected to cold stresses. Table X lists the ratios of shivering/resting  $\dot{V}O_2$  as determined 26 to 50 days after surgery in the remaining 8 cats. As shown, all these animals could shiver as effectively as the intact cats whose shivering/resting  $\dot{V}O_2$ 's are listed in Table VI. Additionally, the drops in rectal temperature/unit time in 0° C to 5° C environment were within the range shown for intact cats in Table VI. On the basis of these experiments no differences were observed in animals with complete, medial or lateral mid and posterior septal lesions. In Cat No. S 13 both the posterior septal (Fig. 27B) and preoptic (Fig. 27C) regions were destroyed. The preoptic tissue was destroyed to sever the intact anterior septal (Fig. 27A) connection with the diencephalon. Figure 28 shows a bilateral medial septal lesion in Cat No. S 11 and Figure 29 a bilateral lateral septal lesion in Cat No. S<sub>6</sub>. In this latter case possibly the entire posterior septal connection with the diencephalon was destroyed (Fig. 29C).

For the first two weeks after surgery these animals were hypokinetic and made no attempts to escape when their cage doors were left open. They were capable of chewing and swallowing food placed in their mouths but would not eat of their own volition. They did not assume bizarre postures and if compelled to move had normal locomotive control. When tested, all animals had regained their preoperative weights by their own spontaneous eating. One cat, S<sub>14</sub>, refused to eat, vomited tube-fed food, yet was capable of chewing and swallowing food placed in her mouth. This cat died 24 days after surgery with a weight of 1.4 kg., as compared to her preoperative weight of 2.4 kg. From the third day after surgery until death, this cat had normal locomotor movements and a normal body temperature. Due to faulty fixation and presentation the brain was unsuitable for histological inspection, but the extent of tissue destruction was stereotaxically aimed to be similar to Cat S<sub>13</sub>.

Comments. In a recent review of anatomical stimulation and ablation studies of telencephalohypothalamic relationships, Gloor (1956) concluded that the limbic system of the telencephalon "is not critically involved in the integration of the very same somato-autonomic mechanisms which it is apt to influence on electrical stimulation..." His conclusion is well exemplified in these particular

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Lesion	Cat No.	Days Post Surgery	$\dot{V}O_2$ $\frac{\text{shivering}}{\text{resting}}$	Rectal Temperature		
				I.	B.	E. $\Delta$
Mid & Posterior	S <sub>5</sub>	50	3.1	38.8	38.4	38.0
Septum (Total)	S <sub>13</sub>	40	2.7	38.0	37.2	36.6
Mid & Posterior Septum (Lateral)	S <sub>1</sub>	34	3.1	38.6	38.6	37.8
	S <sub>2</sub>	32	3.6	38.6	38.6	38.6
	S <sub>3</sub>	32	1.6*	38.6	38.6	38.6
	S <sub>6</sub>	50	2.3	38.5	38.5	38.2
Mid & Posterior Septum (Medial)	S <sub>10</sub>	26	2.9	38.4	38.4	38.4
	S <sub>11</sub>	26	3.2	38.4	38.4	38.2

\*This animal was hyperactive - the low ratio was due to the high resting  $\dot{V}O_2$ . Shivering was quite vigorous in this cat.

Table X. The Effects of Septal Lesions on the Ratio of Shivering to Resting  $\dot{V}O_2$ . Rectal temperature measured in  $^{\circ}C$ . I. Rectal temperature at room air temperature. B. Rectal temperature 15 minutes after exposure to  $0^{\circ}C$  to  $5^{\circ}C$  air. E. Rectal temperature at end of  $\dot{V}O_2$  determination in  $0^{\circ}C$  to  $5^{\circ}C$  air.  $\Delta$  The drop in rectal temperature per unit time during determination of  $\dot{V}O_2$  in  $0^{\circ}C$  to  $5^{\circ}C$  air. Expressed in  $^{\circ}C/\text{minute}$ .

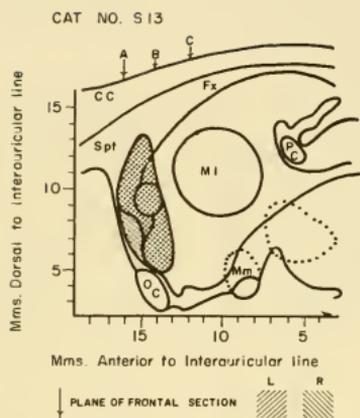


Figure 27. Extent of neural tissue destruction in Cat No. S 13.

