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Hypothalamus and the central control of body temperature

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THE HYPOTHALAMUS AND THE CENTRAL CONTROL OF BODY TEMPERATURE

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In cold-blooded animals, such as amphibia and those fishes which are permanently poikilothermic, internal temperature is practically equivalent to environmental temperature. These animals are not without some inherent device for preventing too great a rise or fall in temperature, but the adaptation of internal to external temperature, although linked to metabolic activities and aided by the chromatophores in the skin under central nervous influence, is too imperfect to be of great value in any extreme variation of climate.

In higher phyla such as birds and mammals, thermoregulation is more complex and possesses the irrefutable advantage of freeing the animal from the direct effects of variations in environmental temperature. Homiothermia, or this regulation of internal temperature at a higher level and much narrower range regardless of wide fluctuations in external temperature, is an evolutionary advance. Between the higher mammals and the lower forms are the monotremes, whose internal temperature, while notably lower than that of mammals generally, is above that of the external air and relatively constant. (Martin, 1903; Pike and Scott, 1915; Morrison, 1946)

Somatic Responses to Variations in Environmental Temperature. The constancy of body temperature depends upon the maintenance of a balance between the heat production and the heat loss of the animal body. The former depends upon the metabolic activity of the tissues alone, the latter on both physiological and physical factors. As far as heat flow from the internal tissues to the skin surface is concerned, we deal with physiological variables; beyond that point, in the heat flow through the clothing to the surrounding air, with physical factors which are largely beyond immediate physiological control.

The function of temperature regulation is not completely developed at birth (when the newborn babe is relatively poikilothermic), nor is that of the adult free from considerable limitations. The progress of its development in children (that is, the increasingly integrated control by the autonomic nervous system) is shown by an increasing constancy in the diurnal cycle, leading to a definite establishment in the second year, even though the range remains still greater than that of adults for several years.

Hardy and Oppel, studying peripheral heat and cold receptors, have shown that radiations of different wave

lengths are effective in producing temperature sensation only in proportion to their absorption by the skin. Since the non-penetrating radiation is the most effective, the depth of the end-organs in the skin must be unimportant. The heat regulatory receptors are provided with more than adequate sensitivity, responding to temperature differences of less than one-tenth degree Centigrade. There is spatial integration by the impulses from the skin as evidenced by the lowering of threshold intensity in irradiating a larger area of skin. The number of cold end-organs is greater than that of heat end-organs, but the spatial summation is poorer, and the threshold more than five times as great as for heat end organs. (Burton 1939) Gellhorn (1938) reports a decrease in errors of localization of warmth stimulation when tactile heat simulation is used instead of radiation, even though no conscious touch sensation is produced.

Geblewicz, studying temporal summation, finds that sensation reaches its plateau in from three to twenty seconds. He finds, paradoxically, that comparing the intensity of stimuli of short duration with a constant stimulus giving rise to the same sensation shows that the maximum effect is reached sooner, the less intense

the stimulus (1937). However, using two successive stimuli separated by a variable interval, he found the thermal receptors behave similar to the visual receptors. (1939) Woll has found that repeated applications of cold (ten degrees Centigrade) to the skin diminishes selectively the thermal discrimination of cold.

Physical regulation. Heat is lost from the body by the following mechanisms: radiation, convection, conduction, evaporation of water from the lungs and skin, raising the inspired air temperature to body temperature, and elimination of urine and feces. Under ordinary conditions, over ninety-five per cent of the total heat loss occurs through radiation, convection, conduction and evaporation. Hardy and DuBois give sample figures for partitioning of total heat loss as follows:

radiation	58%
convection	15%
vaporization	27%

Of course, these vary widely with environmental conditions (Hardy and DuBois, 1940).

The loss of heat by radiation, convection and conduction varies with the air temperature, humidity and movement, the nature and amount of clothing and the quantity of heat produced within the body (metabolism).

The dead body takes from ten to twenty hours to reach the temperature of its surroundings (cooling by these means) but in the living body, other factors operate to keep the temperature constant.

The human skin radiates nearly all infra-red rays, and absorbs rays falling upon it to the same extent. The radiating surface of the human body is about eighty-five per cent of the total surface area (skin surfaces in contact with each other being valueless for this purpose). The main factor influencing heat loss through radiation is the temperature of surrounding objects relative to the temperature of the skin. A high relative humidity slightly reduces the heat lost in this manner.

Convection, the rate of movement of warm air from the neighborhood of a heated object, varies with the temperature of the atmosphere relative to the temperature of the body. Thus clothing insulates against heat loss from the body by trapping dead air in the spaces of the clothing. When the atmosphere is cooler, convection currents are set up which mix the air lying against the skin with the fresh air. Probably the most important factor which influences heat loss by this means is air movement.

At air temperatures higher than 98.6° Fahrenheit, radiation and convection are, for all practical purposes, useless. In this instance, large quantities of heat are lost from the body through the secretion and evaporation of sweat and the exhalation of water vapor. Evaporation from the body surface occurs quite independently of sweat secretion, for the skin is not entirely impervious to water; fluid extravasated from the cutaneous capillaries seeps into the epidermis. The rate of evaporation is reduced by a high relative humidity; it is greatly increased by air movement.

The respirations are increased by a rise in air temperature or by a greater heat production within the body. The heat loss through warming the inspired air and the vaporization of water from the lungs is thereby increased. Physically, it is necessary to reduce pulmonary ventilation to reduce heat loss, yet owing to the increased oxygen consumption and carbon dioxide production, it appears necessary to increase it. During exposure to cold, the respiratory rhythm consists of an inspiratory phase of short inspiratory efforts without any expiratory phase between them, and with expiration finally taking place as a sudden forcible act, the whole pattern then being repeated (Beattie, 1938).

The seat of control over the sweat glands lies in the sympathetic nervous system. These glands are, however, anomalous in their responses to sympathetic and parasympathetic drugs. They are stimulated by muscarine, pilocarpine and acetylcholine, and their secretion is supressed by atropine. The usual stimulus to sweat secretion is a rise in blood temperature which exerts its effect in two ways--directly upon the nervous centers, which is of more importance, and reflexly by stimulation of heat receptors in the skin. In the initial stages of muscular exercise, sweating is due apparently to the discharge of impulses from the motor cortex as it occurs before there is any change in rectal temperature.

Spinal centers for the initiation of sweating exist, and after complete transection of the cord, reflex sweating occurs in the parts of the body below the level of the lesion, but destruction of the sympathetic nerve supply to a part completely abolishes the sweating response to a rise in temperature, but not to pilocarpine. Though usually associated with cutaneous vasodilatation, sweating may occur with constricted

vessels--this is termed cold sweat and is usually psychic (Miller 1942).

At ordinary room temperatures the sweat evaporates as quickly as formed, so that there is no apparent secretion. The loss of sweat in this way together with the evaporation of water from the lungs and from the surface of the body independently of the sweat glands is called insensible perspiration. It varies directly with the basal metabolism. Newburgh found that this accounts for approximately twenty-five per cent of total heat loss during ordinary conditions, excluding periods of intense muscular activity (Burton 1939).

Vascular mechanisms. The factors involved in heat conservation or heat loss are dependent essentially upon reactions of the autonomic nervous system. The vascular system plays an integral part in this as evidenced by redistribution of blood, variations in blood volume, and increased circulation rate.

When the feet are immersed in water above the body temperature, there is a vasodilatation of the skin vessels of the fingers, as shown by a rise in skin temperature. This effect occurs before

there is any appreciable alteration in the rectal temperature. Moreover, it is obtained equally well in hemiplegics. Thus it is obvious that the vaso-dilatation is of reflex origin and that the delay in obtaining the vascular change is due to the deep position of the Ruffini endings in the skin (Beattie, 1938)

The skin vessels may dilate or constrict, and through the diversion of blood from internal regions of the body to the surface, or from the surface to the internal organs, heat loss is increased or diminished, respectively. For example, it has been calculated that at a temperature of thirty-four degrees Centigrade, the quantity of blood circulating through the skin may amount to twelve per cent of the cardiac output. The remainder of the blood volume found in the skin at higher temperatures is largely stored in the liver and spleen, although other internal arterial trunks are also dilated (Burton 1939). These changes may be inaugurated by a change in temperature of the blood supplying the nervous centers; reflexly, through centers in the brain and spinal cord in response to changes in skin temperature as perceived by

stimulation of hot or cold spots; through axon reflexes; and finally by responses of the vessels to direct stimulation by changes in external temperature.

Exposure to cold causes a moderate loss of water from the blood. Some is lost to the skin, muscle, liver and spleen. Bickford and Winton (1933) have shown that a further reduction in the circulating blood volume takes place by an increased flow of urine containing a higher percentage of chlorides. They suggest that cold almost abolishes tubular function but leaves the glomeruli unaffected. Barbour and Hamilton (1925) demonstrated local anhydremia, following section of the splanchnic nerves, by transudation of water into the skin after application of cold. They attribute the migration of water to constriction of the cutaneous arterioles and consequent slowing of the capillary blood flow, which in turn, apparently through oxygen lack, increases the permeability of the capillary wall. Their experiment is open to question on the basis of the degree of cold being sufficient to directly alter the permeability of the capillary by damage to the epithelium. The concentration of the blood

serum and increase in osmotic pressure do not occur in animals which have been treated with ergotoxin to the stage of sympathetic paralysis (Beattie 1938).

