NEUROGENIC HYPERTHERMIA

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Neurogenic hyperthermia is a definite syndrome not infrequently seen in neurosurgical practice. It has been only casually mentioned in the literature and no opinion has been previously ventured as to its etiology.

In its most typical form this condition occurs immediately after cranial operations or head injuries as a marked elevation of body temperature with a very rapid cardiac and respiratory rate and a constant unremitting cutaneous vasoconstriction and anhidrosis.

From experimental clinical and pathological studies there is evidence that neurogenic hyperthermia has its origin in a derangement of the autonomic diencephalic mechanisms which are concerned in normal thermotaxis.

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1. INTRODUCTION

Neurogenic hyperthermia is one of the most common and serious complications with which the neurosurgeon has to contend. However, it has been only casually mentioned in the literature and no opinion as to its etiology has been expressed.

By the use of the term neurogenic or central hyperthermia, we delineate a specific highly characteristic group of clinical cases. As the term signifies these cases of hyperthermia have their origin in a local disturbance of the higher centres controlling heat regulation. A neurogenic hyperthermia which is not infrequently seen after spinal cord injuries will be discussed more fully below. When we use the term neurogenic hyperthermia we are aware that many other types of fever may be fundamentally neurogenic but only secondary to a general systemic toxic or chemical change acting secondarily upon the heat regulating centres in the brain.

Hyperthermia has been confined by some authors to all extreme cases of elevated body temperature (e.g. above 106^{o} F) but this is a pernicious mode of expression for

it puts the emphasis and importance upon quantitative elements in the fever rather than upon the etiological factor. In neurogenic hyperthermia the temperature elevation may be very great but an arbitrary temperature level should not be established above which the body temperature must rise for this would lock out many cases which are fundamentally of the same nature as the more well defined neurogenic hyperthermia.

(a) LITERATURE ON NEUROGENIC HYPERTHERMIA

There has been no clinical study of neurogenic hyperthermia in the literature. Cushing (1932) has, however, mentioned the occurrence of hyperthermia following certain types of brain operations particularly on the cerebellum of children. He has very aptly styled it the "bête noir" of the neurosurgeon. In his studies on the intraventricular injection of pituitrin he found that pituitrin given in this fashion caused a fall in temperature in one case of hyperthermia just as it did in the normal individual. (Cushing 1932 p. 79). Kornblum (1925) in an unsuccessful attempt to reproduce the picture

in experimental animals briefly mentioned some of the outstanding symptoms of the condition. Himwich (1934) has recently classified the more common mechanisims of fever production and discussed in detail those due to dehydration.

The syndrome of neurogenic hyperthermia has never been produced experimentally unless one accepts the "heat punctures" as such. The only intentional attempt to do so was that of Kornblum (1925) who failed to produce hyperthermia by destructive lesions of the basal ganglia in dogs.

(b) LITERATURE ON BODY TEMPERATURE REGULATION

Closely allied to the problem of central hyperthermia from an experimental standpoint is the whole question of heat regulation in the animal. In this controversial and unsettled field there are many experimental facts apparently at great variance with one another. In this place only a brief survey of the most significant and pertinent work will be given.

The dependence of thermotaxis or heat regulation upon the central nervous system was first noted by Brodie (1837) who observed a temperature of 111° F. in a patient with separation of the fifth and sixth cervical vertebrae. Tscheschichin (1866) first postulated a heat centre above the medulla when after transection between the medulla and pons he observed a marked elevation of body temperature. Wood (1880) reported increased heat production after cortical destruction in the dog.

Isaac Ott (1884) was the first to attempt localization of a thermogenic centre by "heat puncture". Two rabbits with punctures in the corpus striatum had a rise of temperature from 101-1/8° to 111-1/2° and 102-3/8° to 107-3/8° respectively. Richet (1884) observed an elevation of temperature after puncture of the anterior part of the brain. The first performance of "heat puncture" is commonly ascribed to Aronsohn and Sachs (1885) who found a rise of body temperature in rabbits after puncture of the corpus striatum from a site anterior to the coronal suture. Baginsky and Lehman (1886) also concluded that the corpus striatum is involved in the regulation of body temperature. Hale White (1890) produced hyperthermia

in rabbits by puncture of the corpus striatum, optic thalamus, and septum pellucidum. In 1891 Ott found that puncture of the tuber cinereum of a rabbit caused a rise of temperature to 109° F. (which he had previously ascribed to the optic thalamus). Bechterew and Sakovic (1897) (quoted by Ott 1914) also found that puncture of the tuber cinereum produced a rise of temperature due to increased heat production. Ito (1899) confirmed the existence of a heat centre in the corpus striatum and Aisenstat (1909) and Streerath (1910) claimed that the maximum temperature was obtained by puncture of the optic thalamus. Nikolaides and Dontas (1911) claimed a centre for heat control and heat polypnoea in the corpus striatum of dogs. Jacobj and Roemer (1912) found that a minute globule of mercury in the third ventricle gave rise to a decided rise of temperature. They also injected irritants into the ventricle and concluded that the hyperthermia of heat puncture was due to distention, irritation and hyperemia of the walls of the lateral ventricles.

From the observation on Goltz's famous dog and on Sherrington's decerebrate preparations it was known that heat control was not impaired by removal of the

cortex while it was completely destroyed when decerebration was done through the mid-brain. Isenschmidt and Krehl (1912) found that rabbits lost all ability to control their body temperature when both telencephelon and diencephalon were removed, but that by shelling out the fore brain alone, the temperature regulating ability remained intact. They concluded that a centre for heat regulation exists in the median part of the caudal portion of the diencephalon. This has been later confirmed in a more convincing fashion by Bazett and Penfield (1922) and the recent well controlled experiments of Bazett, Alpers and Erb (1933).

Isenschmidt and Schnitzler (1914) by destructive lesions found that the parts immediately next to the wall of the third ventricle are no more important for heat regulation than those 0.75 to 3 mm. lateral, and that the fibres on leaving the tuber cinereum lie widely scattered in the ventral and medial part of a cross section. Interesting is the work of Citron and Leschke (1913) who found that after mid-brain section substances such as bacteria, foreign proteins and beta tetra hydro naphthylamine which normally cause a rise of body temperature no longer produce a rise but paradoxically

a fall of body temperature. Hence they concluded that the seat of pyrogenesis is in the diencephalon.

Likewise, Keller and Hare (1932) working with cats found that mid-brain preparations showed no shivering, that it was necessary to keep them in an incubator in order to maintain body temperature, that hyperthermia never resulted from cerebral trauma or infection, that sweating was never observed, and that typical panting was observed only in a few cases when the section was high. Surprisingly, however, in medullary preparations shivering was readily elicited and within a few days they maintained an adequate rectal temperature in unheated cages. The only evident explanation of the behaviour of these medullary preparations is that the section did not sever the fibres controlling heat regulation which lie along the ventral surface of the medulla. No details of method or technique are given in this paper and the latter is the only conclusion possible in view of the mass of conflicting evidence.

Dworkin (1930) attempted to localize the central control of shivering in the rabbit by transecting the brain stem at various levels. Shivering still occurred after complete transection 2 mm. above the calamus scriptorius although there was evidence that after

transection through or below the diencephalon the threshold for this reflex was raised. Sherrington (1924) noted that shivering was absent below the level of a spinal transverse section.

Sachs (1911) found no centres in the thalamus, nucleus caudatus or nucleus lenticularis which on direct stimulation produced a rise of temperature. Sachs and Green (1918) after experiments on 93 cats and rabbits could find no evidence for a cerebral heat centre by stimulation, destructive lesions or irrigation experiments such as produced by Barbour (1912). Prince and Hahn (1918) suggest that this failure may have been due to use of anesthesia. Wilson (1914) after studying the corpus striatum concluded that it can not be termed a heat centre.

Lillian Moore (1918) in studying the effect of punctures of the nucleus caudatus on body temperature found that 78% of all punctures failed to produce a high temperature. Of those that did raise the temperature only one -third involved the caudate nucleus. However, in 1919 she reported that increase of intracranial pressure to 250 mm. of water or more caused symptoms identical with those in fatal puncture cases, increase of

respiratory rate, slowing of heart rate, vaso-constriction, pupillary dilatation and rise of body temperature followed by a fall before death. Later she reported that if the cranial defect through which a puncture was done were closed tightly temperature elevation occurred but did not if the opening were not sealed or if a decompression were done. She then ascribed all of these temperature elevations to increased intracranial pressure but at no time presented definite and convincing data.

Rogers (1919) studied the control of body temperature in pigeons in relation to certain cerebral lesions. The blood flow in the skin of the cat is a function first of brain temperature and second of skin temperature. (O'Connor 1918). In experiments done by Kahn (1904) raising the temperature of the blood in the carotid artery resulted in peripheral vasodilatation, perspiration, and heat dyspnoea. On the contrary cooling of the blood supplying the brain resulted in increased metabolism in the internal organs and a consequent rise in body temperature.

By electrical, mechanical and thermal stimulation of the base of the brain between the corpora mamillaria and a point slightly cephalic to the tuber cinereum Hasama (1929) demonstrated changes in body

temperature. The most sensitive area he found to lie 1 - 3 mm. lateral to the mid-line as had been previously reported by Isenschmidt and Schnitzler (1914). Bruman (1929) concluded that effective localization of a heat centre had not been achieved by the method of "Heat puncture". He measured the temperature changes simultaneously in the liver, skin, and brain by thermo-electric methods after heat puncture. The liver temperature rose first, the skin temperature last. However, the temperature curves in all three places were parallel.

Barbour (1912) found that cooling of the corpus striatum causes a rise of rectal temperature and heating of the same area by water passed through a tube is followed by a fall of rectal temperature. It has been pointed out that this effect may have been due to the tuber cinereum or other adjacent areas. Ott and others have reported similar changes for the tuber cinereum. Barbour and Wing (1913 - 1914) found that antipyretics act in much smaller doses when applied directly to supposed heat centres in the corpus striatum than when given systemically. The same was true for beta tetra hydro naphthylamine which produces a rise of body temperature.