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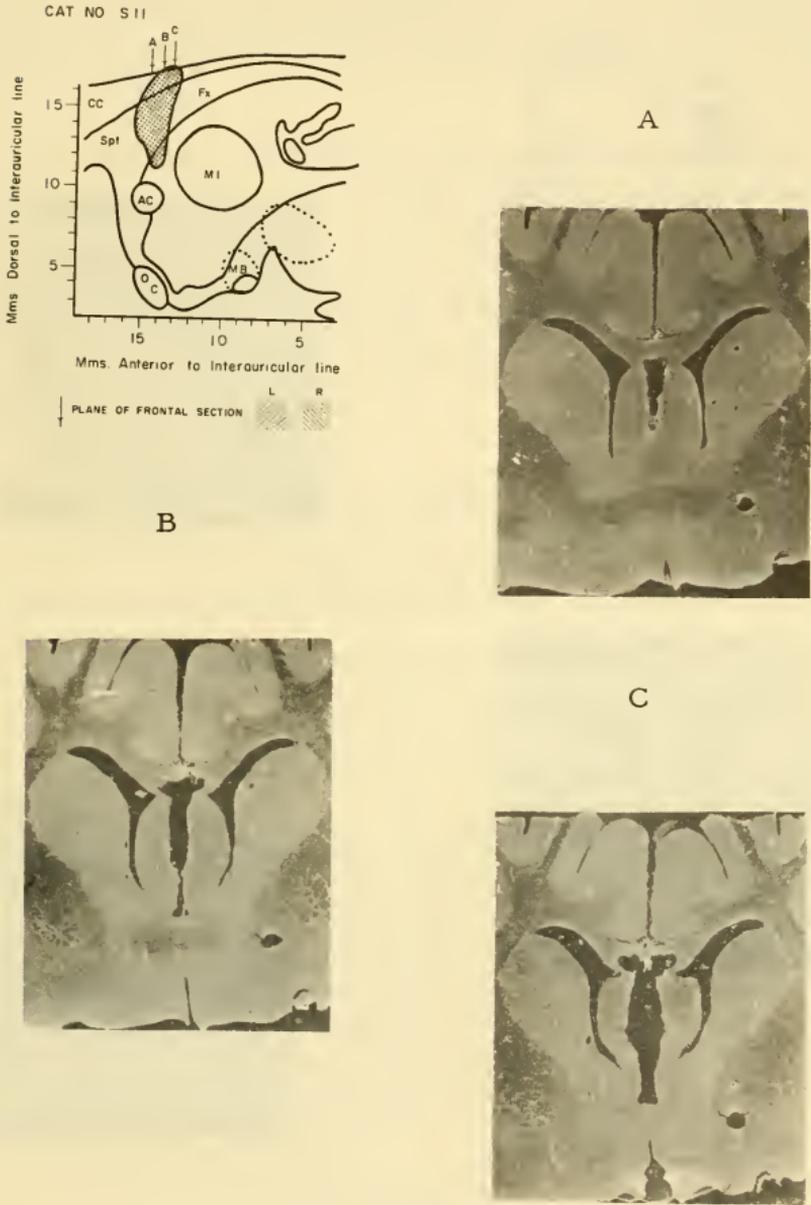
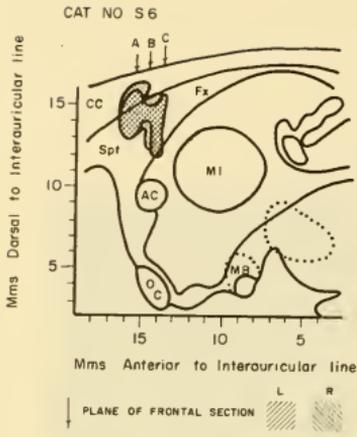


Figure 28. Extent of neural tissue destruction in Cat No. S 11.



B

A



C



Figure 29. Extent of neural tissue destruction in Cat No. S 6.

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studies in that electrical stimulation of a limbic structure, the septum, was shown to affect shivering, yet following ablation of the septum, there was no measureable alteration in shivering's metabolic effectiveness.

The stimulation data indicated with respect to the modulation of shivering, the septum could be separated into medial and lateral regions. It was also mentioned that there is as yet no anatomical basis for assuming efferent lateral septal projections to the posterior hypothalamus and medial projections to the anterior hypothalamus. Additionally, the similar intensity of shivering with medial vs. lateral septal lesions would suggest one of three alternatives:

1. The electrical stimulation data are faulty in suggesting a topographic organization of the septum with respect to shivering.
2. The metabolic method of measuring shivering intensity is too crude to detect subtle differences evoked by septal destruction.
3. The septal influence on the hypothalamus is tonically "silent" only coming into play when either hyperactivated by electrical stimulation or possibly during the formation of reflexes based on classical Pavlovian conditioning or hypnotic suggestions.