Barbour in experiments on the dog, pointed out that concentration of the blood also does not occur when the animal is placed in a cold bath after section of the cord in the lower cervical region. When the osmotic pressure of the blood is raised by the administration of hypertonic saline and without changing the environmental conditions, the insensible water loss from the skin surface and lungs is reduced (Gilman and Barbour, 1933). Concentration of the blood or a rise in its osmotic pressure by itself diminishes loss by evaporation and thus helps to conserve body heat.

The blood changes which occur under increased environmental temperature are mainly due to the loss of fluid in the sweat. If the heat is maintained over a period of two hours there is a true loss of water from the blood in spite of the dilution shortly after the heating begins by taking water into the blood from the extra-cellular and intra-cellular body fluids, and the expulsion of blood from the spleen. The loss of chlorides in the sweat is compensated by

a diminution of urinary chlorides. The secretion of urine per unit-time diminishes.

No change in cardiac output occurs with a rise in environmental temperature until this exceeds thirty degrees Centigrade; above this, there is a moderate increase in minute volume. When the isolated mammalian heart is perfused with blood at temperatures above that of normal, the heart rate rises proportionally with the temperature. In animals under a deep anesthesia a rise in body temperature produces the same effect, but in man the pulse rate rises with the rectal temperature, but the increment is not as great as would be expected in the fully anesthetized individual. On the other hand, gradual cooling of the unanesthetized human body in air results in a gradual increase in pulse rate which varies in different individuals. There is early a well-marked vasoconstriction and a rise in blood pressure. Both of these effects are absent if the sympathetic chain has been removed (Burton 1939).

Chemical regulation. Chemical regulation of body temperature is a matter of increased or decreased heat production through alterations in the metabolic rate of the individual. According to Barbour (1921),

chemical regulation comes into play only at temperatures below fourteen or fifteen degrees Centigrade, but Hardy and DuBois have demonstrated that heat loss increases rather abruptly and the metabolic rate rises when the air temperature falls below twenty-eight degrees Centigrade. Under exposure to moderate cold, there is a rise in oxygen consumption paralleling an increase in muscle tone, but under less extreme conditions of cold, the oxygen consumption may not rise perceptibly. This is due to the fact that there is a reduction of heat loss from the skin by the con - striction of peripheral blood-vessels, shunting the blood to the liver and spleen. If this reaction is not sufficient, heat production is increased. Only when the blood temperature begins to fall does the rise in muscle tone occur, to be followed by shivering, then generalized rigor, and if all this fails, by final relaxation (Beattie 1938).

During the phase of vasoconstriction without increased muscle tone, there is a rise in blood sugar (Swift 1932); but once there is increased muscle tone or shivering the blood sugar level remains constant. When the body is immersed in very cold water, the blood sugar level may fall, due apparently to a very rapid utilization of carbohydrate.

The regulation of heat loss by means of a water shift to the skin is at best a wasteful though effective process. Short-time experiments have failed to offer any conclusive evidence as to decreased metabolism as a result of heat, but many observations made in the tropics under conditions of high external heat and high relative humidity demonstrate a reduction of oxygen consumption amounting to approximately ten per cent below the Benedict standard for the individual.

Gelineo (1935) had shown that there is an "adaptation" to high external environmental temperatures, provided the period of observation is long enough and the environmental temperature is sufficiently controlled. Thus it would seem that the lowering of the basal metabolic rate is a possible means of adapting the body to withstand high temperatures, but it is unknown whether or not this method is of much value in man.

The increase in muscle tension, which gradually grows more marked as temperature falls is the indication of increased muscular work, and therefore, increased oxygen consumption. When shivering commences, the oxygen consumption increased rapidly and more

heat is produced in the muscles (Adolph and Molnar, 1946). Swift (1932) noted an increase in metabolism amounting to four hundred per cent above normal when shivering was severe.

The degree of shivering or increased muscle tone depends to a large extent on the exact physical conditions. Exposure to a specific temperature in a closed room gives a heat loss much less than in the open, but if the body is immersed in water at the same temperature, heat loss is greater and shivering is more severe. The initiation of shivering seems to depend more on the temperature gradient between skin and air than on a specific external temperature.

It would seem obvious that shivering is a reflex act. During the inspiratory efforts of a typical cold respiration pattern as described above, shivering may be initiated or exacerbated. Beattie (1938) postulated, therefore, that the flow of cold air over the respiratory membranes of the nose stimulates the sensory vagal endings therein, to produce shivering by thalamic-thermosensitive centers and extrapyramidal nervous pathways to the muscles.

Uprus, Gaylor and Carmichael (1935) suggest that skin stimulation is not the adequate stimulus for shivering in man. They advance the view that cooling of the blood in the superficial capillary network in the skin results in the activation of a thermo-sensitive center in the brain at least as high as the midbrain.

The generalized muscular activity resulting from the application of cold to the skin suggests, also, that the thermo-sensitive zone is high up in the central nervous system and in close connection with the extrapyramidal pathways to the motor nuclei. Uprus, Gaylor, Williams and Carmichael (1935) found that shivering in patients suffering from hemiplegia was just as marked on the affected side as on the normal side of the body.

Increased muscular activity in response to cold is also mediated on a hormonal basis, as the endocrines play an important part in temperature regulation of the body. Cannon observed that exposure to cold caused an increase in the rate of the denervated heart (Cannon, 1932). It has also been reported that the serum taken from an animal exposed to cold raises the metabolism of a second animal into which it is

injected. If the first animal has undergone ablation of the thyroid, the accelerated metabolism was not observed in the second animal.

However, the secretion or liberation of the thyroid hormone is not an immediate response to cold, but appears only after fairly constant and long exposure. This, coupled with its persistent action for some time after discontinuance of the initial stimulus would lead to the conclusion that it is not of value in ordinary moment to moment adjustments to temperature variation, but may exert an effect after prolonged exposure to cold.

The adrenal secretion exerts a calorigenic effect which is immediate and of short duration; it is liberated in increased amounts following short exposure to cold (Miller, 1942).

Cannon (1932) introduced sufficient quantities of cold water into the stomachs of cats to produce a heat debt of nine hundred calories. Under these conditions, shivering rarely occurs or is only of short duration. The heart rate is accelerated due partially to the liberation of adrenalin. He regards this response as the first phase in the reaction of the body to cold. The second phase is shivering,

which is initiated when heat debts greater than nine hundred calories are produced. If the adrenals are inactivated the above heat debt is usually followed by shivering which may last as long as fifteen to seventeen minutes. Cannon's experiments on human beings demonstrated that the mechanism of the cold reaction is identical with that of the lower animals. He concludes that "when the heat producing service of the adrenal medulla is lacking, the shivering mechanism is resorted to" and that the essential purpose of the adrenalin secretion in the first phase of the cold reaction is to accelerate the bodily metabolism. (Cannon, 1932)

THE HYPOTHALAMUS

The three principle divisions of the diencephalon, the epithalamus, thalmus and hypothalamus, are well-defined in the brain of a three months' human fetus. In transverse section may be seen a pair of plates on either side of the third ventricle. These plates, with the roof and floor, from the walls of the third ventricle. The dorsal plates thicken to form the thalamus and the ventral placques become the hypothalamus. They meet at an angle on either side--the hypothalamic sulcus. In sagittal section, the thalamus proper is seen as an oval eminence in the lateral wall of the third ventricle.

The epithalamus lies above the sulcus dorsalis which forms the dorsal boundary of the thalamus. Below the thalamus, and separated from this structure by the sulcus hypothalamicus, lies the hypothalamus.

The hypothalamus forms the floor and lower part of the walls of the third ventricle. In it are developed such structures as the optic chiasma, the supraoptic commissures, the tuber cinereum, infundibulum, neurohypophysis and th mammillary bodies. Anteriorly the hypothalamus is poorly

demarcated from the parolfactory region of the telencephalon (the so-called septal area, which receives, among other connections, the medial root of the olfactory tract). Just in from of the anterior commissure and optic chiasma (arbitrarily taken as the anterior border of the hypothalamus) lies the preoptic region, a part of the telencephalon, in which originiates a column of greay matter which runs continuously through the hypothalamus to the tegmental region of the mid-brain. Close alongside this column of great matter in the lateral hypothalamus the medial forebrain bundle runs in an antero-posterior direction; it contains fine myelinated and unmyelinated fibers connecting the ventro-medial areas of the olfactory cortex and the preoptic and hypothalamic areas.

Caudally, the hypothalamus is continuous with the central grey matter and tegmentum of the midbrain. Thus it may be conveniently described as extending from the region of the optic chiasma to the caudal tip of the mammillary body. Laterally, it is directly continuous with the subthalamic region. The subthalamus has been indicted in some descriptions of the hypothalamus as synonomous with the latter,

but it is to be regarded as the pathway of all the elements of the lateral forebrain bundle which pass from the cerebral hemispheres to lower levels and link up the basal ganglia and the neopallial cortex with the brain stem and spinal cord. The efferent side of the lateral forebrain bundle is concerned chiefly with the control of the skeletal muscular system.

In a cephalocaudal direction, three hypothalamic regions may be conveniently recognized: the pars supraoptica (in relation of the optic chiasma), the tuber cinereum to which is attached the stalk of the hypophysis, and a caudal or mammillary region, continuous behind with the central grey of the iter. Each of these regions contains groups of nerve cells, some of which are diffuse and ill-defined, being nothing more than slight local condensations of cells, or only to be distinguished by their relation to certain fiber tracts, while others are better demarcated and consist of cells of a characteristic type.