Freund and Grafe (1912) studied heat regulation after section of the spinal cord at various levels. They concluded that section of the spinal cord gave rise to two types of disturbance. After section of the thoracic cord the animal could maintain its body temperature within limits,

"Regulationsbreite", of variation of environmental temperature, but outside of these limits the body temperature varied. directly with the former. After section of the cervical cord the animal became absolutely poikilothermic. Basal metabolism after sections in the thoracic region is increased, but is normal at normal body temperature after section of the cervical portion of the cord. Gardiner and Pembry (1912) concluded from a clinical study that the general effect of lesions of the spinal cord, barring complications such as infections, was to deprive the patient of heat regulating power in proportion to the extent of paralysis.

Meyer (1926) advanced the theory that the diencephalic centre for regulation of body temperature includes an aggregate of cells the stimulation of which influences the sympathetic nerves, bringing about a rise of temperature, and another aggregate, the stimulation of which influences the parasympathetic nerves, bringing about a fall in temperature. In general it has been shown that the sympathetic system mediates metabolic processes through which heat is liberated, while the parasympathetic system mediates metabolic processes through which heat is conserved.

The heat regulation mechanism of the body was dealt with by Barbour (1921) in an extensive review. He quotes Filehne as having shown that for the initiation of the processes which regulate against overheating no rise of

blood temperature is necessary. The latter author showed that in a bath up to the neck at 41° to 42° C. sweating of the forehead began prior to any change in rectal temperature; plunging a hand in cold water stopped this sweating at once. He points out (quoting Meyer) that the fatal effects of overheating an animal are due to the accumulation of acid. Those forms of life having the highest CO_2 output and therefore the greatest accumulation of acid in the tissues are the most sensitive to heat. Barbour explains the pathogenesis of fever as follows:- When toxins or poisons reach the tissues catabolic changes are initiated which increase the affinity of tissues for water (a breakdown of larger molecules into smaller ones of greater number with consequent increase of osmotic pressure). This reduces the blood volume, especially at the expense of surface blood, and the skin becomes cold (chill). This in turn arouses nervous regulation against cold, thus exaggerating processes of vasoconstriction and blood concentration. As has been shown repeatedly, without certain parts of the hypothalamus there is no infectious fever, and unless the water loss from the blood is extreme, as in Woodyatt's sugar dehydration, the nervous mechanism is undoubtedly involved in the production of the fever.

Richet (1898) believed that temperature control is a reflex phenomenon with the temperature of the centre

playing a part only after a considerable change has occurred. Another theory is that of Bazett (1927). He concludes that control is exerted entirely reflexly, sensory impulses of cold inducing one type of response and those of warmth the other. The temperature centre would under ordinary circumstances integrate these conflicting impressions.

Heat production is a characteristic of all living tissue, but in the animal body muscular contraction has been regarded as the chief if not the only source of practical importance, Bayliss (1927). However, the fact that a curarized animal becomes poikilothermic and has a body temperature varying directly with that of the environment is no proof of the exclusive importance of skeletal muscle in heat production. Langley (1918) has shown that curare paralyzes all pre-ganglionic fibres including cardio-inhibitory, vasoconstrictor and adrenalin producing fibres. Consequently the peripheral organs of heat regulation are paralyzed.

Cannon et al (1927) have demonstrated in beautiful and unassailable experiments the importance of the sympathetic nervous system in heat regulation. They found in their cats, with all of the peripheral sympathetic nervous system removed, that the animal has no power to maintain a normal temperature in a cold environment.

Cannon found with the denervated heart preparations that adrenalin was secreted in response to the establishment of a heat deficit even in the absence of shivering. Hence this is evidence that there is a chemical control (Rubner) against cold by increase of heat production in the resting animal without increase of heat production by muscular contraction (Physical control). Moreover, this means that although the skeletal muscles may furnish a large part of the heat produced in the body they do not necessarily do so merely by contraction. The large viscera must be important sources of heat. The liver is consistently at a higher temperature than other parts of the body and must be the cause of considerable heat production. Bazett and McGlone (1929) found that the temperatures in the muscles of the forearm of human subjects were, under normal conditions commonly 1^{o} to 2^{o} below rectal temperature. This is conclusive proof that the skeletal muscles are not the sole important source of heat production but that the viscera such as the liver which have a still higher temperature than the rest of the body are very important sources of heat production.

Wyman and Tum Suden (1932) working on rats, report that the suprarenal cortex is necessary for maintenance of normal body temperature in a cold environment.

Rats which have no suprarenal medulla are able to maintain their temperature normally. The action of the medulla must be sought by other means.

Much progress has been made in the investigation of the centra/control of the autonomic nervous system since Karplus and Kreidl (1909) did their first work. Cushing (1932) observed marked fall of body temperature after the intraventricular injection of pituitrin and pilocarpine. This is due presumably to the strong parasympathetic discharges of central origin with cutaneous vasodilatation and sweating. Lawrence and Dial (1932) repeated these experiments on dogs but found only equivocal lowering of body temperature after pituitrin and a definite rise of temperature after administration of pilocarpine intraventricularly.

Penfield (1930) in his description of diencephalic autonomic epilepsy observed that " --- during the most severe series of attacks the temperature fell well below normal. Neither the very transient shivering that followed each severe attack nor the occasional attacks of shivering of longer duration seemed to cause a noticeable rise in temperature. The irritative source was an encapsulated tumor which periodically pressed upon the thalamus of both sides". Strauss and Globus (1930) described three unusual cases of tumor of the third ventricle which

ran a febrile course without any other adequate explanation. In each of the three cases a neoplasm of the sub-thalamic region with variable involvement of the hypothalamus and thalamus was found. Bassoe (1920), Parker (1923) and Rabinowitsch (1925) have reported similar cases which have been mistaken for encephalitis because of their febrile course. However, temperature elevation is not a usual symptom of third ventricle tumors before operation, (Andre Thomas, DeMartel Schaffer and Guillame 1932 , Allen and Lovell 1932 , and Fulton and Bailey 1929), and hyperthermia is relatively frequent after operation.

A clinical study of the temperature elevations after lumbar and ventricular punctures was made by Gordon (1929). He concluded that disturbances in the physical relationships of the cerebro-spinal fluid perhaps producing a mechanical irritation of the walls of the third ventricle plays an important part, if not paramount role, in the rise of temperature following these punctures. However, Torkildsen and Penfield (1933) state that in the majority of cases rise of temperature following spinal injection of air is accompanied by the appearance of white and sometimes red blood cells in the urine. They conjecture that the unabsorbable portion of the

air appears in the cerebral sinuses in minute bubbles which have a direct effect on the small capillaries of the kidneys when they reach them. By the use of oxygen the temperature rise was eliminated as were other undesirable after effects of air injections. This view finds experimental support in the observation of Cushing (1902) who observed air emboli in pial veins when intracranial pressure was increased by use of air. Normally the most important means of heat elimination is by radiation and conduction from the skin. This form of heat loss is controlled by increased or decreased vasodilatation. Fulton et al (1934) working on monkeys report that extirpation of the pre-motor area causes a loss of the ability to respond to increased environmental temperatures by cutaneous vasodilatation. There was no disturbance of the vasoconstrictor mechanism on exposure to cold. These observations have not yet been confirmed on man. Deighton(1933) reviews the physical factors in heat elimination.

III. METHODS OF INVESTIGATION

This investigation has been approached from two directions; first, an attempt to produce the syndrome of neurogenic hyperthermia in animals; and

second, an exhaustive clinical and pathological study of the patients with hyperthermia of central origin. In the first part we will review the experimental work which has been carried out on 75 cats and 3 monkeys.

An experimental study of central hyperthermia is intimately related to the study of the entire subject of heat regulation and particularly to the localization of a "heat centre" in the brain and to all nervous functions concerned in the control of a normal constant body temperature. From an experimental standpoint the control of environmental conditions is of fundamental importance in the study of thermotaxis. Dry bulb temperature, humidity, and air movement are the most important factors and if the experimenter does not control these or note their variations accurately he may be led to entirely erroneous conclusions. Another obstacle in this work is the use of anesthetics, all of which destroy the ability of an animal to control its temperature. "Dial" and the other barbiturates because of their long anesthetic duration and their action on the diencephalon (Keeser E and J, 1927) are particularly objectionable. In any dose from a minimum anesthetic to a lethal dose the barbiturates

given to the cat produce a poikilothermia with a fall in temperature under ordinary room conditions. Some of the cases of hyperpyrexia in human beings following barbiturate poisonings may be due to a poikilothermia with the patient in higher environmental temperatures. Even in a poikilothermic individual the body temperature is considerably greater than the environment due to the internal heat production. The essential feature of poikilothermia is direct variation of body temperature with environmental temperature.

A cat anesthetized at room conditions has a fall of rectal temperature of from 5 to 15°F. (3 to 8°C) unless it is warmed artificially e.g. on a heated operating table. Because it can be terminated relatively rapidly and because the animal regains normal temperature control within 3 to 5 hours later, ether is the anesthetic of choice and has been used in all of our work.

Our studies to date are based on experiments on 75 cats and 3 monkeys. The work was carried out from August 1933 to April 1934. The animals were kept in a room the maximum range of dry bulb temperature

readings being from 20°to 30°C. except for a short period of airing each morning. The maximum variation of wet bulb temperature readings was from 17° to 24° C. Air movement was negligible except for a short period during the morning when the windows were open for airing. Under these conditions the rectal temperatures of normal unoperated cats were found to average 102° F. (39° C.) with a range shown in Table 1. Readings were made with certified rectal thermometers inserted into the rectum 6 cm. for a minimum of 3 minutes. Temperatures were taken in the morning before feeding and the late afternoon 6 hours after feeding. No constant diurnal variation was noted. No significant post-prandial temperature change was noted. Even vigorous struggling and excitement for short periods up to 5 minutes did not elevate rectal temperature in normal cats. More prolonged activity might do so in the normal animal but does not in the high decerebration or decortication with sham rage phenomena as will be shown later.