My opinion is that the first alternative is acceptable for the posterior septum but not for the midseptum. The second alternative is of little value in this form of experimentation in that shivering intensity waxes and wanes, increasing the oxygen consumption from two to fourfold in the same or a sequence of cats from day to day. The third alternative is the most attractive, but is subject to experimental proof involving the recording of electrical activity of different septal loci in unanesthetized animals during:

1. the nonshivering state.
2. the cold-induced shivering state.
3. the conditioned reflex shivering suppressed state.
4. the conditioned reflex induced shivering state.

Since the last three have never been attempted, the task, though formidable, appears of considerable value in elucidating the role of the telencephalon in such a primarily hypothalamic controlled phenomenon such as shivering.

SUMMARY

The results may be summarized as follows:

(1) Decerebrate cats cannot shiver in the cold but can make tremulous spasmodic movements of limited metabolic effectiveness during rapid cooling. Such movements are more a response to a nociceptive stimulus than a form of organized temperature regulating response.

(2) The intensity of shivering in decorticate cats is depressed for a short time after surgery even when such animals are "autonomically" hyperactive. Within four post-operative weeks the autonomic hyperactivity ablates and shivering returns to its pre-operative intensity. It is thus concluded that the net telencephalic influence on shivering is not inhibitory but either a balance of inhibiting and facilitating influences or neither.

(3) Normal shivering involves the integrity and activation of the dorsomedial posterior hypothalamus. Cutaneous vasoconstriction is controlled by neurons within the dorsolateral posterior hypothalamus.

(4) Shivering can be both instigated and suppressed by septal stimulation with higher stimuli intensities than are necessary to evoke or suppress shivering during hypothalamic stimulation.

(5) Shivering can be suppressed by ventrolateral posterior hypothalamic stimulation, and it seems that this suppression is mediated at a more caudal level than the hypothalamus.

These results suggest that septal modulation of shivering is secondary to hypothalamic control of the function. There are probably other secondary control systems within the telencephalon that can also facilitate and suppress shivering by modifying hypothalamic activity. This is suggested by the fact that not all telencephalic

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projections to the hypothalamus traverse the septum. I would like to suggest that study of these secondary telencephalic control systems is as important as study of the primary control systems in that it may lead to an understanding of how man's attitudes, moods and emotions can modify temperature regulatory mechanisms. Obviously many experiments must be designed and executed before we can hope to understand the neurology of temperature regulatory responses evoked by hypnosis and classical Pavlovian conditioning. In such a context, the work here reported with respect to septal versus hypothalamic control of shivering is a minute aspect of the much broader problem of how the higher nervous system can modulate functions primarily controlled by the hypothalamus.

That these results have implicated the dorsomedial region of the posterior hypothalamus in the production of shivering and the dorsolateral region in cutaneous vasoconstriction is of value in offering an explanation of the many seemingly diverse results in the literature. However, it tells us little more about the physiology of shivering.

However, by localizing control of shivering to a specific region of the brain, it should be possible to implant micro-electrodes and monitor the activity of single neurons whose function is related to the production of shivering. If we can next discover cells within the hypothalamus whose role is blood temperature detection and if we can further find cells in the thalamus and/or hypothalamus whose role is detection of skin temperature, then we can begin to study the adequate physiological stimulus necessary to evoke shivering. Obviously before one can study the neurogenesis of a function, the neural regions involved in affective and effective aspects of the function must be localized. It is in this context that these experiments reported today may be of some value to a future investigation of the neurogenesis of shivering.

In conclusion I would like to thank the Arctic Aeromedical Laboratory for the privilege of attending and addressing this symposium. The aim of Dr. Hemingway's UCLA group has been to utilize a variety of neurophysiological techniques in studies of the physiology of body temperature regulation. It has been a privilege to work in this laboratory under Dr. Hemingway's guidance, which is deeply

appreciated. Dr. Walter Freeman's encouragement in the transection experiments is also appreciated, as are Dr. Yojiro Kawamura's most valuable contributions to the design and execution of the stimulation experiments.

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### DISCUSSION

DR. FREEMAN: You are familiar with the experiments in which electrodes are implanted in the septal and hypothalamic areas whereby animals can be induced to stimulate their own brains, as power to avoid this self stimulation. I wonder, one often hears phrases as "trembling with joy" and "quaking with fear." How do you think such manifestations of tremor activity are related to the shivering process?