A sagittal plane passing through the anterior pillar of the fornix roughly separateds a medial from a lateral hypothalamic area. The lateral area, which adjoins the subthalamus and pes pedunculi,

is narrow in its rostral and caudal portion, but in the region of the tuber it expands considerably. It contains scattered groups of large darkly-staining cells, the lateral hypothalamic nucleus which forms a bed-nucleus for the medial forebrain bundle, and two or three sharply delimited circular cell groups known as the nuclei tuberis which often produce small, grossly-visible eminences on the basal surface of the hypothalamus. They consist of small pale multipolar cells surrounded by a delicate fiber capsule about which are found the large cells of the lateral hypothalamic nucleus. The greater condensation of the large cells around the fornix has been called the perifornical nucleus.

The lateral hypothalamic nucleus is also known as the nucleus mammillo-infundibularis, and nucleus tubero-mammillaris. It is very ill-defined, being essentially an interstitial nucleus ofthe medial forebrain bundle. Rostrally, it runs directly into the lateral preoptic nucleus in front of the optic chiasma, while behind it is continuous with the tegmental grey matter of the midbrain. Laterally it is bounded by the subthalamus and the cerebral peduncle.

The connections of the lateral hypothalamic nucleus are obscure. They are doubtless mainly supplied through the medial forebrain bundle, and the nucleus therefore probably forms a link through which the medial olfactory areas of the cerebral hemisphere are brought into functional relation with other hypothalamic nuclei situated more medially. Rioch (1931) has described connections with the thalamus proper which he demonstrated with Weigert preparations; his results need experimental verification.

The supraoptic region, extending approximately from the level of the anterior margin of the optic chiasma to the tuber cinereum, contains two of the most striking and sharply defined hypothalamic nuclei, the paraventricular and the supraoptic nucleus, both composed of large, often bipolar, deeply staining cells, which frequently possess several nuclei. The Nissl substance is peripherally distributed and in the cytoplasm are found inclusions of colloidal material which have been regarded as evidence of secretory activity (Clark, 1938). Both nuclei are very vascular; in each, the relation between cells and capillaries is exceptionally intimate.

Both nuclei send fibers to the posterior lobe of the hypohphysis. In topographical position, however, the two nuclei contrast rather strongly, the paraventricular nucleus lying closely against the ependymal lining of the third ventricle, the supraoptic nucleus being very superficial.

The paraventricular nucleus, in coronal sections, forms a verticle band of cells lying close alongside the third ventricle, extending anteriorly to the ventral margin of the anterior commissure, and reaching from just above the optic chiasma upward to the level of the hypothalamic sulcus where it adjoins the midline nuclei of the thalamus. It widens somewhat at its dorsal extremity. In sagittal section the nucleus is seen to be a broad flat plate of cells that extends over a considerable part of the dorsal level of the hypothalamus and reaches as far forward as the level of the anterior margin of the optic chiasma. The cells are large, packed closely together and frequently multinucleate. Some of the large cells may be pierced by endocellular capillaries.

The fibre connections of the paraventricular nucleus have only been surmised, but it is fairly

certain that some of the fibers of the stria habenularis take origin in the nucleus and run dorsally to the epithalamus. Some investigators describe hypophyseal connections via the tuber cinereum. From a rostral direction the nucleus receives contributions from the septo-hypothalamic tract; caudally it appears to contribute to the formation of the fasciculus longitudinalis dorsalis bringing the hypothalamus into direct relation with the motor nuclei of the cranial nerves (Clark, 1938)

The supraoptic nucleus is composed of predominately bipolar cells, large and closely packed; it straddles the lateral portion of the optic chiasma. Scattered isolated cells or small cell groups appear to form an incomplete bridge between the two extremities of the nucleus. Detailed histological study has failed to demonstrate any fiber connections with the optic tract; the main connections of the supraoptic nucleus are with the stria habenularis, the more caudally situated hypothalamic nuclei, the paraventricular system of fibers and with the hypophysis.

In the tuberal region the hypothalamus reaches its widest extent. Topographically, the tuber

cinereum is an oval eminence of grey matter lying between the optic chiasma and the mammillary bodies; suspended from it by a peduncle is the pituitary gland. In the main part of the tuber (hollowed out by the infundibular recess of the third ventricle) are two fairly well-defined condensations of small rounded cells lying close to the ventricle on either side. These are the ventromedial hypothalamic nucleus and the dorsomedial hypothalamic nucleus. They are separated from the lateral hypothalamic area by the fornix.

The ventromedial hypothalamic nucleus bears the closest topographical relation to the hypophysis. It usually forms a dense mass of cells in close relation to the ependymal layer. It receives fibers from the stria terminalis and has numerous connections with most of the components of the medial forebrain bundle.

The dorsal nucleus of the tuber cinereum is usually less well-defined. It lies immediately dorsal to the ventromedial nucleus and the two are sometimes called the substantia grisea. Besides being connected with neighboring groups of cells and the medial forebrain bundle, there is some evidence that the

dorsomedial hypothalamic nucleus contributes to the periventricular system of fibers.

The junctional zone between the tuber cinereum and the mammillary region is occupied by rather loose collections of large oval or rounded cells scattered in a matrix of smaller ones--the posterior hypothalamic nucleus. The large cells are especially numerous in man and extend caudally over the mammillary body to become continuous with the ventricular gray and tegmentum of the midbrain. The cells resemble those of the lateral hypothalamic area and are often included with the latter in a single and more extensive nuclear mass, the mammilloinfundibular nucleus of Malone. These large cells appear to give rise to a great proportion of the periventricular system of fibers and as such are believed to furnish most of the efferent hypothalamic fibers to the lower portions of the brain stem and spinal cord.

In close relation to the ventromedial nucleus of the hypothalamus and close to the ependymal lining of the infundibular recess is a collection of small cells which Krieg has called the arcuate nucleus. It is intimately related to the hypophyseal

fasciculi to which it probably contributes fibers, and it receives accessions from the medial forebrain bundle as well (Clark, 1938).

The mammillary portion consists of hemispherical aggregations, the mammillary bodies, covered dorsally by the caudal cells of the posterior hypothalamic nucleus. Topographically, it is the most differentiated part of the hypothalamus. In man, the mammillary bodies are associated with two remarkably well-defined tracts, the fornix and the fasciculus mammillo-thalamicus.

The mammillary body itself consists almost entirely of a homogeneous spherical mass of small cells sharply circumscribed by a capsule of white fibers. This is the large medial mammillary nucleus. Lateral to this is the small intermediate or intercalated mammillary nucleus (lateral mammillary nucleus of Le Gros Clark), composed of even smaller cells, flanked ventrally and laterally by a well-defined group of large cells, the lateral mammillary nucleus (intercalated nucleus of Le Gros Clark). This receives fornix fibers and provides the origin of the mammillary peduncle.

The fornix system consists of fibers collected from the whole extent of the hippocampus; the main part of the tract runs down as the anterior column to the mammillary region, penetrating the hypothalamus, where it is surrounded by the nucleus perifornicalis. Some fibers leave the main bundle to terminate in the septal region and the preoptic area; others have been described as ending in the periventricular nucleus and the tuber cinereum. Many terminal fibers of the fornix, after giving collaterals to the mammillary body, cross in the supramammillary decussation and pass down to the tegmentum of the midbrain. Clark (1938) believes, however, that almost the entire anterior column ends in the medial and lateral mammillary nuclei and in the nucleus intercalatus.

The mammillo-thalamic tract takes origin from the medial mammillary nucleus, and probably also from the nucleus intercalatus and the lateral mammillary nucleus. The tract runs from the lateral mammillary nucleus dorsally with a slight forward inclination to the anterior nuclear group of the thalamus. The mammillo-thalamic tract serves as a pathway through which hypothalamic impulses can be

conveyed to the somatic part of the thalamus and also provides a route through which thalamic activities can be brought to bear on the mammillary complex.

The mammillo-tegmental tract takes origin principally from the medial mammillary nucleus and curves backwards to reach the midbrain where it can be traced immediately ventral to the oculomotor nucleus as far as the ventral tegmental nucleus. It is regarded as an efferent path from the mammillary body to the brain stem.

The mammillary peduncle contains fibers which may be seen to detach themselves from the region of the main bundle of the medial lemniscus, pass up on either side of the interpeduncular nucleus finally to terminate in the lateral nucleus of the mammillary bodies. There is some evidence that this tract provides an afferent path for sensory impulses from the brain stem to the mammillary body and thence to the hypothalamus as a whole. It is uncertain just what the exact nature of these sensory impulses is (Ingram, 1940).

The periventricular fibers arise primarily from the large cells of the posterior hypothalamic nucleus and run close to the ependymal lining of

the third ventricle. These fibers are both myelinated and unmyelinated; they pass first dorsally in the periventricular grey. Some terminate in the dorsomedial thalamic nucleus and in some of the midline nuclei, intermingled with fibers which pass from these thalamic nuclei to the hypothalamus. This two-way connection brings the hypothalamus in relation with the neopallial cortex, since the latter is reciprocally connected with the dorsomedial thalamic nucleus.