We attempted to produce hyperthermia of undoubted neurogenic origin by experimental means. Our method of attack was first, the production of destructive

lesions of various sizes and locations, second, stimulation of the hypothalamus, third, stimulation or attempts to release thermogenic centres by the local application of strychnine sulphate after the method of Dusser de Barenne (1916) and fourth, the effect of increased intracranial pressure. Operative procedures were carried out under ether anesthesia with no preliminary medication unless otherwise noted. During operation the table was kept warm by electric bulbs beneath it and fluctuations in body temperature were noted by an indwelling rectal thermometer. Postoperatively if the animals did not show evidence of regaining normal temperature control within 5 hours they were supplied with artificial heat at intervals until they regained temperature control. Selected animals were exposed to high temperatures and to low temperatures and their reactions to these were studied in comparison with that of a normal animal.

The best procedure for approach to the hypothalamus of the cat in a recovery experiment is the subtemporal. The temporal muscle is transected at the level of the zygoma and reflected upwards. After rongeuring away the bone over the temporal lobe the dura is incised and the temporal lobe is elevated bringing into view the

optic nerve, carotid artery, infundibulum and oculomotor nerve. By using a probe or an electrode bent at right angles one can stimulate or destroy any portion of the hypothalamus at will without injury to other portions of the brain. For use on the infundibular region a straight electrode can be used. By the intravenous injection of from 5 - 10 cc. of 25% sodium chloride just before starting the exposure is much improved and the whole procedure simplified because of brain shrinkage. (10 - 15 cc. are required in the average monkey). These volumes of hypertonic solution have been shown repeatedly to have no effect on the normal temperature curve following an operation with ether anesthesia. In a few cases the hypothalamus of the cat has been approached from above by splitting the corpus callosum. This method has been used particularly when foreign substances such as gum tragacanth have been implanted in the third ventricle.

1V RESULTS OF EXPERIMENTAL STUDIES

In 8 cats attempts were made to produce destructive lesions or extirpation of part or all of the body of the caudate nuclei. The long slender tail of the caudate nucleus could not be removed of course. In two cats the temperature remained down at 95°F. (35°C.), 7° F. (4° C) below normal. In none of the remaining animals were the lesions limited strictly to the caudate nucleus but caused more or less damage to contiguous regions particularly the thalamus, internal capsule, and the lateral ventricle (inevitable). In two animals there was a partial necrosis of one caudate nucleus. One of these animals showed good ability to control its temperature. During the 24 hours post-operative they both had a rise of temperature but not more than would be expected with any brain operation attended by a like amount of tissue destruction. One of these animals was given typhoid vaccine to which he responded by a rise of temperature such as seen in normal controls.

In 4 cats lesions were made in both caudate nuclei. All of these animals showed ability to maintain

a normal temperature. There was no unusual rise of temperature during the first 24 hours, only 2-3° F. (1 - 1.5° C.) such as is usually seen with any destructive lesion of the brain. In only one animal (P.259) was there complete destruction of both caudate nuclei, (caput). This animal was poikilothermic for 48 hours and then maintained a temperature between 100° and 103.6° F. (37.8° - 39.7° C.) (normal) until death on the fifth post-operative day. We may conclude from these experiments that lesions of a destructive nature to the caudate nuclei, neither unilateral nor bilateral, disturb temperature regulation nor produce hyperthermia in the cat. However, there may be a rise of 1° - 3° F. (0.5° - 1.5° C.) during the first 24 hours after experiment and slight irregularities for three or four days later.

The hypothalamus being the most promising locus for the solution of our problem we attacked it from every angle. In 45 cats destructive lesions were made. These were in every conceivable location and distribution; unilateral, bilateral and ranging in size from a stab wound ~~to~~ .5 mm. in diameter to

coagulation necrosis of the entire hypothalamus (Figs 1 - 5). Some of the lesions were made by mechanical means with a probe or scalpel while others were made with bipolar and unipolar electrodes. For our purpose by far the best method of producing destructive lesions was the high frequency coagulating current from a Majestic electro surgical unit with a voltage of from 60 to 90. Electrodes of desired shape and size were easily made from nichrome wire coated with celloidin up to the tip.

Of animals with destructive lesions only 6 (13%) had a rise of temperature to 105° F (40.6°C.) or above during the first 24 hours following production of the lesion. The normal temperature of the cat is 102° to 102.5°F (38.9° - 39.2° C) with a range as in table 1 and following ordinary operative procedures on the brain there is usually a transitory reactionary rise of temperature to a point between 104° and 105° F (40°- 40,5° C). Consequently rises of temperature above 105° F (40.56° C) help differentiate specific local temperature reactions from the more indiscriminate non-specific reaction. Four of these six cases were caused by small puncture lesions (Fig. 1 p.287) in the region of the infundibular nuclei (Winkler and Potter 1914). One of the remaining cases had a more

extensive lesion involving the hypothalamus (Fig.2, p.290) and adjoining thalamus at a more rostral level. The last case with a temperature of 106° F (41.1° C) for a few hours was due to tragacanth in the third ventricle (Fig.3, p.384). In none of these animals was the high temperature maintained for more than a few hours, but tended to fall steadily and rapidly. Other destructive lesions have been made in the infundibular region without any remarkable effects on body temperature (Fig.4, p.338). The small lesions in the infundibular nuclei with a rise of temperature 4 or 5 degrees F. above normal for a short period are the so called "heat puncture" effects and are apparently what led Ott (1914) and others to localize a heat centre in the tuber cinereum. These temperature rises of short duration are often seen after intracranial manipulations. Clinically neurogenic hyperthermias of this type are fundamentally allied to the more fatal forms. Both the clinical and experimental hyperthermias of this sort are evidently due to an irritative process because of their short duration and favourable termination. As we have seen from a review of the literature and from our own work, these effects may be obtained from a wide distribution in the basal ganglia and hypothalamus.

The exact localization of a heat centre to the area just superior and caudal to the corpora mamillaria by Bazett, Alpers and Erb (1933) led us to try partial and complete bilateral destructive lesions in this region. Complete bilateral destructive lesions of this region produced a poikilothermia (Fig. 5, p 366) while unilateral lesions (Fig.6, p 388) had no remarkable effect on the body temperature which was elevated about 2° F (1.0° C) for 48 hours, and then returned to normal. Even very massive unilateral lesions of the caudal part of the hypothalamus or mid-brain failed to produce any change in the temperature (Fig. 7, p 394) nor did bilateral lesions at the level of the corpora mamillaria bring about any remarkable change if they did not destroy the ventral portion of the section (Fig.8, p 395). In the latter case, with destruction of the ventral portion of the section as in Fig.5, the animal became poikilothermic, confirming the work of Isenschmidt and Krehl (1912), Isenschmidt and Schnitzler (1914), Bazett and Penfield (1922) and Bazett, Alpers and Erb (1933) as to the localization of a thermoregulatory centre.

Varied lesions have been produced in the more anterior portions of the hypothalamus without any characteristic changes in the body temperature. Five

decerebrations have been done. Three of these were at or below the level of the corpora mamillaria and the animals were poikilothermic. The other animals had a decerebration which left all of the hypothalamus intact. In spite of great hyperactivity of the type described by Bard (1928), they had no hyperthermia. In fact their temperature was subnormal unless the environmental temperature was distinctly elevated. Conditions suggestive in part or in whole of "sham rage" (Bard 1928) were frequently observed in lesions involving the portion of the hypothalamus anterior to the infundibulum but never posteriorly. Even unilateral lesions in the former region were sometimes followed by some of these manifestations, such as protrusion of claws and active movement of the extremities. The only conclusion to be drawn is that if the phenomenon of "sham rage" is due to release of lower centres from cortical control, this influence must be relayed by way of the anterior hypothalamus. Moreover, these violently excited states are observed where there is strictly unilateral destruction of the anterior part of the hypothalamus. No suggestion of any "sham rage" or excitement has ever been observed when the destructive lesion involves the posterior hypothalamus. In fact cats with lesions

of this type are almost always stuporous or somnolent if the lesion is bilateral. However, if the lesions in this region are incomplete or unilateral (p;394, p.395, Figs. 7 & 8), pseudo affective reflexes and running movements such as are seen in decerebrate cats occur. In other words, these pseudo affective reflexes seem to depend for their appearance upon the integrity of the most caudal portion of the hypothalamus which is literally dove-tailed into the mesencephalon in the cat. Cardiac irrégularities were observed in two cats. These were in the form of a sinus arrythmia which is normally not observed in cats. In several cats extreme constant hyperpnoea was observed after lesions of the hypothalamus between the chiasm and the corpora mamillaria.

Following the suggestion of Dusser de Barenne's work (1916) on sensory localization in the cortex and thalamus by the use of strychnine sulphate (1% stained with toluidin blue) we applied this method to the hypothalamus in several cats. The theoretical assumption was that by breaking down the synaptic connections in the temperature centre we could obtain a tonic nervous discharge giving rise to hyperthermia. In one case we got no effect on rectal temperature from injection of 0.05cc of 1% strychnine sulphate solution and in the other cases we produced generalized convulsions, due

undoubtedly to escape of strychnine into the third ventricle. We have not exhausted this method, but it does not warrant our pursuing it further. The technical difficulty of localizing the application in this region in the cat is too great for practical purposes.

In cats under light "Dial" anesthesia (0.3cc Kilo bd. wt. intraperitoneal) the body temperature was observed during stimulation of the hypothalamus with faradic currents of various strengths. This was approached both from above by splitting the corpus callosum and from the side by elevating the temporal lobe. No significant change was observed in the rectal temperature. However, the chances are that "Dial" anesthesia might mask any change if it did occur. Consequently in two cats under direct vision a bipolar electrode constructed according to the technique previously described was inserted in the tuber cinereum, brought out under the temporal lobe, and anchored in the bone. Twenty-four hours later when the cat had recovered from anesthesia and had a perfectly normal temperature he was stimulated through this electrode with a faradic current of varying strength up to periods of an hour at a time. There was no change in rectal temperature. The animal was then killed and the position of the electrode in the hypothalamus checked.