DR. STUART: First, we must distinguish between pathological tremors that are 4 to 7 cycles/sec, in which the agonist-antagonist activity is alternating, and the 9 to 11 cycles/sec shivering tremor, in which the agonist-antagonist activity is synergistic. Physiological tremor (e.g., finger tremor) is also 9 to 11 cycles/sec in the adult but slower in youngsters, and to my knowledge there is no information as to whether or not it is an alternating or synergistic tremor. I do not think anyone has ever subjected "trembling with joy" or "shaking with fear" to neuromuscular examination, but I would think they are more closely allied to hypothalamically-induced shivering than to non-hypothalamically induced pathologic tremor. There is, of course, one difference in that shivering accomplishes something for the animal (i.e., an increase in heat production without an increase in external work), whereas the tremors you mention seem of little biological value. I would like to add that Dr. Kawamura and I have produced alternating tremor by stimulation of a prosencephalic locus that is anatomically different from those loci whose stimulation evoked shivering. Additionally, Dr. Hemingway, Dr. George, and I recently completed some experiments that demonstrated that reserpine blocks shivering but produces an alternating tremor, whereas atropine, which is known to block pathologically induced alternating tremor, has no effect on shivering.

DR. FREEMAN: In other words, you draw a period of distinction between pathological tremors which are not related to shivering and other physiological tremors?

DR. STUART: Yes, but the differences between physiological tremor (microvibration) and shivering are more obscure. My personal feeling (subject to experimental confirmation) is that shivering is a cold-induced exaggeration of the amplitude of the neurological component of physiological tremor. Dr. Earl Eldred and I are particularly interested in patterns of alpha and gamma motorneuron and muscle receptor discharges during diverse tremors. The literature on some aspects of this will be reviewed shortly (Stuart, D. G., E. Eldred, and Y. Kawamura. Neural regulation of the rhythm of shivering. In "Temperature - Its Regulation and Control in Science and Industry." C. M. Herzfeld (ed.) Washington, Reinhold Publishing Corp. In press 1961). I feel your question is most pertinent but cannot be answered satisfactorily until more experimental evidence has accumulated.

DR. CLARK: I would like to mention the figure that I showed of one of Keller's dogs. It has a lesion that fits in beautifully with what you have been saying because it went much further dorsal medially than it did laterally, so it would spare those crosshatch areas you have outlined in your drawing but would have hit the medial ones.

DR. STUART: With respect to the role of the hypothalamus in shivering, I believe that the data from our laboratory are in agreement with Keller's data.

DR. CLARK: And that dog, of course, could pant but could not shiver.

DR. MINARD: I would like first of all to express my great appreciation to the laboratory and to the speakers for a very illuminating two and a half days. There are two statements I would like to make just to throw them out for possible criticism or disagreement; and the reason I am doing this is because there will be some studies reported from the Naval Medical Research Institute on humans in which these two statements are fairly basic in the interpretation of the results. The first of these statements is that the posterior hypothalamus is blind to temperature; that is, that it has not been possible to elicit responses by changing the temperature of the posterior hypothalamus. The second of the two statements is that in a shivering animal, heating of the anterior hypothalamus will

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inhibit shivering. Now, if these two statements are incorrect, I should like to know about it now, before I take this information back to the laboratory.

DR. STUART: In reply to your second statement, a report of the suppression of shivering by heating the anterior hypothalamus is not new. It was reported by Magoun and co-workers in 1938, by Hemingway and co-workers in 1940, and more recently by Ström and co-workers, and Freeman and Davis. Today I have reported the suppression of shivering during septal, anterior and posterior hypothalamic stimulation. The suppression during septal stimulation and the comparison of stimulus intensities at the three loci is new information, but the suppression during electrical stimulation of the anterior hypothalamus confirms the previous work of Hemingway, Forgrave and Birzis and Andersson, Grant and Larsson. Therefore, there is nothing in this work to conflict with your second statement.

Your first statement that the posterior hypothalamus is blind to temperature has no direct relation to these experiments which are concerned with localization of neural regions related to the efferent (motor) arm of shivering rather than the reception of temperatures. However, I would like to comment on your statement to the extent that it relates to a neurophysiological problem and involves neurophysiological techniques of investigation. The experimental evidence on which you base your statement involves, I believe, gradient calorimetry and very accurate measurements of temperature at various body sites. Such experiments have obviously been of great value, but before accepting the fact that the posterior hypothalamus is blind to temperature, I would expect reasonable experimental evidence showing that the firing pattern of single hypothalamic neurons is reversibly altered by cooling and warming, and evidence that such neurons are in the anterior hypothalamus and not the posterior hypothalamus. Since an animal with anterior hypothalamic lesions can shiver, it might well be that third or second order skin temperature neurons impinge upon posterior hypothalamic neurons and that their discharge is capable of instigating and maintaining shivering. None of these things have ever been demonstrated and they will, I believe, involve microelectrode experimentation.