However, a majority of the periventricular fibers turn caudally, collect to form a longitudinal bundle immediately below the posterior commissure, and descend to lower portions of the brain stem. Some of the fibers appear to terminate in the superior and inferior quadrigeminal bodies. Most of them pass back immediately ventral to the aqueduct to form the longitudinal (dorsal) bundle of Schütz, the termination of which is obscure.

The afferent fibers to the hypothalamus include the olfactohypothalamic fibers from the basal olfactory region, most of which come to the hypothalamus in the medial forebrain bundle. Other afferents are included in the fornix, the mammillary peduncles and

the periventricular system. The hypothalamus also receives fibers from the retina which detach themselves from the optic tract and terminate in the supra-optic and the ventromedial hypothalamic nucleus.

The connections of the hypothalamus with the posterior lobe of the pituitary have been well established for man. They are unmyelinated fibers which arise principally from the supraoptic and periventricular nuclei and form a well-defined bundle, the supraopticohypophyseal tract. A smaller bundle, the tuberhypophyseal tract, is contributed by the medial cells of the tuber cinereum.

The possibility of a cortical control of the vegetative nerual apparatus in the hypothalamus is clearly of great significance. It is therefore fitting to consider the fiber paths by which the hypothalamus is related to the neopallial cortex. It is possible for impulses to be conveyed from the hypothalamus to the gyrus cinguli by way of the mamillo-thalamic tract and the thalamo-cortical fibers from the anterior nucleus of the thalamus; there is also evidence that impulses may be conducted in the reverse direction.

Another cortical connection is to be found with the prefrontal regions of the cerebral cortex which constitute a projection area for the medial nucleus of the thalamus; it has been established here, also, that fibers run in the reverse direction (Ingram 1940). The medial nucleus is connected directly to the periventricular system. On the basis of experiments such as those of Fulton and Ingraham (1929), (who made an incision in the prechiasmatic region of the medial surface of the hemisphere of cats and thus altered profoundly their emotional behavior and reactions) direct fronto-hypothalamic pathways have been postulated, but these have not been traced anatomically. This, and the bypasses from the frontal region to the zona incerta and septal region, thence to the hypothalamus, may be even more important in cortical control of the vegetative nervous system than the tract from the gyrus cinguli.

Hunsicker and Spiegel (1934) found that the descending corticifugal tracts to peripheral parts of the autonomic system are topographically related to the pyramidal tract, and they believe that both pyramidal and extrapyramidal conduction of corticifugal

impulses to the autonomic centers of the cord exist. Also in 1934, Fulton, Kennard and Watts produced evidence that in monkeys, the motor representation of the autonomic system in the cortex lies in the premotor area. In their experiments, stimulation in this region led to vigorous peristaltic movements of the gut while extirpation produced disturbances in viscero-motor, vasomotor and sudomotor activities.

Blood supply. Every artery to the hypothalamus takes direct origin from the circle of Willis at the base of the brain. The preoptic region is supplied by the anterior cerebral arteries as they converge to meet at the anterior communicating artery. The portions immediately lateral and posterior to the optic chiasma are vascularized directly from the internal carotid artery. This area includes part of the tuber cinereum, supraoptic nucleus and periventricular nucleus. The mosre caudal and lateral parts of the tuber are supplied from the posterior communicating artery, as are the dorsomedial and lateral hypothalamic nuclei and parts of the mammillary bodies; these latter also receive a branch from the posterior cerebral artery.

The hypothalamic nuclei are also linked with the hypophysis by a hypophyseo-portal system of vessels which ascend in the hypophyseal stalk. This induces direct hormonal integration between the hypothalamus and the pituitary, and gives rise to much speculation as to the basic significance of this relationship. The peculiar endocellular capillary networks in some of the nuclei have already been commented upon as suggestive evidence of secretory activity in the hypothalamus.

EARLY CONCEPTS OF HYPOTHALAMIC PHYSIOLOGY

No field of medicine illustrates more strikingly the wisdom of close cooperation between clinical and experimental study than the history of hypothalamic function. The hypothalamus has been known anatomically about as long as has the thalamus. Its early background is associated with the great school of Viennese pathologists, clinicians and pharmacologists. Since "thalamus" is said to mean "bed-chamber", hypothalamus presumably means "under the chamber" (Walker, 1938).

The first observations bearing on hypothalamic function came from Karl Rokitansky in 1842, who from his vast experience in the dead house observed that infectious processes involving the base of the brain were frequently associated with grave gastric disturbances, and at times with gastric hemorrhage or perforations of the stomach or duodenum. The incidence of this association was sufficient to lead Rokitansky to postulate an imbalance in the regulation of visceral organs which was in some way conveyed by the vagus nerve. (Fulton 1940)

That ended the subject until 1890 when Mauthner who was at that time a Viennese pathologist, ascribed

the somnolence of epidemic encephalitis to involvement of the region of the base of the brain lying posterior to the sella turcica. Righetti (1903) and Italian, gave this view support in a report of a large series of cerebral tumors in which sixty-one per cent of those occurring at the base exhibited abnormal somnolence.

Since that time, there has existed a period of confusion between symptoms referable primarily to disturbances of the diencephalon and those attributable to the pituitary itself. In 1884 Fritzsche and Edwin Klebs described a case of acromegaly with autopsy and drew attention to the profound hyperplasia of the pituitary and thymus. Neither they, nor Pierre Marie, who in 1886 also described a case of acromegaly, associated the condition with a primary disturbance of the pituitary. However, slowly it came to be recognized that there was an association between acromegaly and pituitary adenoma and in 1892, Onanoff, a Russian student of Babinski, described a tumor of the pituitary which had destroyed the gland without causing acromegaly. In 1900, Babinski pointed out that the young woman also exhibited an arrest of sexual development (Fulton 1940).

In 1901, the scene shifted once more to Vienna when Alfred Fröhlich published his memorable report of a tumor of the hypophysis without acromegaly in which the patient showed not only arrested sexual development, but also a distinctively distributed adiposity and a peculiar skin texture. The fundi showed optic atrophy with complete blindness on the left and a temporal hemianopsia on the right. Fröhlich felt that the tumor must be large, but he failed to aportion part of the symptom complex to involvement of the base of the brain.

Erdheim in 1904 was the first to insist that the adiposity in this syndrome was due to involvement of the base of the brain. Not much emphasis was placed upon experimental work to demonstrate this and it remained for Percival Bailey and Bremer (1921) to prove that a primary lesion of the hypothalamic area in a dog would cause a similar picture.

In the meantime, the experimental physiology of the hypothalamus had developed along other channels, again in Vienna. Karplus and Kreidl (1909-1914) made attempts to electrically stimulate the hypothalamus. They demonstrated pupillary dilatation,

sweating, change of heart rate, defecation, salivation and contraction of the bladder resulting from faradic stimulation in the areas about the walls of the third ventricle. To exclude the possibility of stimulation of descending pathways from higher centers, they first removed the cerebral hemispheres and allowed time for degeneration of fiber tracts; the results were unchanged.

Tracing the pathways involved, they found they descended into the medulla and the cervical levels of the spinal cord and that they were completely abolished on a given side when the cord was hemi-sected between the seventh and eighth cervical or when the upper thoracic anterior roots of the sympathetic chain were removed, thus establishing the hypothalamus as the center of control of the sympathetic nervous system. (Fulton, 1940)

CENTRAL CONTROL OF TEMPERATURE

The remarkably stable body temperature of warmblooded animals may be taken as evidence of an efficient thermostatic control. Heat is continuously formed in the body--even at rest, and of course, an increased amount is formed during muscular activity. It is necessary, in order to maintain a constant body temperature, that heat loss be adjusted to heat production, a process made more complicated by changing environmental temperature. The facility with which this balance is maintained has long been considered a basis for assumption of neurogenic control of body temperature.

Exploration to discover the thermal center was begun as early as 1870 by Brücke and Günther, and by the turn of the century, many experimenters had succeeded in producing disturbances in heat regulation by puncturing some part of the brain (Miller 1942).

Early investigators of the cerebral cortex failed to conclude that excision of the cortex has any enduring effect on thermal regulation (Miller 1942). However, in the hands of Eulenburg and Landois electric stimulation of the cortex in

dogs initiated a fall in skin temperature, and Pinkston, Bard and Rioch (1934), also working with dogs, and Fulton (1934) using monkeys, gave support to their conclusions. More recently, Beattie (1938) observed that temperature regulation became restricted, but not abolished, after ablation of the cerebrum of the dog. Darrow (1937) found that the secretory response of the forelimbs may be elicited by stimulation in the premotor cortex and that an increased chronic palmar sweating may follow extirpation of this area.

A central apparatus for the induction of fever was identified within the corpus striatum and the thalamus by a number of pioneer workers, and these were at one time considered the chief sites for the control of normal intrabodily temperature (Richet 1884, Ott 1891, Sachs 1911, Moorehouse 1911, Barbour 1921, and Rogers 1919, 1922). Observations made while applying local heat to the corpus striatum confirmed the fact that heating this region induced general systemic temperature effects (Prince and Hahn 1918), but Moore (1918) suggested that the thermal influence upon the corpus striatum was the indirect consequence of

heat applied to an transmitted from other brain areas handled during the course of the experiment. About this same time, investigators in Germany began to question the supremacy of the corpus striatum with respect to thermal regulation. They pointed out that this structure could not well possess any delicate rheostat character since variations in temperature brought to bear upon this region, as in direct intracranial heating or cooling experiments, had to be several degrees above or below normal to produce a response which was then not instantaneous. In addition to this, extirpation of the corpus striatum failed to produce a loss of temperature regulation (Miller 1942).