Separate studies are under-way on the effect of increased intracranial pressure on body temperature. Pressure was not a factor in any of the above experiments for a large decompression was always made. Whatever effect increased pressure has on the body temperature is probably exerted on the same diencephalic mechanism as normally regulates body temperature. To determine the effect of a more or less localized increase of pressure, a small piece of dry gum of tragacanth was implanted in the depths of the third ventricle. As this gum imbibed fluid it gradually increased to many times its original size (12 times) finally producing pressure sufficient to cause a large cerebellar cone (Fig.3,p 384). The temperature curve observed in this experiment is not distinctive but is that seen with other cases when the tuber region is involved in a lesion (Fig.1 and Fig.4). To date 3 monkeys have been studied with observations of temperature before and after operation. Lesions were made with a unipolar electrode passed into the hypothalamus through the lamina terminalis just above the optic chiasm. In one monkey (Fig.10 N-122),who showed no significant temperature change after operation, the lesion was a mid line symmetrical destruction of the supraoptic portion of the hypothalamus and extending back into the very lowermost portion of the infundibulum. In another animal (Fig.9 N-121), the lesion

extended further back destroying that portion of the brain stem superior and caudal to the corpora mamillaria as well as the infundibulum. The latter monkey had an absolute poikilothermia for four days until it died. Due to proximity to a heating lamp its rectal temperature rose to 109.6° F. before death. From these two cases we have good evidence that a heat control centre in the monkey is located in approximately the same place as it is in the cat, namely at the level of or just caudal to the corpora mamillaria.

Increased respiratory rate is a frequent if not constant finding in central hyperthermia. Likewise hyperpnoea is frequently seen by the experimentalist working with the hypothalamus. A polypnoea centre was described in the tuber cinereum by Isaac Ott (1887). Other investigators have repeatedly mentioned its occurrence but have not attempted to localize it to any sharply defined area. The most recent work in which its occurrence was noted, but merely commented upon, is that of Leiter and Grinker (1934). Ranson et al (1934) report that with stimulation, using the Horsley-Clarke apparatus, they obtained increase of respiratory rate in wide distribution over the hypothalamus as far anterior as the optic chiasm. Anterior to the chiasm weak stimulation gives rise to decrease in respiratory rate and symptoms of parasympathetic hyperactivity. In this

connection the recent work of Dikshit (1934) is very interesting. He found that minute amounts of acetyl choline (0.001 - 0.002 mg.) produced apnoea when injected intraventricularly in the cat. Because stimulation of the central end of the vagus produced the same result he postulated that this substance was released in a parasympathetic centre when the vagus was stimulated. He found suggestive increase of acetyl choline in the spinal fluid and brain after parasympathetic stimulation.

In our studies we have noted hyperpnoea after faradic stimulation of the hypothalamus, after destructive lesions and after the injection of normal saline and of strychnine in the region of the third ventricle. This suggests very definitely that the hyperpnoea observed with hyperthermia is truly of central origin and not merely secondary to the elevation of temperature because hyperpnoea can be obtained from loci in immediate proximity or identical with the temperature centre.

V. RESULTS OF CLINICAL AND PATHOLOGICAL INVESTIGATIONS

From a clinical standpoint it is often difficult to determine whether a given case is one of neurogenic hyperthermia or not. All other conditions such as infection, dehydration or increased intracranial pressure must be carefully ruled out. Temperature rises due to increase of intracranial pressure are perhaps due fundamentally to the same nervous mechanism as other neurogenic fevers, but from a practical standpoint they should not be included in the group because their etiology and therapy is so obvious.

In neurosurgical practice there are all degrees of temperature elevation of neurogenic origin. Many would confine the term hyperthermia to those striking dramatic cases with a temperature of 105° F. or above and respiratory rate with a rapid pulse and a rapid tragic termination. This viewpoint would be to limit a diagnostic term to those cases of a syndrome which were fatal. The same picture in attenuated form is seen with recovery. There are other cases with nothing but a rise of temperature which are very frequent and are certainly of neurogenic origin. Only by watching and studying carefully all of these cases can we conquer the "bête noir". All types of temperature elevation

following intracranial manipulation have been studied. Besides the general features special observations on skin temperature, environmental conditions, piloerection, vasoconstriction and response to therapeutic measures have been made.

The clinical picture of a classical case of central hyperthermia is unmistakable. Soon after an intracranial operation or less frequently after head trauma there is a rapid rise of temperature to a high level. This is preceded and accompanied by a cold dry skin, particularly of the extremities. The coldness of the skin, the lack of perspiration, and oftentimes the piloerection are striking and constant. The cardiac rate is tremendously elevated and the heart races at a furious rate until it finally succumbs in exhaustion. The respiratory rate is also greatly increased. In the severe typical hyperthermia the vasoconstriction is constant and unremittent. Even the application of local physical measures, such as moist heat, do not diminish the vasoconstriction. Illustrative of this type of hyperthermia we wish to describe briefly the following case -

L B - N 2146 - A child of four years, who was well until three months previous to admission,

since which time she had had paroxysmal attacks, during which she would fall to the floor and go into opisthotonos. During the same interval she had had weakness of the right hand and a notable personality change. For two months previous to operation she had had weakness in the right leg, vomiting and an internal strabismus. The objective findings before operation were bilateral papilloedema , bilateral weakness of the sixth cranial nerve, weakness of the left ninth cranial nerve, bilateral positive Babinski phenomena, weakness of the grip of right hand, and increased deep reflexes of the right arm and leg. The temperature, pulse and respiration were normal before operation

A sub-occipital craniotomy was performed on November 24, 1933 and a small amount of tumor was removed from the floor of the fourth ventricle. The body temperature rose immediately after operation and stayed between 102° and 104.6° F. (38.9° - 40.4° C.) until death, less than 24 hours later. The pulse rate rose to above 200 per minute and the respiratory rate ranged between

30 and 60 per minute, the skin was cold and dry and there was marked piloerection. At autopsy the tumor was found to infiltrate the entire medulla and appeared on the ventral surface of the pons to form a bridge over the basilar artery.

In this case the neurogenic hyperthermia was produced by one of two mechanisms. It may have been due to a differential involvement of efferent fibres of the hypothalamic regulating centre or it may have been due to a secondary involvement of the centre itself perhaps by pressure or displacement. The latter mechanism is more probable in the hyperthermias following suboccipital craniotomies where there is not such definite evidence of the bulbar involvement as in this case. In man under ordinary conditions of room temperature 70% of heat loss from the body occurs by radiation and conduction from the skin. Obviously in central hyperthermia there is inadequate heat loss because of paralysis of one of the chief means of increasing heat elimination, vasodilatation. Recently Fulton et al (1934) have reported this very phenomenon, failure of vasodilatation of the skin to occur with warm environment, following extirpation of the contralateral pre-motor area in monkeys. This may furnish

a possible mechanism for the production of hyperthermia by functional or organic alteration of the frontal cortex, particularly in these hyperthermias which follow operations on the frontal lobe. However, it must be borne in mind that this finding has not yet been confirmed in man and the experimental evidence is not beyond question. Moreover this mechanism would perhaps be less frequent than one acting on the lower hypothalamic centers for vasoconstriction which have been so frequently demonstrated.

Another outstanding characteristic of the classical central hyperthermia is the lack of perspiration. Even though the body temperature is extreme there is not the slightest dampness anywhere, not even in the axillae. Perspiration is another mode of heat elimination which is quantitatively most important with elevation of body temperature. The sweat glands are under the control of the sympathetic centers (Karplus and Kreidl 1909) and have a central representation in the posterior hypathalamus in a center which is part of that compound of centers which controls heat regulation. A constant feature of hyperthermia is an extremely rapid cardiac rate. Whether this is primarily due to the lesion in the central nervous system or whether it is secondary to the rise of body temperature can not be ascertained. However, there are

several reasons why it is more likely due to primary injury of a hypothalamic center controlling the heart. The tachycardia is constant, early and extreme. It often appears to be the cause of fatal termination due to cardiac failure. The cardiac rate is much higher than it would be if merely secondary to the rise of body temperature. The severe constant tachycardia is one of the most valuable prognostic signs in those cases which are headed for a fatal termination.

Hyperpnoea is a constant feature of those cases of hyperthermia which terminate unfavourably. However, there are many true cases of neurogenic hyperthermia which do not exhibit increased respiratory rate. In man respiration is of minor importance in connection with heat regulation, a situation quite different from that in the cat or dog as will be pointed out below. Hyperpnoea is normally never seen in man exposed to high temperatures but when it appears in these cases of neurogenic hyperthermia it may appear as a heat regulatory mechanism against high temperatures, such as panting in the dog or heat polypnoea in the cat; perhaps the appearance in man of an atavistic functional mechanism due to derangement of the normal mechanisms of heat elimination.

We have made isolated observations on the effect of various drugs on hyperthermia. If the central hyperthermia

is really due to an effect on a hypothalamic mechanism with persistent vasoconstriction a substance acting on these centers should relieve the vasoconstriction. Such is the case with the barbiturates which were proved by Keeser E.& J. (1927) to act on the diencephalon. In one patient with a high temperature and a very cold skin, the skin temperature increased definitely with the intravenous administration of sodium anytal and the patient eventually recovered from hyperthermia. Pilocarpine was tried subcutaneously in one case but was without effect on the body temperature. It acts on the peripheral structure with this mode of administration. Cushing (1932) in his work on the intraventricular injection of pituitrin found that it lowered the elevated temperature as well as the normal. Therapy of this type may prove useful when the ventricles can be easily tapped.

Study of autopsy material from cases which died with a central hyperthermia are impressive for the wide variety of lesions. However, they have one feature in common, the possibility of direct or indirect involvement of the hypothalmic temperature control centers or their efferent fibres. In only two cases were small localized lesions found in the hypothalamus both of which were in the caudal part of the hypothalamus (Fig. 11-H.A.) corresponding to the temperature center in lower animals. Several other specimens showed localized haemorrhages around the aqueduct of Sylvius. In another case there was extensive destruction

of the hypothalamus, complete on the left side and partial on the right side, by an infiltrating tumor. Several cases showed marked pressure on and displacement of the hypothalamus. One frontal lobe astrocytoma was not accompanied by any change in the hypothalamus and the hyperthermia in this case may be accounted for on the mechanism previously discussed. In the hyperthermias following operations in the posterior fossa there is always the possibility of direct or indirect effect on the efferent fibres of heat regulation in the brain stem. Just as likely is the possibility of displacement of the temperature center near the infundibulum or other secondary effect.