DR. FREEMAN: The only evidence that I know that bears directly on this is the series of attempts that Davis and I made to heat and

cool directly in the posterior hypothalamus as distinct from the anterior hypothalamus. The results we got were not as clear-cut by any means as results we got from the stimulation anteriorly. I believe one can sum the case up by saying that the term you used, "blind," is not adequately descriptive. One must think of sensitivity to thermal changes in two contexts: one in which the sensitivity is either specifically related to a sense organ or sensory receptor as Dr. Hensel described, and the other in which any physical event can alter neuro-function. Presumably, these nerve cells in the posterior hypothalamus are like any others. If you cool them off enough, their activity will be impaired. If you heat them up enough, it may be increased for a while, but eventually it will be impaired. Therefore, in the physiological range of body temperature or brain temperatures of 35° C to 41° C, one would be willing to say, under most circumstances, there is no thermosensitivity, but outside of this range, there may be critical thermosensitivity in the sense that gross impairment of function of these cells may take place.

DR. MINARD: Thank you very much.

DR. HEMINGWAY: I may add one thing to that. Many years ago as Dr. Stuart mentioned, I heated the anterior hypothalamus with surface electrodes, and also the posterior hypothalamus. Heating the anterior hypothalamus would cause instantaneous cutaneous vasodilatation and shivering would stop, but there was no effect whatsoever on temperature regulation when the posterior hypothalamus was heated. One interesting thing occurred, which I am not sure was significant: the animals went to sleep immediately upon heating the posterior hypothalamus, but there is no rectal temperature regulation.

DR. HENSEL: We found the same result as did Dr. Freeman. As yet, we have seen only these reactions during cooling the anterior hypothalamus, but I would agree completely with your statement that there is no tissue in the body which is completely blind to temperature, of course. It is a matter of qualitative activity and of the direction. Some are excited and some are inhibited.

DR. MINARD: You might say compared to the anterior hypothalamus, it is relative.

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DR. HENSEL: You can see it also in the receptors. I think there are more receptors reacting to temperature than blind to temperature, but the question is the quantitative sensitivity.

DR. HEMINGWAY: May I add one more thing? This work of Stuart's was designed to explain the findings of Andersson. He did find this interesting thing, that in the posterior hypothalamus there is a region which when stimulated produces shivering and it is much more sensitive than any other part of the hypothalamus. But in the septal region where Andersson was working, it is possible to find both inhibition and facilitation of shivering. And, an interesting thing, of course, you can take out this entire septal region with no effect on shivering.

REFERENCES

1. Adams, T. and B. C. Covina. Racial variations to cold stress. *J. App. Physiol.* 12:9, 1958.
2. Akert, K. and F. Kesselring. Kaltezittern als Zentrale Reiz-effect. *Helv. physiol. pharmacol. Acta* 9:290, 1951.
3. Andersson, B. Cold defense reactions elicited by electrical stimulation within the septal area of the brain in goats. *Acta physiol. scandinav.* 41:90, 1957.
4. Andersson, B., R. Grant, and S. Larsson. Central control of heat loss mechanism in the goat. *Acta Physiol. Scandinav.* 37:261, 1957.
5. Andersson, B. and N. Persson. Pronounced hypothermia elicited by prolonged stimulation of the "heat loss centre" in unanesthetized goats. *Acta Physiol. Scandinav.* 41:277, 1957.
6. Andersson, B., N. Persson and L. Strom. Post-stimulatory electrical activity in the pre-optic "heat loss centre" concomitant with persistent thermoregulatory response. *Acta Physiol. Scandinav.* 50:54, 1960.
7. Aring, C. D. Shivering and the cerebral cortex. *Am. J. Physiol.* 113:3, 1935.
8. Ban, T. and F. Omakai. Experimental studies in the fiber connection of the amygdaloid nuclei in the rabbit. *J. Comp. Neurol.* 113:245, 1959.
9. Barbour, H. G. Hypothalamic control of water movement in response to environmental temperatures. *Ass. Res. Nerv. and Ment. Dis.* 20:449, 1939.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