A group of investigators have claimed that the center for heat control resided in the thalamus (Rogers 1928). In many experiments, a violent rise in temperature has been associated with damage inflicted to the thalamus. Beattie (1938) ascribed a thermosensitive center for heat control, at least so far as the initiation of shivering in response to cold, to the caudal half of the medial portion of the thalamus. His evidence has not been

generally confirmed and indeed Ranson (1940) checked the work of earlier workers and concluded that "there would seem, therefore,to be no reason to attribute any essential part of temperature regulation to the thalamus." (Ranson 1940)

The pons and medulla too were suspected of governing the behavior of bodily temperature because in man and other higher animals a decline or rise in temperature was observed with injuries to this region. The experimental preparation with the brain removed down to the mesencephalon becomes cold-blooded or poikilothermic--the animal cannot hold its normal body heat or resist the penetra ion of environmental heat or cold. However, it is still not clear whether the temperature is deranged because sensory impulses from the skin cannot reach higher brain centers or whether the absence or dysfunction of such centers is subordinated to the activity of lower centers guarding the fundamental processes of heat production, conservation and dissipation. Reflex shivering in furred animals (cats, rabbits) can take place when only the lower half of the medulla is intact (Dworkin 1930) and such medullary reflex centers

may be present in man, but according to Beattie (1938) there seems to be little doubt that they are of secondary importance.

In 1912, Freund and Strasmann found that rabbits with transection of the thoracic cord retained some capacity for temperature regulation, but those with section of the lower cervical cord were poikilothermic (Ranson 1940). Sherrington (1924) made observations on dogs with spinal transections of twenty-one to five hundred eighty-nine days duration, and he also found a marked difference between thoracic and cervical spinal transections.

Gordon Holmes (1915) reported ten cases of spinal injuries of warfare with lesions in the lower part of the cervical enlargements characterized by subnormal body temperature. In four of the nine cases autopsied, the lesions were practically complete; in the other five, incomplete transverse lesions were present. These cases were slightly poikilothermic, but Holmes had seen cases of complete or very severe injury between the fifth cervical and first dorsal segments in which these symptoms were not present. In several cases of partial or unilateral lesions in the cervical cord, he reported hyperthermia.

Foerster reported hyperthermia in several cases of acute total transection of the cervical cord which he believed due to a destruction of the descending thermoregulatory paths; he also reports a return of thermoregulation after a time if the patient lived. This he regarded as due to the cord becoming autonomous, but he failed to describe any adequate check made to determine that the transections were anatomically complete, and the results he observed could easily have been explained on the basis of subsiding edema and inflammation. His patients may have been spared the hypothermia suffered by Holmes' patients by the solicitous nursing care received by the former (Erickson 1939).

Thauer began investigations on chronic spinal rabbits with the hope of clearing up the discrepancies between such clinical observations as those of Foerster and experimental observations such as those of Sherrington. His rabbits suffered an initial poikilothermia, but soon regained a capacity for temperature regulation which was not significantly impaired by removal of the spinal cord

below the transection, by section of the cervical sympathetics or by subdiaphragmatic section of the vagi; he concluded that the periphery, when entirely separated from the central nervous system, is able to maintain the normal temperature of the body, and while he does not deny that a higher center may exist which has some significance for temperature regulation, he states that his results are inconsistent with the idea of an indispensable temperature regulating center. He found no significant difference between cervical and thoracic transections (Burton 1921). His work may be criticized on the basis of there being a possibility of incomplete transection here also, but if his work were completely substantiated, it would require a complete reorganization of many of the present conceptions of temperature regulation. It is one of the avenues open for further investigation.

Temperature regulation in spinal cats has been studied in great detail by George Clark. In his experiments, cats with low cervical transections were found to be able to adjust themselves to slowly varying temperatures within a certain narrow

range. It has been postulated (Ranson 1940) that this is due to a metabolic change on a hormonal rather than neurological basis.

All these lines of attack converged and brought into focus the realization that, whereas none of these structures could be completely exonerated of possessing an influence on thermoregulation, not one of them proved to be the chief repository of temperature control. In 1884, when research on thermal centers was very young, Ott had written of the hypothalamus as an important heat regulating station. He found that a unilateral puncture into the anterior region of the hypothalamus frequently produced a hyperthermia, but that bilateral punctures were more constant in producing an increase in rectal temperature. This effect was not noted when equivalent punctures were placed elsewhere in the central nervous system (Ott 1884).

The significance of this work was not fully appreciated until two decades later when Isenschmid and Schnitzler (1914) using the more reliable ablation approach, substantiated fully Ott's correct localization of the cephalic thermogenic center in the hypothalamus. Of particular importance in

the evaluation of this work was their realization of the limitations of drawing conclusions from acute experiments about localization of function. For this reason, they attempted to carry out chronic experiments, when initial edema and trauma from handling could be eliminated. Their rabbits lived from three to thirteen days or longer after the operation, which time was too short to produce degenerative processes. They never observed that an initially disturbed heat regulation became normal, but they often witnessed a developing disturbance of temperature balance. They concluded that the part of the diencephalon lying on the optic chiasma and in front of the posterior edge of the chiasm was unnecessary for heat regulation.

These investigators also found that heat regulation was not preserved in cases of complete transection through the middle of the tuber, and they assumed that the anterior part of the tuber could be claimed as the location of the center for heat regulation, but they were frank in stating that they did not know if the function of the caudal part of the tuber cinereum was maintained after such

a section or not. They believed that there is no part of the central nervous system lying caudal to the tuber cinereum which alone, without cooperation of the tuber, is able to maintain heat regulation.

These authors were unable to locate with certainty the heat regulating center any closer than within the tuber cinereum. The part immediately surrounding the third ventricle had no more importance for this function in their experiments than the parts lying several millimeters distant laterally. The pathways which carry forth impulses from the tuber cinereum lie in the caudal part of the midbrain scattered over the ventral and medial part of the transverse section. Even in the anterior part of the midbrain they are not joined in tight bundles. Isenschmid and Schnitzler found that a part of these conduction paths are able to maintain perfect heat regulation even when an important part of the remaining paths are eliminated (Blair and Keller 1946).

Nikolaides and Dontas in 1911 were the first to contribute evidence of definite localization of the heat loss mechanism in the cephalic brain stem. They studied the ability of dogs to pant and noted

the rectal temperature at which panting began before and after the slicing of the brain stem at various levels. It was these investigators who originated the use of the superheated incubator or "hot box" which was later used by Keller and Ranson. Nikolaides and Dontas observed that panting could never be elicited after a complete transection through the brain stem at any level below the caudal extent of the corpus striatum. Complete transections through the cephalic extent of the corpus striatum, or incomplete transections at lower levels did not eliminate panting, but in many instances did raise the rectal temperature at which panting began--termed the panting threshold.

These results were thrown open to question when Nemoto and Sato in 1929 demonstrated that polpneic responses to heat were not affected seriously by removal of the corpus striatum or by a transection passing dorsoventrally between the diencephalon and mesencephalon to the substantia perforata (Bazett, Alpers and Erb 1933).

Moorhouse (1911) showed that warming the carotid blood entering the head caused sweating, peripheral vasodilatation and hyperventilation in experimental

animals, and he inferred that these effects were produced by direct activation of regulating centers in the brain by the rising temperature of the blood. This view has received support from experiments in which parts of the brain were heated directly (by warm water passing through a closed tube inserted in or applied to the desired region, or by open irrigation with warm saline). Barbour (1912, 1919) described a fall of the rectal temperature in rabbits following warming the corpus striatum. This was accompanied by peripheral vasodilatation. Cooling the corpus striatum caused an increase in rectal temperature.

Hashimoto (1915) reported the same results. In his experiments, he found the left side was predominant. Prince and Hahn (1918) working with cats, also found a fall in body temperature resulting from heating this area. Moore (1918) confirmed the antipyretic action of warming this region, but showed that the corpus striatum was not specifically related to the effect. Sachs and Green, a year earlier, had been unable to observe any constant result of warming or irritating the corpus striatum in various other ways. (Sachs and Green 1917).

Bazett (1927) pointed out that the effects obtained by Barbour and others were probably produced at some distance from the site of heating in the corpus striatum because of the high temperatures used to obtain reactions.

In 1929, Hasama found a fall in body temperature to result from warming the base of the hypothalamus and preoptic region in the cat; he observed a profuse sweating on the footpads during this procedure (Ranson 1940). Irrigation of the third ventricle with warm saline was shown to produce polypnea and panting in the dog by Hammouda (1933). These observations appear to indicate that a rise in intracranial temperature is able to activate the heat loss mechanisms.