VI DISCUSSION

When studying heat regulation and alterations in body temperature it is always necessary to control the many factors which may effect the end result, that is, the body temperature. Physiologically body temperature is the result of a proper balance of heat production and heat elimination. Each of these processes are in turn modified by physical changes in the environment and by physical and chemical changes in the animal body itself. Any disturbance in the nervous control of body temperature increases the effect of the physical characteristics of the environment. In the external environment the factors of especial importance are humidity, air movement and dry bulb temperature. The part played by changes in physical characteristics of the circulatory media has been recently studied extensively by Barbour (1934) and found to be controlled by the hypothalamic temperature center.

The factors that concern us most directly are those under control of the nervous system. The importance of these in heat production have already been fully discussed. In the human being the avenues of heat elimination vary under different conditions. Under normal or average conditions 70% of the heat is lost by radiation and conduction from the skin. lesser amounts are lost by skin evaporation, lung evaporation, cooling effect of air on the lungs and finally a certain

amount of heat is lost with the excreta of the body. Under conditions of increased environmental temperature secretion of sweat and its evaporation from the skin partake to a greater and greater extent in the elimination of heat from the body. Man differs in one important essential from the lower animals in his mode of protection against high temperature. All lower animals increase their heat elimination by increase of respiratory rate or panting, and this is by far their most important means of protecting against increase of body temperature. However, in man exposure to a high external temperature does not cause panting or anything like it. When the body temperature is elevated the respiratory rate may increase secondary to the increase of metabolism but not sufficiently to perceptibly increase heat elimination. In man the most important means of increasing heat elimination are by vasodilatation of the skin thus increasing radiation and conduction and by perspiration thus losing heat by the chilling effect of evaporation.

The fundamental physiological derangement in many central hyperthermias is an inadequate heat elimination due to a constant and unremitting cutaneous vasoconstriction and anhidrosis. The typical cases are always manifest by a cold dry skin, particularly of the extremities. We have no direct observations on heat production in these cases but the metabolism is said to be no higher than it would be secondary to the elevation of temperature. Neurogenic hyperthermias

not infrequently follow operations on the frontal lobes. The work of Fulton et al (1934) may be significant in this connection if it can be confirmed in man. In monkeys he found that extirpation of the pre-motor area caused a failure of the opposite extremities to respond to warmth by vasodilatation as did the normal members. There was a paralysis of vasodilatation. These cortical autonomic centers, if they exist, must act through diencephalic centers. Theoretically most parts of our usual picture in hyperthermia may be explained by several local actions on the same mechanism, which accords roughly with the clinical and pathological picture. Destruction of parasympathetic centers in the hypothalamus or paralysis of its efferent fibres would give rise to a compensatory over activity of the sympathetic centers. Similarly a stimulative or irritative process involving the sympathetic centers would bring forth the same phenomena which all lead to decrease of heat elimination and increase of heat production.

The heat regulating center as located by Bazett, Aplers and Erb (1933) is intimately related to or part of the sympathetic centers in the diencephalon. Most cases of central hyperthermia can be explained by local disturbance of the heat regulatory center or by local involvement of its efferent fibres which have been traced through the ventral and medial portion of the brain stem by Isenschmidt and Schnitzler (1914) If this center or these tracts are destroyed the animal becomes poikilothermic and its temperature usually falls. Hence in

neurogenic hyperthermia we must be dealing with a differential destruction of the fibres or of the centre leading to a decrease of heat elimination or an irritative lesion of the fibres leading to increased heat production. This viewpoint is in keeping with the pathological findings. They are not such as would produce the former but merely a partial destruction or an irritaion of these centers and efferent fibres.

Some of the temperature rises following cerebral operations can be compared directly to the classical "heat punctures" in animals and which by different workers have been localized in divers portions of the basal ganglia, tuber cinereum and ventricular walls. However, these temperature rises are of relatively short duration and are not comparable to the usual typical neurogenic hyperthermia. Clinically this type of temperature change is seen after many cranial operations as a short lived spike of fever for the first 24 or 48 hours after an intracranial operation. They may be explained by irritation of afferent fibres to the hypothalamic heat center.

Mention is made here for the sake of completeness of the hyperthermias following not infrequently injury of the spinal cord. Gardiner and Pembrey (1913) made a clinical study of patients after traumatic transection of the spinal cord and found that the temperature may rise above normal, (hyperthermia) fall below normal (hypothermia) or remain at the normal although the capacity for regulation is impaired

In a paraplegic patient the body is divided into two portions; the non-paralyzed and the paralyzed. In the former the capacity to regulate temperature is present in the latter it is absent. The site of the lesion in the spinal cord will determine the relative proportion of the two parts, and for this reason cases of section of the spinal cord in the cervical region will show the greatest variations from the normal temperature. In the paralyzed portions of the body there is no control over the production or loss of heat and production rises and falls with the body temperature. Sweating is absent in the paralyzed part, even if the temperature is abnormally high and the non-paralyzed parts are sweating profusely. This may cause hyperthermia or hypothermia but the former is much more common in warm hospital beds. However, some cases of cervical cord injury have a hyperthermia in what seems to be a cool environmental temperature and are seen to have a constant marked vasoconstriction of the cutaneous vessels and absence of sweating. The suggestion is made here that the unremitting vasoconstriction and anhidrosis are a manifestation of an upper motor neuron paralysis of the lumbosacral sympathetic outflow comparable to a spastic paralysis of the pyramidal system. In other words, the cells of the intermediolateral column may be released from control of a higher motor center in the hypothalamus. This would explain very adequately part of the mechanism of the production of hyperthermia after spinal cord injury but would not supplant the

primary mechanism which was described by Gardiner and Pembrey.

These considerations and our own experiments on cats and monkeys have convinced us that some of the so called neurogenic hyperthermias after cranial operations may be due to high temperature environmental conditions surrounding a fundamentally poikilothermic individual.

VII SUMMARY

Neorogenic hyperthermia is a definite syndrome of relatively common occurrence in neurosurgical practice. In its most typical forms it occurs shortly after intracranial operations or head injuries as a rapid rise of temperature, rapid cardiac and respiratory rate, constant and unremittent vasoconstriction, anhidrosis, and frequent fatal termination. More frequent than this dramatic picture are the many rises of temperature after brain operations which are fundamentally of the same origin. Needless to say other causes of fever such as infection, dehydration, and increased intracranial pressure should be ruled out before making this diagnosis.

Theoretically hyperthermia may be due to an increase of heat production or decrease of heat elimination or a

summation of both processes. Experimental studies on seventy five cats and three monkeys have revealed no constant locus for the production of a syndrome of hyperthermia. The reason for failure to reproduce the syndrome in cats may be due to the fundamental difference in heat elimination in man and the cat. The hypothalamic temperature control centre in the monkey is found to be similar in location to that in the cat.

From experimental, clinical and pathological investigations there is evidence that neurogenic hyperthermia is due to an imbalance of the autonomic diencephalic mechanism of normal temperature regulation. The pathological changes underlying this derangement are due to a variety of local changes affecting the hypothalamic centres for temperature control or perhaps even more frequently their afferent or efferent fibres.

To Dr. Wilder Penfield I am greatly indebted for the suggestion of this problem, and for many ideas in its investigation.