10. Bard, P. Temperature regulation in chronically decorticate cats and dogs and in decerebrate cats. In *Temperature*, American Institute of Physics, to be published in 1961.
11. Bard, P. and M. B. Macht. The behavior of chronically decerebrate cats. Chap. 4 in *Neurological Basis of Behavior* (edited by G. E. W. Wolstenholme and C. M. O'Connor) Little, Brown, and Co., Boston, 1958.
12. Bazett, H. C. and W. G. Penfield. A study of the Sherringtonian decerebrate animal in the chronic as well as the acute condition. *Brain* 45:185, 1922.
13. Bazett, H. C., B. J. Alpers, and W. H. Erb. Hypothalamus and temperature control. *Arch. Neurol. and Psych.* 30:728, 1933.
14. Benzinger, T. H. The sensory receptor organ and quantitative mechanism of human temperature control in warm environment. *Fed. Proc.* 19, Suppl. 5:32, 1960.
15. Birzis, L. and A. Hemingway. Descending brain stem connections controlling shivering in cats. *J. Neurophysiol.* 19:37, 1956.
16. Birzis, L. and A. Hemingway. Shivering as a result of brain stimulation. *J. Neurophysiol.* 20:91, 1957.
17. Birzis, L. and A. Hemingway. Efferent brain discharge during shivering. *J. Neurophysiol.* 20:156, 1957.
18. Blair, J. R. and A. D. Keller. Complete and permanent elimination of the hypothalamic thermogenic mechanism without affecting the adequacy of the heat loss mechanisms. *J. Neuropath.* 5:240, 1946.
19. Bond, D. D., T. Clark, M. D. Randt, G. Bidder, and V. Rowland. Posterior septal fornical and anterior thalamic lesions in the cat. *Arch. Neurol. and Psych.* 78:143, 1953.

20. Bykov, K. M. *The Cerebral Cortex and the Internal Organs.* (translated and edited by W. H. Gantt) Chemical Publishing Co., New York, 1957.
21. Carpenter, M. B. *The neuro-anatomical basis of dyskinesia.* Chap. II, *Pathogenesis and treatment of Parkinsonism.* (edited by W. S. Fields), Chas. C. Thomas, Springfield, 1958.
22. Chatonnet, J. *Nervous pathways in the chemical regulation against cold.* This symposium.
23. Clark, G., H. W. Magoun, and S. W. Ranson. *Hypothalamic regulation of body temperature.* *J. Neurophysiol.* 2:61, 1939.
24. Dusser de Barenne, J. G. *Recherches experimentales sur les fonctions du systeme nerveux central faites en particulier sur deux chats dont le neopallium avait été enlevé.* *Arch. neerland. Physiol.* 4:31, 1920.
25. Dworkin, S. *Observations on the central control of shivering and heat regulation in the rabbit.* *Am. J. Physiol.* 93:227, 1930.
26. Eliasson, S. and G. Ström. *On the localization in the cat of hypothalamic and cortical structures influencing cutaneous blood flow.* *Acta Physiol. Scandinav.* 20, Suppl. 70:113, 1950.
27. Folkerts, J. F. and E. A. Spiegel. *Tremor on stimulation of the midbrain tegmentum.* *Neurol. Conf.* 13:193, 1953.
28. Fox, C. A. *Certain basal telencephalic centers in the cat.* *J. Comp. Neurol.* 72:1, 1920.
29. Fox, C. A. *The stria terminalis, longitudinal association bundle and precommissural fornix fibers in the cat.* *J. Comp. Neurol.* 79:277, 1943.
30. Frazier, C. H., B. J. Alpers, and F. W. Lewy. *The anatomical localizations of the hypothalamic center for the regulation of temperature.* *Brain* 59:122, 1936.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

31. Freeman, W. J. and D. D. Davis. Effect on cats of conductive hypothalamic cooling. *Am. J. Physiol.* 197:145, 1959.
32. Fuster, J. M. and S. J. Weinberg. Bioelectrical changes of the heart cycle induced by stimulation of diencephalic regions. *Exp. Neurol.* 2:26, 1960.
33. Gessler, H. and K. Hansen. Über die suggestive Beeinflussbarkeit der Wärmeregulation in der Hypnose. *Dtsch. Arch. f. Klin. Med.* 156:352, 1927.
34. Gloor, P. Telencephalic influences on the hypothalamus. Chap. VI in *Hypothalamic-Hypophysial Interrelationships* (edited by W. S. Fields) Chas. C. Thomas, Springfield, 1956.
35. Hall, E. Efferent pathways of lateral and basal nuclei of the amygdala in the cat. *Anat. Rec.* 136:205, 1960.
36. Hammel, H. F., J. D. Hardy, and M. M. Fusco. Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. *Am. J. Physiol.* 198:481, 1960.
37. Heath, R. G. *Studies in Schizophrenia.* Harvard University Press, Cambridge, 1953.
38. Hemingway, A., P. Forgrave, and L. Birzis. Shivering suppression by hypothalamic stimulation. *J. Neurophysiol.* 17:375, 1954.
39. Hemingway, A., T. Rasmussen, H. Wickoff, and A. T. Rasmussen. Effects of heating the hypothalamus of dogs by diathermy. *J. Neurophysiol.* 3:329, 1940.
40. Hensel, H. Recent advances in thermoreceptor physiology. This symposium.
41. Hess, W. R. *The Functional Organization of the Diencephalon.* Greene and Stratton, New York, 1957.