The most convincing evidence of the effect of localized heating of the brain was reported in 1938 by Magoun, Harrison, Brobeck and Ranson. They activated the heat loss mechanisms, including panting and sweating by local heating of the preoptic and supraoptic region in cats under urethane anesthesia. The heat was provided by a high frequency alternating current of low voltage passing between two electrodes inserted into the brain, four

millimeters apart and parallel to each other, with the aid of a multiple needle carrier and the Horsley-Clarke instrument. The electrodes were inserted vertically from above downward and stopped every two millimeters on the way down to allow for the passage of the heating current at these levels and for the observation of its effect. By repeated punctures at two millimeter intervals from before back, some medially and some laterally placed, it was possible to explore the brain and locate any regions which were specifically responsive to heat. Not more than two or three pairs of punctures were made in any one animal. Thermocouple readings taken between the electrodes within the brain and one millimeter from the nearest electrode showed a rise in temperature of approximately three to six degrees Centigrade according to the voltage. The high tissue temperatures evoked (forty to forty-three degrees Centigrade) caused localized damage in some of the experiments.

Extensive exploration of the forebrain and midbrain of the cat revealed only a limited region from which responses to heating could be obtained. The responses were the same as those obtained by

heating the entire animal, but the rectal temperature never rose. The region from which these reactions were elicited was sharply localized. The rostral portion of the area was located in the preoptic and supraoptic regions between the optic chiasma and the anterior commissure and extended forward beyond them. Continued backward from this region through the dorsal part of the hypothalamus and ventral part of the thalamus was another area which gave reactions of the same kind but was much less responsive, and the reactions were weaker. The reactions to heating were always obtained from within four millimeters of the midline in the preoptic region and diencephalon, never from the lateral parts of the hemisphere. The reactions obtained were due specifically to local heating since the high frequency current used could not stimulate. (Magoun, Harrison, Brobeck and Ranson 1938).

In 1929, Keller found it desirable to repeat the work of Nikolaides and Dontas because of the observation that light anesthesia polypnea could be, in some instances, functionally eliminated by the surgical manipulations in exposing the brain

stem without actually placing a lesion in the brain tissue. He deemed it possible, therefore, that the heat loss cells were not located anterior to but were actually caudal to Nikolaides and Dontas' sections, and that they were merely temporarily paralyzed by the trauma of the transection. He felt that if this were true, the heat loss cells would return to their normal functioning state if such preparations could be maintained to chronicity. His investigations yielded results entirely compatible with these probabilities. (Keller 1930) Later it was found that when the entire hypothalamus was selectively isolated or macerated, the ability to pant was not only spared, but was more easily elicited than normally (Keller and Hare 1932). Subsequently, Keller reported that to a limited extent, certain of these types of preparations retain the ability not only to pant, but also to adjust to a warm environment in an adequate manner (Keller 1938).

Bazett, Alpers and Erb (1933) removed the cerebral hemispheres and part or all of the diencephalon in cats and kept the animals alive for periods averaging from three to seven days. One

decerebrate cat lived nineteen days. They found that transections behind the hypothalamus abolished temperature regulation, but cats in which only the anterior hypothalamus was destroyed and the caudoventral parts left intact were able to keep the body temperature up to normal in a comfortably warm room, and they developed a febrile response to injury or infection. However, ability to react to overheating was abolished. These observations were confirmed by Teague and Ranson (1936), who also demonstrated that a heat loss deficit was, at least in some instances, permanent after anterior hypothalamic lesions.

In 1934, Barbour, investigating the localization of body vapor pressure reflexes to environmental temperature, studied cats with transverse sections of the brain stem. In the normal animal, the vapor pressure decreases with cold and increases with warmth, but the poikilothermous animal shows no osmotic pressure response to cold. He found the critical point for the preservation of this reflex to be the tuber cinereum of the hypothalamus. The reflex was completely abolished following complete transection posterior to the mammillary bodies; the

supraoptic nucleus and cell groups dorsal or ventral to the tuberal region were not essential for the activation of these responses to changing temperatures.

Frazier, Alpers and Lewy (1936) demonstrated total loss of temperature control in cats with bilateral destruction of the substantia grisea of the third ventricle. There was no hyperpnea, no panting, no shivering. Vasomotor responses were lacking. The cats in these experiments showed a sustained hypothermia, but no hyperthermia. Some of the cats were observed to have minor disturbances with unilateral lesions in the lateral portion of the hypothalamus, but these men also decided that the lateral portion was not essential to temperature regulation. In their series, a bilateral loss of the nucleus tubero-mammillaris was necessary for a complete loss of temperature regulation.

Abbie (1939) states that the preoptic region (regarded as predominately parasympathetic in nature) gives rise to transient hyperpyrexia when damaged, and damage to the posterior-lateral portions causes poikilothermia.

Barbour worked with the relation of the anterior and posterior hypothalamic nuclei to anhydremic responses to cold in monkeys in 1939. He found that a disturbed regulation against cold with the water-shifting responses undisturbed resulted from a bilateral lesion involving the mammillary bodies, the mammillary bodies and the lower half of the thalamus, or the area between the preoptic nucleus and the optic chiasm to the center of the hypothalamus.

Reversal of the water-shifting responses with disturbed regulation against heat, but not cold resulted from destruction of both preoptic nuclei, or of the right preoptic nucleus only, or of the area above the preoptic nuclei to the massa intermedia of both thalami. Regulation against cold was disturbed and the water-shifting responses were reversed in those monkeys with bilateral brain stem transections at the level of the exit of the third nerve, or extending from the superior colliculus to the foramen of Monroe. As a control, eight monkeys with lesions in outlying regions were observed to show no change in water-shifting responses. He concluded that in the monkey, the

water-shifting responses to cold are mediated through the anterior hypothalamic nuclei, and the anterior and posterior hypothalamus are centers for regulation against heat and cold (Barbour 1939).

Observations made on animals decerebrated at various levels are not altogether satisfactory because so much of the brain is removed, because the preparations thus obtained differ greatly from normal animals and because parts of the brain stem remaining in place may have been rendered functionless by anemia, hemorrhage and inflammatory reactions. Observations made on animals with lesions placed with the Horsley-Clarke apparatus furnish more reliable information because the lesions are sharply defined, while all the rest of the brain is left undamaged, and because such animals can be kept and studied for as long as desired and are normal except for the disturbances in temperature control, changes in emotional reactions and a tendency to drowsiness, all of which are symptoms resulting directly from the hypothalamic lesions (Bard 1928, Kennard 1945, Ranson 1940).

With this in mind, Ranson, Fisher and Ingram (1937) studied monkeys in which lesions were placed bilaterally in the hypothalamus with the aid of the Horsley-Clarke instrument. Their observations are not entirely complete, and it must be borne in mind that the monkey normally has a very unstable temperature regulating mechanism. Normally, the temperature varies over a range of several degrees and frequently shows increases as a result of emotional excitement or struggling. Monkeys also do not compensate well for high temperatures.

Most of the animals showing a tendency to have a subnormal temperature after operation were kept for a time in an incubator, but some were kept from the start under ordinary room conditions. The monkeys were observed for several weeks and then killed and the brains prepared for microscopic examination.

Impaired heat regulation was evidenced when monkeys with hypothalamic lesions were kept in a moderately warm room. Of a series of twenty-nine monkeys, eight showed hyperthermia after operation, thirteen demonstrated a more or less prolonged hypothermia and eight showed no significant

deviations from normal when kept in a moderately warm room. Four of these last were not subjected to extremes of temperature so the extent of tem - perature regulation remaining intact can not be judged.

The eight monkeys showing hypothermia recovered within a few hours so they could maintain a normal temperature at normal conditions, but they lost heat rapidly on exposure to moderately low temperatures as did the four animals which never showed real hypothermia under the usual room conditions. Little difference could be determined on exposure of these monkeys to moderately high external temperatures, save that those which had been operated upon were never observed to sweat. When these animals were subjected to gradually increasing box temperatures, they were less resistant than the normal animals. In all eight animals showing hypothermia, the lesions destroyed or seriously damaged bilaterally the region dorsal and lateral to the rostral end of the mammillary body, including the part of the nucleus to the ansa lenticularis which lies in this area as well as the intervening part of the lateral hypothalamic

nucleus. Any of the nuclei lying rostral to the mammillary bodies may be intact in an animal showing hypothermia (Ranson, Fisher and Ingram 1937).

In most of the animals showing hyperthermia, the temperature returned to normal on the first or second postoperative day. The responses to cold in these animals were not tested. In seven of these eight monkeys, the lesions involved the rostral part of the lateral hypothalamic area and the region around the fornix bilaterally. In one animal this region was involved unilaterally. The anterior hypothalamic area was usually intact. No relation between damage to the thalamus and variations in thermostatic control could be detected, and in some of the controls, monkeys with lesions limited to the thalamus were able to regulate their temperature normally.

Thus it becomes clear that postoperative hyperthermia develops in the monkey when bilateral lesions are made in the lateral part of the rostral portion of the hypothalamus. Hypothermia develops when the bilateral lesions are situated dorsolateral to the mammillary bodies. The more caudally placed lesions cause impairment of ability to

regulate against both heat and cold (Ranson, Fisher and Ingram 1937).

Two years later (1939) Clark, Magoun and Ranson studied the disturbances resulting from lesions placed in the hypothalamus with the Horsley-Clarke apparatus in a large series of cats. The lesions were of varying size and location, but in every case an attempt was made to produce lesions which were as nearly bilaterally symmetrical as possible. These experiments were sufficiently conclusive to warrant their detailed description. Preceding the operation, daily observations were made of the cat's rectal temperature for a week or more and tests were made of the ability of the animal to regulate its body temperature in the hot box and the cold box. After the operation the cats were kept for one or more days in an incubator at about thirty degrees Centigrade and thereafter at room temperature which averaged around twenty-four degrees (Centigrade). Daily observations were made of the rectal and environmental temperatures for two weeks or more. Tests were made in the hot and cold boxes about a week after the operation and repeated on the second and

fourth weeks and in some cases after even longer intervals as deemed desirable.