VIII ILLUSTRATIONS

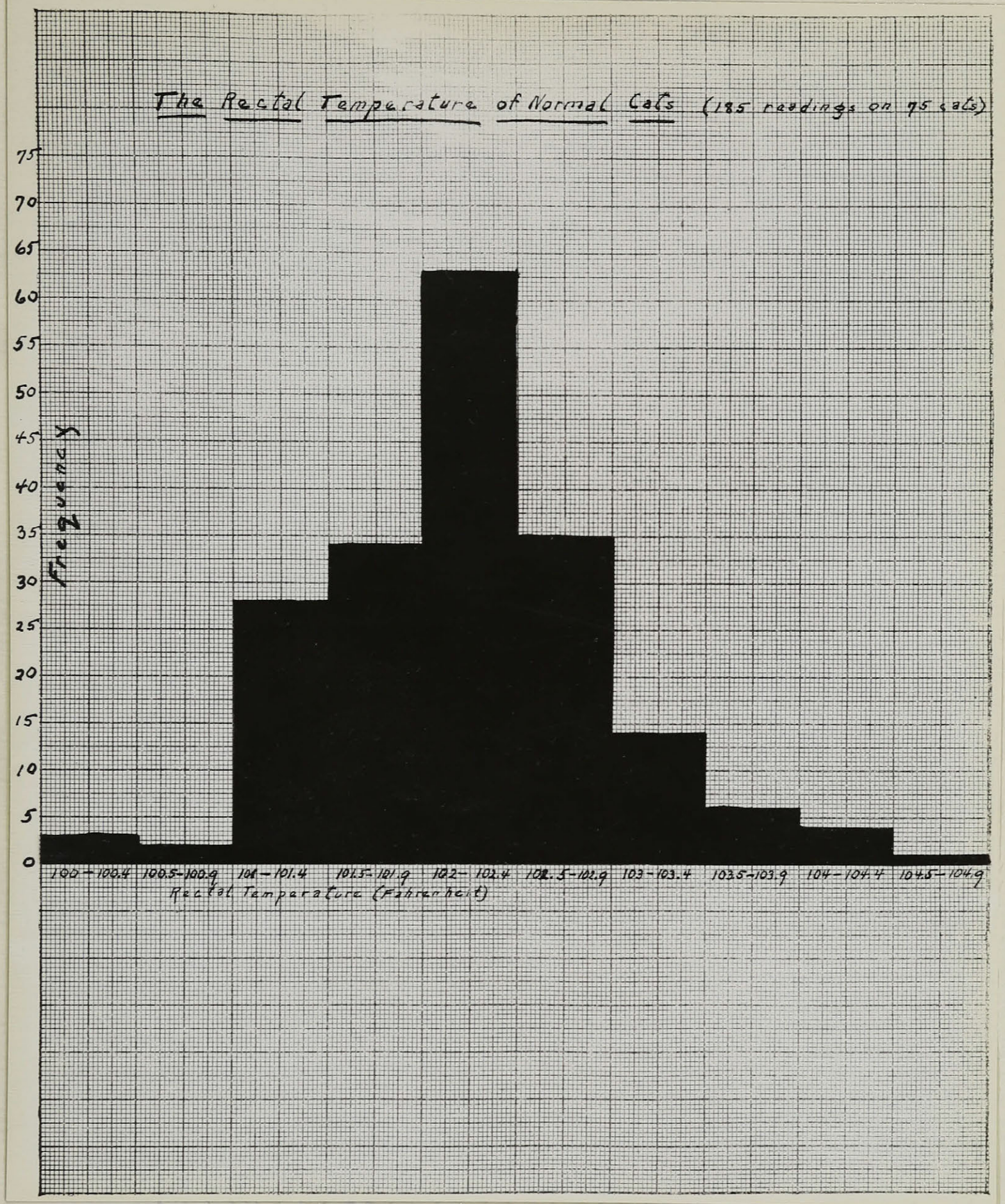
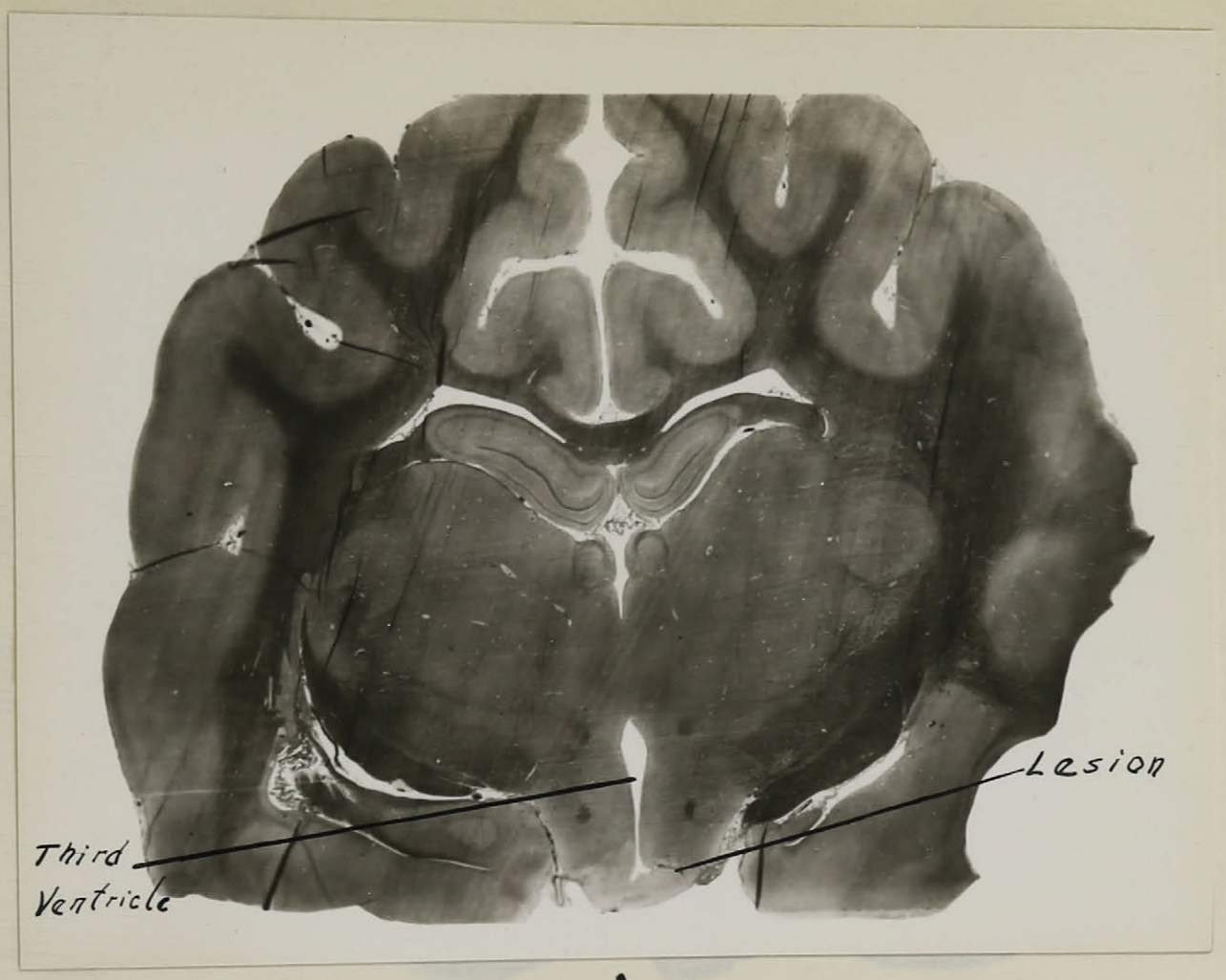
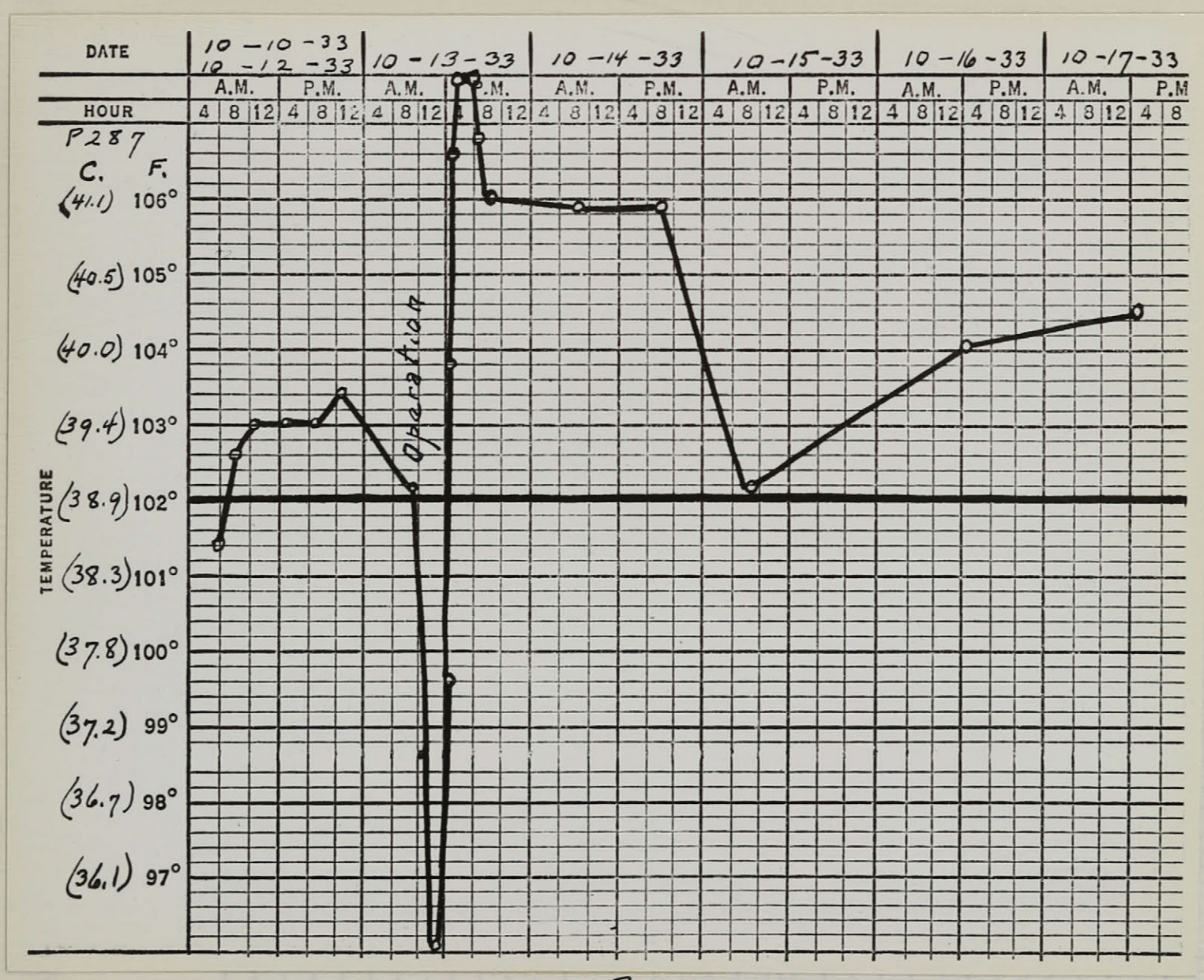


TABLE I

Graph showing rectal temperatures of normal cats.