42. Isenschmid, R. and L. Krehl. Über den Einfluss des Gehirns auf die Wärmeregulation. Arch. f. exper. path. 70:109, 1912.
43. Isenschmid, R. and W. Schnitzler. Beitrag zur Lokalisation des der Wärmeregulation verstehenden Zentralapparat in Zwischenhirn. Arch. exp. path. pharmak. 76:202, 1914.
44. Jacobson, F. H., P. H. Craig, and R. D. Squires. Cessation of shivering following forebrain lesions in anesthetized cats. Fed. Proc. 19:44, 1960.
45. Jenkner, F. L. and A. A. Ward, Jr. Bulbar reticular formation and tremor. Arch. Neurol. and Psych. 70:489, 1953.
46. Kaada, B. R. Somatomotor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. Acta Physiol. Scandinav. 24, Suppl. 83, 1951.
47. Keller, A. D. The separation of heat loss and heat production mechanisms in chronic preparations. Am. J. Physiol. 113: 78, 1935.
48. Keller, A. D. Neurologically induced physiological resistance to hypothermia. Ann. N. Y. Acad. Sc. 80:457, 1959.
49. Keller, A. D. and W. K. Hare. The hypothalamus and heat regulation. Proc. Soc. Exp. Biol. Med. 29:1069, 1932.
50. Koikegami, H., H. Hiroshi and A. Kimoto. Studies of the functions and fiber connections of the amygdaloid nuclei and periamygdaloid cortex. Experiments on gastrointestinal motility and body temperature in the cat. Fol. Psych. and Neurol. Japonica 6:76, 1952.
51. Kundt, H. W., K. Bruck and H. Hensel. Das Verhalten den Hautdurchblutung bei Kühlung des Vorderen Hypothalamus. Naturwissenschaften 44:496, 1957.

## ROLE OF THE PROSENCEPHALON IN SHIVERING

52. Lauer, E. W. The nuclear pattern and fiber connections of certain basal telencephalic centers in the Macaque. *J. Comp. Neurol.* 82:215, 1945.
53. Liebermeister, K. Physiologische Untersuchungen über die quantitativen Veränderungen der Wärmeproduction. *Arch. f. Anat. u. Physiol.* p. 520, 1860.
54. Magoun, H. W., F. Harrison, J. R. Brobeck, and S. W. Ranson. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* 1:101, 1938.
55. McLean, P. D. The limbic system with respect to two basic life principles. *The Central Nerv. System and Behavior, Transactions of the Second Conference* (edited by M. A. B. Brazier), Josiah Macy Jr. Foundation, New York, 1959.
56. McLean, P. D. and J. M. R. Delgado. Electrical and chemical stimulation of fronto-temporal portion of limbic system in the waking animal. *E. E. G. and Clin. Neurophysiol.* 5:91, 1953.
57. Nauta, W. Hippocampal projection and related neural pathways to the mid-brain of the cat. *Brain* 81:207, 1958.
58. Ott, I. The thermogenic center in the tuber cinereum. *Med. Bull.* 17:246, 1895.
59. Pinkston, J. O., P. Bard, and D. Rioch. Responses to changes in environmental temperature after removal of portions of the fore-brain. *Am. J. Physiol.* 109:515, 1934.
60. Pribram, K. H. and L. Kruger. Functions of the "olfactory brain". *Ann. N. Y. Acad. Sc.* 58:109, 1954.
61. Ranson, S. W. and H. W. Magoun. The hypothalamus. *Ergebn. Physiol.* 41:56, 1939.
62. Richet, C. La frisson comme appareil de regulation thermique. *Compte. Rend. Soc. de Biol.* 44:896, 1892.