Very large lesions in the hypothalamus resulted in the death of most of the animals, but large lesions of the anterior groups were less fatal than those of the posterior or middle groups. Lesions in front of the anterior commissure resulted in an increasing incidence of subnormal temperature with the lapse of time postoperatively. If the preoptic region was intact, the animal gave a normal response in the hot box, but if the preoptic region was destroyed, he failed to pant.

Large lesions of the middle group destroyed most of the hypothalamus from the chiasma to the caudal border of the attachment of the hypophyseal stalk. Two cases involving the mammillary bodies were fatal; these died with subnormal temperatures. Hot box tests were performed on six of these cats. Five failed to pant before the rectal temperature reached forty-one degrees Centigrade, when they were removed from the hot box. The sixth cat panted at thirty-four degrees (rectal temperature). Large lesions of the posterior hypothalamus were so universally fatal that no hot or cold box tests

were performed; these animals all had subnormal temperatures prior to their death.

Small to moderate-sized lesions were made in the medial part of the anterior hypothalamus in seventeen cats. They produced no easily recognizable symptoms. The cats had normal daily temperatures subsequent to the operation except that a considerable number showed transient hyperpyrexia the day following the operation. The cold box reactions were normal. In the hot box, there was some increase in the panting temperature level and a decrease in the final respiratory rate. The lesions all lay close to the midline.

Moderate-sized lesions in the lateral part of the anterior hypothalamus caused much greater disturbance in temperature regulation than did those more medially placed. Of the eight cats in this series, three had lesions placed so far laterally as to damage the medial edge of the basis pedunculi and internal capsule. The medial forebrain bundle in the region between the fornix and internal capsule above the optic chiasma was destroyed in these. The remaining five cats had assymmetrical lesions so that the medial forebrain bundle was

seriously damaged only unilaterally. The post-operative temperatures were normal or above in all save one cat, which had a temporary hypopyrexia. The hyperpyrexia observed in six cats disappeared by the third postoperative day. Those three cats with symmetrical lesions showed a marked loss in ability to prevent over-heating. In the cold box tests, these cats first showed a greater than normal drop, but were not abnormal one month postoperative. The five cats with assymmetrically placed lesions showed an early loss in ability to prevent overheating, but by the end of the first month, they reacted normally in hotbox tests; they showed no abnormalities in the cold box tests.

Moderate-sized lesions placed laterally in the posterior part of the hypothalamus cause a great impairment of the ability to regulate against both heat and cold. These seven cats had lesions at the level of the mammillary bodies which generally involved the Fields of Forel and interrupted fibers from the lateral hypothalamic area to the central grey matter. In all but one, the lesions were fairly symmetrical bilaterally. In that one, the left lateral hypothalamic area was destroyed, but the

right was intact. That lesion was in the midline, so as to interrupt fibers descending on the left side into the mesencephalic tegmentum as well as any fibers entering the central grey through the supramammillary decussation. This cat showed marked disturbances in temperature regulation as long as one month after operation. On the morning after operation, these cats were lethargic, and had subnormal rectal temperatures which had returned to normal by the seventh day. In the cold box, they demonstrated a decreased ability to prevent loss of body heat; two cats recovered some of this ability. In the hot box, they were unable to regulate efficiently against heat.

Moderate-sized lesions placed medially in the caudal part of the hypothalamus caused little disturbance in temperature regulation. Three cats had unilateral and one cat had bilateral lesions destroying the mammillary bodies. Although the authors realized the difficulty in measuring sweating and shivering, they believe that shivering occurred less often in the operated than the non-operated cats. A delayed hypothermia in one cat was postulated to be the result of toxic absorption from the lesion.

These authors concluded that the region specifically responsive to heat lies above the optic chiasma in the neighborhood of, and below, the anterior commissure. It may send fibers back in the medial forebrain bundle to the lateral hypothalamus. They state that the transient hyperthermia in cats, monkeys and man after lesions in the anterior hypothalamus and suprachiasmatic region may result from irritation of the centers for heat formation and heat conservation in the hypothalamus while the heat loss center is destroyed or cut off. Bilateral destruction of the caudal part of the lateral hypothalamus destroys the center for heat formation and conservation and interrupts descending pathways which ordinarily regulate against excessive heat (Clark, Magoun and Ranson 1939).

Beaton, McKinley, Berry and Ranson (1941) again resorted to localized heating of the brain of the monkey by diathermy. They found an area in the ventrocaudal part of the telencephalon between the optic chiasma and the anterior commissure which gave a maximum sweating response and polypnea. This is the area which has been here referred to as the preoptic region. The effect was not observed

after stimulating the area three millimeters lateral to the midline. There was no extensive destruction and the effects ceased with the cessation of stimulation, so no descending pathways were interrupted. In the cat, there can be demonstrated a zone of diminished response extending through the dorsal hypothalamus; such an area is nonexistent in the monkey and dog (Beaton, McKinley, Berry and Ranson 1941).

Artificial faradic stimulation of the posterior hypothalamic area produces sharp and prompt vasoconstriction and thus decreases the heat loss from the skin. It also produces a mobilization of carbohydrate reserves and pilo-erection (Walker 1940). If unchecked, this leads to hyperthermia, but it is counterbalanced in the normal individual by mechanisms brought into play by the anterior hypothalamus (Miller 1942).

Blair and Keller (1946) introduced a semi-quantitative method of assaying varying degrees of impairment in the heat regulating functions, believing that in the past, too many reports were based on the subjective interpretations of the investigators. In their experiments, all tests

were made with the animals under basal conditions and in postabsorptive stages. Constant temperatures of the incubators were maintained by thermostatic control; the heat was distributed uniformly throughout the box.

They tested the ability of an animal to prevent a fall in its rectal temperature by observing the difference tween rectal and environmental temperatures and noting whether a fall in rectal temperature occurred, and if so, the relative rate of fall when the animal was abruptly submitted to an environmental temperature of ten degrees Centigrade as a criterion for heat maintenance. The test was continued for eight hours or until the rectal temperature fell to or below thirty degrees Centigrade. The presence or absence of shivering, and the time of its appearance were noted under each circumstance.

Heat loss was evaluated by the ability of an animal to prevent an undue rise in rectal temperature when submitted to a warm environment of thirty-three, thirty-six and thirty-eight degrees Centigrade for eight-hour periods. Respiratory rate, panting and polypnea were followed closely. The

test was terminated if the rectal temperature rose to forty-three degrees Centigrade.

These quthors frequently found it impossible to test high midbrain preparations because they are exceedingly prone to maniacal activity with an increase of rectal temperature, and such results had to be thrown out.

In these experiments, the heat maintenance mechanisms were completely and permanently eliminated in a dog whose sole tissue defect was isolation of the hypothalamic grey, or severance of its caudal connections. If only a small amount of the caudal portion of this grey remained undisturbed, considerable of the ability to prevent a fall in rectal temperature was retained. Evidence was encountered which indicated that at the hypothalamic level, there are separate neural elements for the shivering and non-shivering thermogenic functions.

They also concluded that over-all heat loss mechanisms can be spared in the presence of a complete and permanent elimination of the heat production mechanism. Heat loss powers were markedly impaired in certain dogs which retained considerable heat maintenance ability by virtue of the intact portion

of the caudalmost hypothalamic grey matter. An explanation of this seemingly paradoxical situation could logically be the basis for further research; although several hypotheses are offered, none have been conclusively proven or universally accepted (Blair and Keller 1946).

References to the clinical aspects of the central regulation of temperature in man are legion in the literature. In addition to those discussed below, Cloake (1927), Frazier, Alpers and Lewy (1938), Gardiner and Pembry (1912), Holmes (1915), Kornblum (1925), Strauss and Globus (1931), Jung, Doupe and Carmichael (1937), and Dott (1938), and Kennedy (1940) are but a few of those who have written on the subject. Even so, a disturbance of temperature regulation which can be shown to be hypothalamic in nature is still sufficiently an oddity to be reportable in the literature.

Allen and Lovell (1932) reported eight cases of tumors involving the posterior part of the third ventricle. Of these, five developed severe hyperthermia immediately postoperatively and died.

Alpers (1936) described two cases of supra-sellar cyst with terminal hyperthermia. In the first, the tumor filled the entire space between the hippocampal gyrii, extending from the optic chiasm to the anterior border of the pons and producing compression and flattening of the optic chiasm, optic nerves and the floor of the diencephalon. Histologically, the floor of the diencephalon was destroyed as was the entire floor of the third ventricle, thus destroying the substantia grisea of Malone. The second case showed a deep excavation in the floor of the diencephalon which proved to involve the substantia grisea and tuber cinereum.

Davison and Selby (1937) reported a rarer instance of hypothermia which was associated with polydipsia, polyuria, adiposogenital dystrophy, hypersomnia, absent sense of smell and bilateral primary optic atrophy. This proved to result from an angioma extending from the floor of the third ventricle to the sella turcica and from the optic nerves to the mammillary bodies. The nerve cells of the substantia grisea and the nuclei of the tuber were completely destroyed, the mammillary bodies partially so.