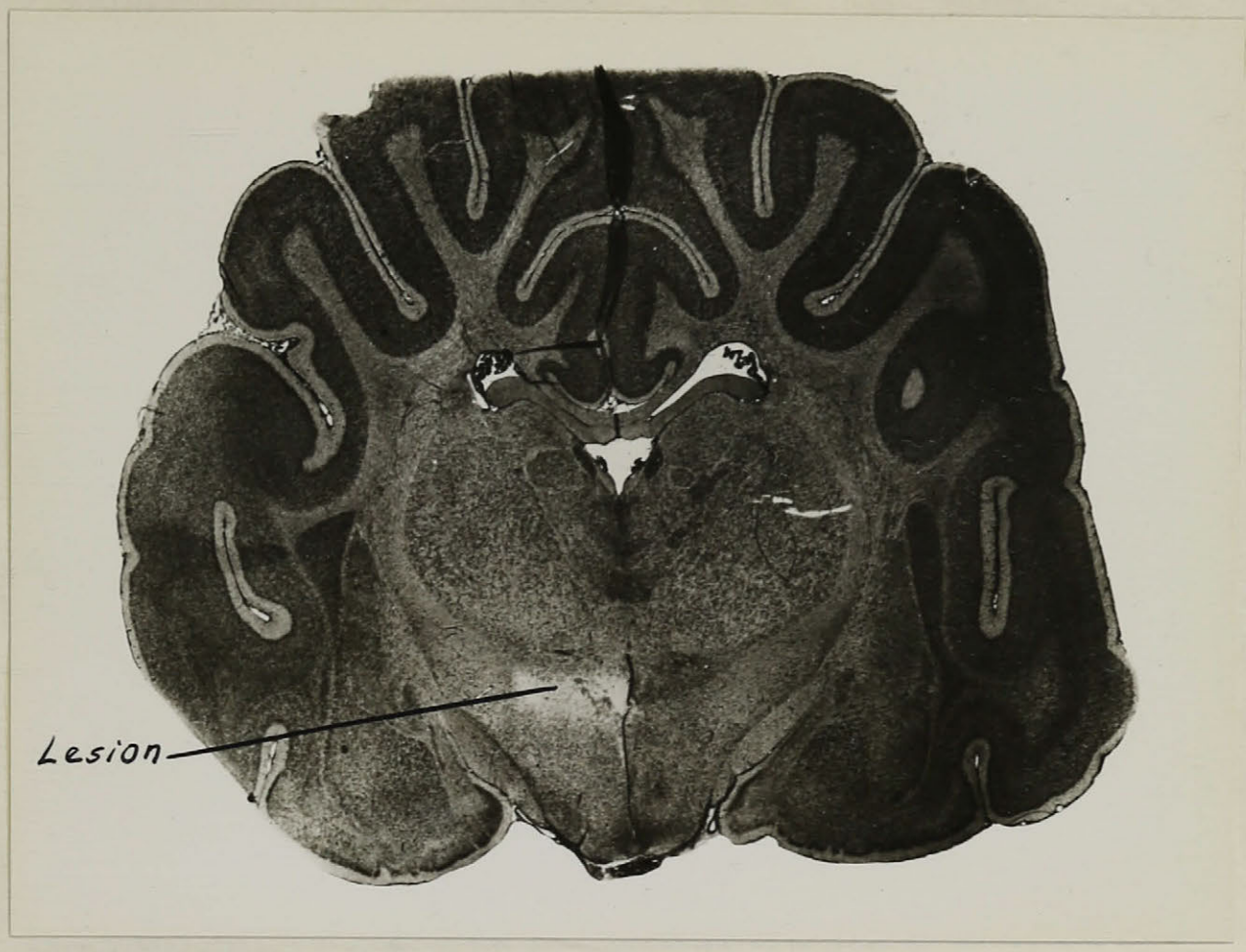


A.

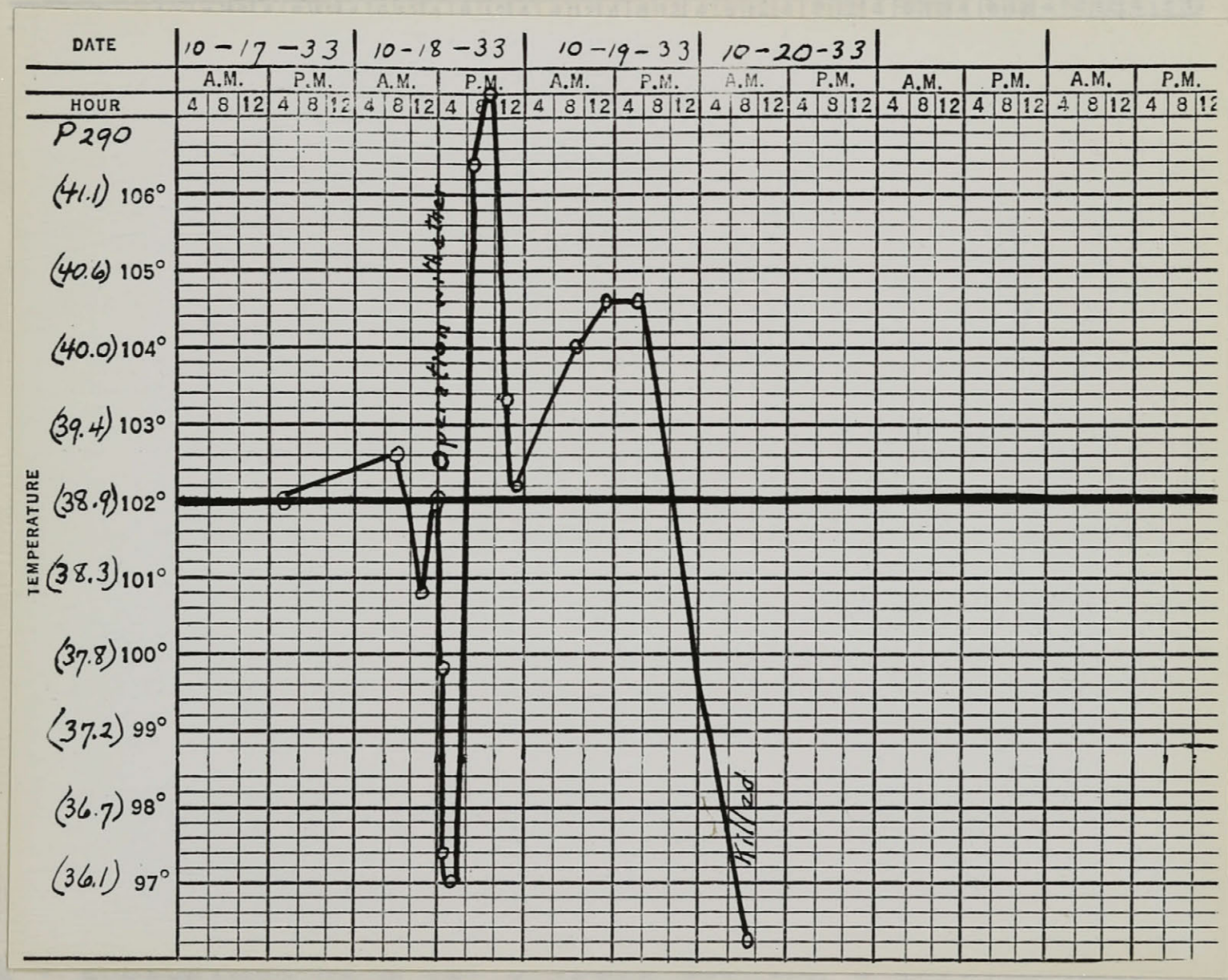


B.

FIG. 1 A - Coronal section of cat's brain showing small puncture lesion in infundibular nuclei of hypothalamus (Loyez stain).
B - Chart showing rectal temperature of above cat before and after production of this lesion.



A.

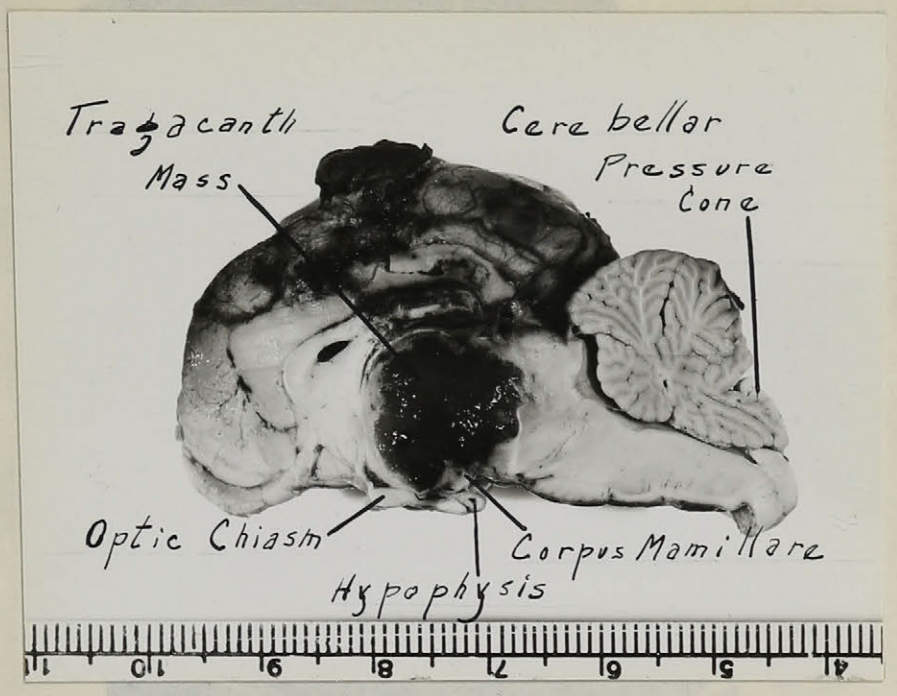


B.

FIG. 2 P.290

A - Coronal section showing unilateral lesion of medial and lateral hypothalamic nuclei (stained with thionin).

B - Temperature chart of this cat before and after production of this lesion.