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63. Scholander, P. F., H. T. Hammel, J. S. Hart, D. H. Messurier, and J. Steen. Cold adaptation in Australian aborigines. *J. Appl. Physiol.* 13:211, 1958.
64. Sprague, J. D. and M. Meyer. An experimental study of the fornix in the rabbit. *J. Anat.* 84:354, 1950.
65. Wycis, H. T., E. G. Szekely and E. A. Spiegel. Tremor on stimulation of the mid-brain tegmentum after degeneration of the brachium conjunctivum. *J. Neuropath. and Exp. Neurol.* 16:79, 1957.
66. Wyndham, C. H. and J. F. Morrison. Adjustment to cold of bushmen in the Kalahai Desert. *J. Appl. Physiol.* 13:219, 1958.

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### EPILOGUE

DR. HANNON: There is one final thing in our Symposium. We have been talking a lot about the maintenance of body temperature. Dr. Irving, from Arctic Health Research Laboratory, has brought out the term "peripheral heterothermy." Would you care to give us a few words, Dr. Irving?

DR. IRVING: First, I want to express my thanks to Colonel Quashnock for the gracious manner in which he represented himself and the Air Command as our host, to Pat Hannon for his kindness in inviting me here for the extremely interesting program that has been presented, and to you, my friends and colleagues, I want to express my gratitude for having been introduced through your discussions to subjects which were rather strange to me, for I usually look only at the periphery of animals. You have indicated some remarkable physiological complexities and some of the methods by which the warm-blooded animal system for communicating information is able to apply its very large capability for converting energy to the purpose of maintaining its individuality and specificity.

I think that references to warm-blooded animals, as distinct from those that are cold-blooded, should emphasize the large order of the disposable conversion of energy that the warm-blooded animals have in comparison with cold-blooded animals. I think we should also consider that from time to time, the central body temperature of the warm-blooded animals may rise three degrees or so, and that it regularly falls half a degree or a degree during sleep. Schmidt-Nielson's thirsty camels even elaborated this ability to modify the body's temperature to a cooling of some six degrees during the night time, making a total range of nine or ten degrees diurnally in an undoubtedly homeothermous animal.

Animals which are covered with fur and fat utilize their insulation. These materials are, however, inflexible insulators and animal producers of heat must utilize some variable insulator for the dissipation of heat. In cold climates this is effected by large variations in the temperature of the exposed extremities.

One of the interesting examples of heterothermous tissues that John Krog and I observed was the foot of the seagull which, while

its body temperature was around  $41^{\circ}\text{C}$ , maintained visibly active circulation in the thin web of the foot when it was kept on a cold plate so that the tissue temperature recorded by a thermocouple was close to freezing. We have a number of examples of that sort: the tail of the muskrat which John Krog and I observed and which Kjell Johansen plans to observe further, cools in ice water to near that temperature while the central part of the animal's body is  $38^{\circ}\text{C}$  warmer.

There are other examples of this variation in tissue temperature according to topographical anatomy as well as according to time. In recent work I studied a cold-acclimatized student who wears only a thin robe in Alaska, winter or summer. I was able to observe him last winter as he sat for an hour in a cold freezing room with only the light clothing that he had on when he was here yesterday. During much of that time, his toes and those of a colleague of his similarly lightly clothed remained at temperatures below ten degrees, and yet during that time they did not complain of pain. By their report of sensitivity to touch and their report of warming one toe as compared with another during the cyclic rewarming process, it was indicated that tolerance of cold was accompanied not by insensitivity but perhaps by even refined sensitivity and careful monitoring, both conscious and unconscious, of the thermal state in their tissues.

What happens to the information system operating with thermolabile components? I have recently been making observations on the detection of impact of small drops of mercury falling through a given distance and found that after a bit of practise I could get a regular threshold for the perception of the kinetic energy of the just detectable impact when my finger was at  $35^{\circ}\text{C}$ . But when the finger was cooled to about  $22^{\circ}\text{C}$ , the kinetic energy required to produce a detectable impact was elevated some five or six times. For some weeks in successive trials, the relation between temperature and threshold remained regular.

We are thus presented with a problem incidental to thermal regulation which may provide a valuable clue to the nature of the communicating system by which animals maintain their integrity: how is it that the communication is effected through an extraordin-

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arily labile system, and yet ends up with retention of central information that is consistent with the steady existence of individuals and species.

I mention these things by way of digression from the theme of your program because in a meeting like this, I suppose that we do not have to end up with a consensus of opinion. I believe that we have rather complete accord as to the value of many different opinions about physiology, and I find that pleasant, stimulating, and hopeful.