Also in 1937, Davison and Friedman reported poikilothermia in a newborn child as a result of an infiltrating neuroblastoma. The floor of the third ventricle consisted only of the pial membrane. The entire ventricular system was dilated. There was marked pallor of the fiber tracts through the hypothalamus and the hypothalamus itself was necrotic or filled with tumor tissue, especially the mesial nuclei.

In 1939, Erickson described a clinical syndrome which he termed neurogenic hyperthermia. The picture is a rapid rise of rectal temperature, relative warmth of the trunk, icy dryness of extremities, anhydrosis, usually hyperpnea and tachycardia. It does not give rise to discomfort or malaise (Riddoch 1938). The patient is usually quiet. Neurogenic hyperthermia is frequently seen after operations in the neighborhood of the pituitary fossa, third ventricle, posterior fossa or within twelve hours after head injuries. Erickson believes there is no precisely localized center for over-all control of temperature in the hypothalamus and that an acutely increased intracranial pressure may cause poikilothermia.

He also states that a general anesthetic causes derangement of the thermotaxic centers. Adequate nursing care is his only suggestion for treatment of this type of fever (Erickson 1939).

Morgan and Vonderahe (1939) described cellular changes in the hypothalamic nuclei in thirteen patients who died of heat stroke. They found two types of cell changes--one indicative of considerable damage in the past with cell degeneration taking place slowly at the time of death. This was most marked in the nucleus periventricularis, the supraoptic region and the lateral part of the tuber. The other cell change was acute, and they believed it to be the result of the heat stroke proper. It was seen most universally in the nucleus tubero-mammillaris, substantia grisea and the supraoptic region. The nucleus tubero-mammillaris resembled the picture produced by typhoid injections.

Vonderahe (1940) states that the hypothalamus is involved in all grave illnesses and the temperature regulation is impaired. He cites the fever of infection as an example. This author also reports a case of fracture of the base of the

skull followed by diabetes insipidus, drowsiness and subnormal temperature.

Bailey (1940) has observed that in craniopharyngiomas, the body temperature is often subnormal with occasional bouts of fever. Other symptoms vary with the patient's age. In other intracranial tumors, such as gliomas and metastatic carcinoma, hypothalamic symptoms occur late.

Davison (1940) reported five cases of hyperthermia with hypothalamic involvement, two of hypothermia and one of poikilothermia. Four of the five cases of hyperthermia revealed destruction of the rostral part of the hypothalamus; the fifth showed destruction of the caudal part, but pressure on the rostral portion was not ruled out. The hypothermia resulted after transection of the brain stem between the pons and medulla and severance of the caudal part of the hypothalamus. The poikilothermia was observed in a baby with internal hydrocephalus. Especially the lateral and medial hypothalamic nuclei were destroyed.

Zimmerman (1940) discussed three cases which were unusual in that most clinical evidence has been unsatisfactory for discrete localization of centers

of function as the lesions are usually very extensive; Zimmerman's cases had discrete small lesions. The first was a meningeal lipoma destroying the ventromedial tuberal nuclei, part of the right mammillary body and the right mammillothalamic tract. This produced hyperthermia for a year. The second, also showing terminal hyperpyrexia, but of only a week's duration, was the result of a pinealoma implant in the median eminence and the ventromedial tuberal nuclei. The third instance of hyperpyrexia was a dural metastasis from an ovarian sarcoma producing compression of cranial nerves bilaterally, while displaying only a single metastatic nodule in the floor of the third ventricle and thus destroying the ventromedial hypothalamic nuclei. He also discusses two cases, one of hyperthermia following massive cerebral infarction with ischemic changes in the hypothalamus, and one of hypothermia following calcification in the basal ganglia, cerebral cortex, cerebellum, and postero-lateral group of hypothalamic nuclei--which run truer to the established form of reported cases.

One of the most recent writings concerning this subject is that of Engel and Aring (1945).

They report a hypothalamic attack with thalamic lesion lasting from bith until death at the age of eighteen. Autopsy revealed a cystic degenerative lesion involving chiefly the dorsomedial and lateral nuclei of the right thalamus, apparently acquired at birth, and associated with repeated paroxysms of hypothalamic overactivity. Emotional excitement seemed to prove the stimulus for the onset of febrile attacks which began abruptly, persisted with marked fluctuations for several days and declined by defervescence. The onset was sometimes preceeded by coldness or even a chill. It sometimes declined suddenly with profuse sweating, warm extremities and flushing. The fever was reduced by antipyretic drugs. Engel and Aring believe that although the hypothalamic nuclei were intact in this boy, there was a definite imbalance, possibly due to the thalamic interruption of cortico-hypothalamic tracts.

DISCUSSION AND SUMMARY

"The nervous mechanism of heat regulation, therefore, seems to string from the cortex to the medulla, implicating the striatum, hypothalamus, midbrain, pons and medulla, whether by centers or by pathways. In this mechanism, the hypothalamic region seems to come closest to acting as a center. Certainly it is the most important part of the mechanism. To say, however, that this is so indicates only in a general way the function of the hypothalamic region in the regulation of temperature. It is essential to know what parts of the hypothalamus are important for regulation and how this regulation is effected." (Alpers 1936) Thus did B. J. Alpers summarize the state of our knowledge in 1936. And so, essentially, might it be summarized today.

The difficulties encompassed in this research may be more fully appreciated when one realizes that the hypothalamus comprises four grams in a total brain weighing twelve hundred grams. It represents one three hundredth of the total brain volume, and could actually be easily contained in a teaspoon. In man, furthermore, this structure

is doubled upon itself as a result of the enlarged sella turcica. Yet this grossly insignificant area has been claimed, and with a greatly impressive weight of evidence, to house the "Board of Control" for the entire autonomic nervous system. Here are found integral centers for not only heat loss and heat production, but also cardiovascular regulation, water, carbohydrate, fat and protein metabolism, control of sex function, including supervision of the endocrines directly and indirectly concerned with reproduction, gastrointestinal regulation, kidney and bladder function, sleep and waking, and many others. In this organ is kept a constant vigil over the internal environment.

Thus it is not to be wondered at that the shroud of mystery surrounding the mechanisms involved in central control of body temperature have not been more deeply and conclusively penetrated.

It is apparent that heat regulation is accomplished by a dual mechanism--the processes of heat production and conservation being balanced against heat dissipation. Both groups of antipodal phenomena appear to have anatomic representation in the hypothalamus and it was the consensus of many

investigators before 1940 that there are two separate centers of temperature controll--the centers for heat production residing in the lateral portion of the posterior hypothalamic area, while heat loss is governed to a large extent by the anterior hypothalamus--especially the supraoptic and preoptic areas (Ranson, Fisher and Ingram 1937; Magoun, Harrison, Brobeck and Ranson, 1938; Clark 1938; and Ranson 1940). This hypothesis fits nicely with the higher incidence of clinical and experimental hyperthermia, and many catastrophic effects of lesions of the intervening regions were explained as having interrrupted descending fibers or integrating pathways between the two areas. Also, as mentioned above, stimulation of the posterior hypothalamic area initiates a series of sympathico-adrenal responses which increase heat production and diminishes heat loss, while faradic stimulation of the anterior hypothalamic areas initiates the counter mechanisms of heat loss.

But this theory may be questioned when attempting to explain the occurrence of sweating in the presence of peripheral vasoconstriction or "cold sweat"--an everyday occurrence.

Neither is this theory adequate to explain the conclusions of Blair and Keller (1946) that the over-all heat loss mechanism can be spared in the presence of a complete and permanent elimination of the heat production mechanism, while the reverse has been admitted for at least two decades. Why does a tissue defect grossly limited to the anterior hypothalamus eliminate or impair the heat loss mechanism which is at least partially retained when the entire hypothalamus is removed? The answer to these questions may well explain some of the antagonistic results obtained by early investigators.

Among the possibilities advanced by these authors (Blair and Keller 1946) is that the heat loss cells (as yet anatomically undistinguished) are distributed throughout the hypothalamus and the cephalic part of the midbrain, the latter capable of functioning after removal of the hypothalamus, or failing to function after experimental lesions as a result of operational trauma. The theory of individual variation of location for the heat loss cells has also been advanced.

At any rate, today more investigators are cautioning that specialization of representation

may be more apparent than real. Miller (1942) likens the intra-, and extra-hypothalamic areas to "an extensive keyboard on which the hypothalamus is able to strike a range of thermal effects," but suggests that the anterior and posterior regions may register dominant responses.

The adequate physiological stimulus or stimuli which call these centers into play in response to changing internal environment have been as yet only suspected. Increased temperature of the blood bathing the cells was postulated, but many effects are noticed before any variation in rectal temperature is recorded. Extremely sensitive cold and warmth receptors have been demonstrated in the skin; do they have counterparts in the visceral organs? The very slight variants which prove adequate stimuli normally have not been attained experimentally.

There is a need for a more standardized type of investigative procedure. Many results are difficult to evaluate because the conditions of the experiments were so varied as to make comparison on a standard basis impossible. Far too many conclusions were subjective ones by the authors. Some early work that has proven incomplete or inconclusive

could well be repeated in the light of improved technique, apparatus, and definite goals.

The subject of central regulation of body temperature is far from closed. It may eventually be discovered that the range of thermal control in the body is accomplished by quantitative variations of a single, not a dual, process with the hypothalamus serving as a vital instrument in this regulation.

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