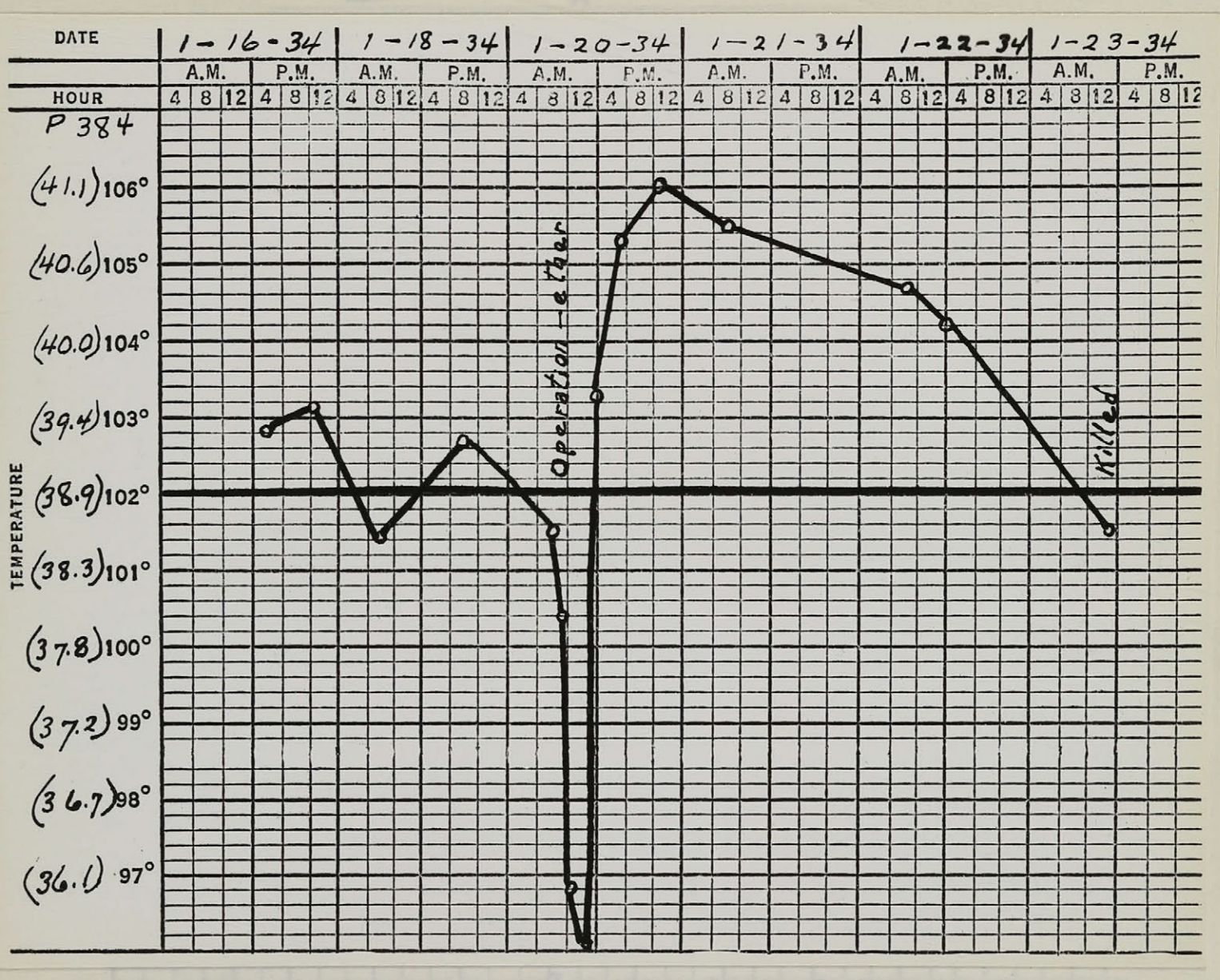
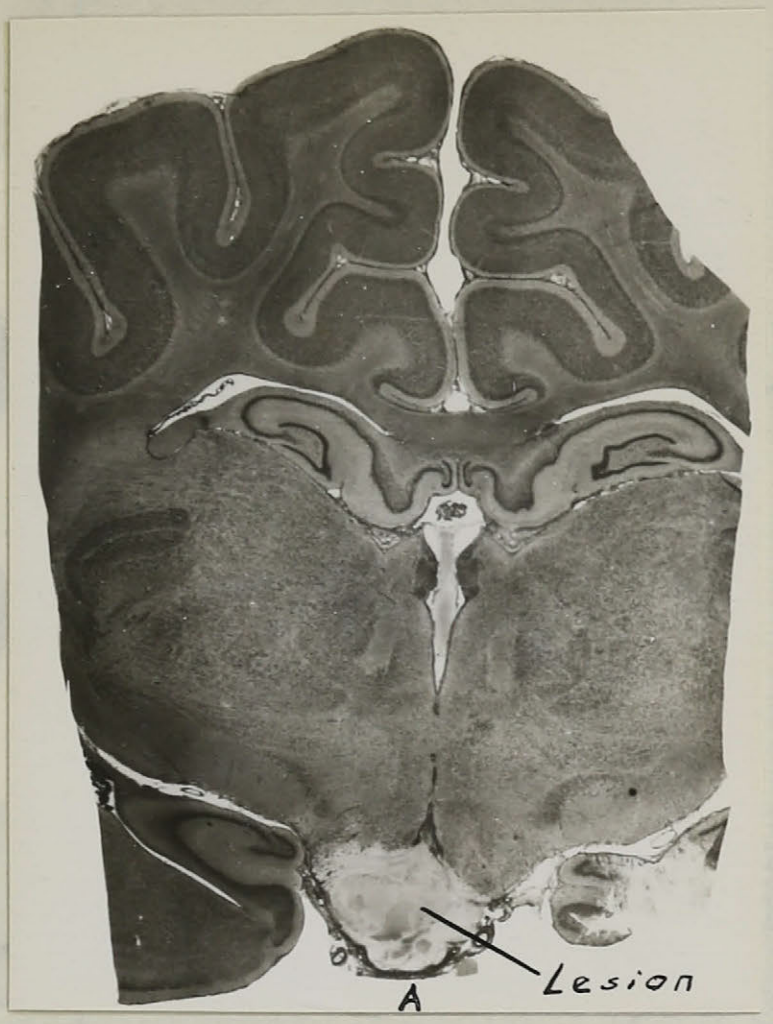


FIG. 3 A - Photograph of a cat's brain showing a swollen mass of tragacanth in the third ventricle and a marked cerebellar cone. At the time of introduction the foreign body was only one twelfth of this size.
B - Chart showing rectal temperature before and after production of this lesion.



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(36.1) 97°																																			

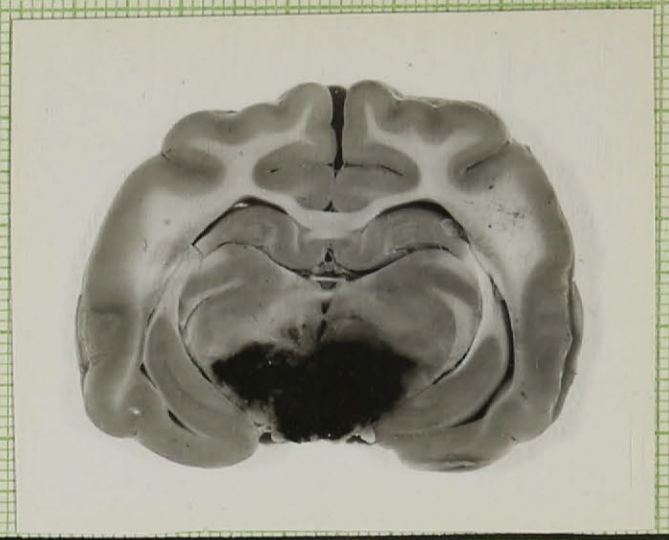
TEMPERATURE

Operation

B.

FIG. 4, A - A coronal section through a cat's brain showing complete bilateral destruction of the infundibulum.
B - Temperature chart before and after production of this lesion.

Fig. 5 — P366 - Curve showing rectal temperature of a cat poikilothermic after production of lesion at the level of the corpora mamillaria as shown in the photograph.



F. C.

110 (43.3)
108 (42.2)
106 (41.1)
104 (40.0)
102 (38.9)
100 (37.8)
98 (36.7)
96 (35.6)
94 (34.4)
92 (33.3)
90 (32.2)
88 (31.1)
86 (30.0)
84 (28.9)
82 (27.8)
80 (26.7)

Rectal Temperature

Normal pre-operative temperature.

Operation with production of lesion shown above.

Kept at room temperature

Placed in heated cage at 55°C.

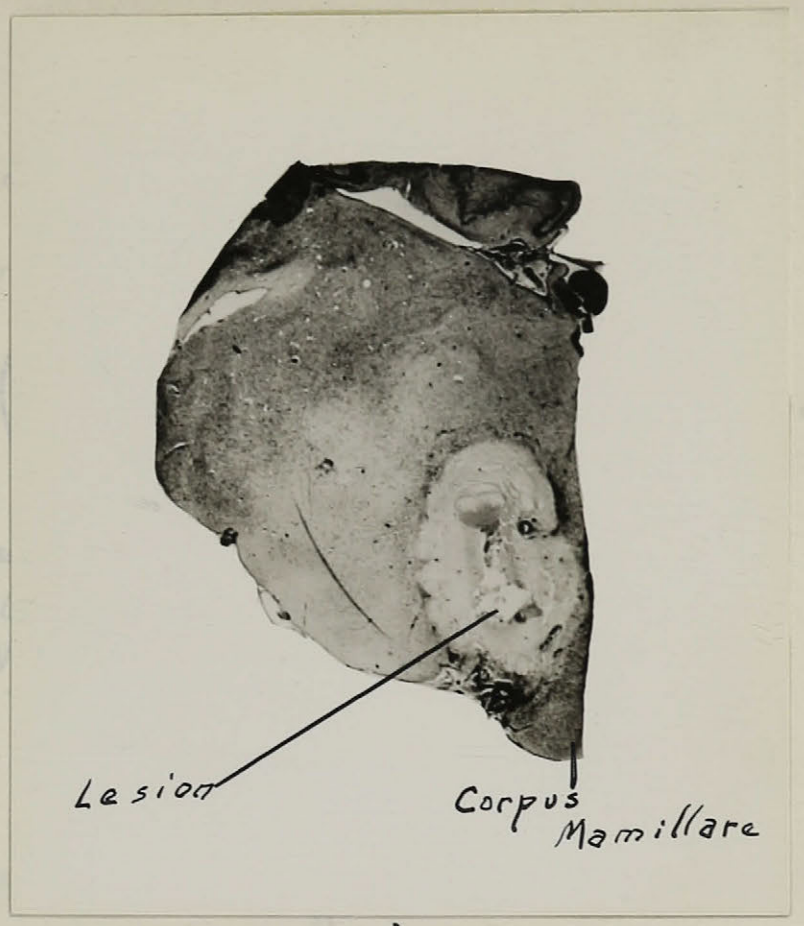
Placed on cold floor at 10°C.

12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12

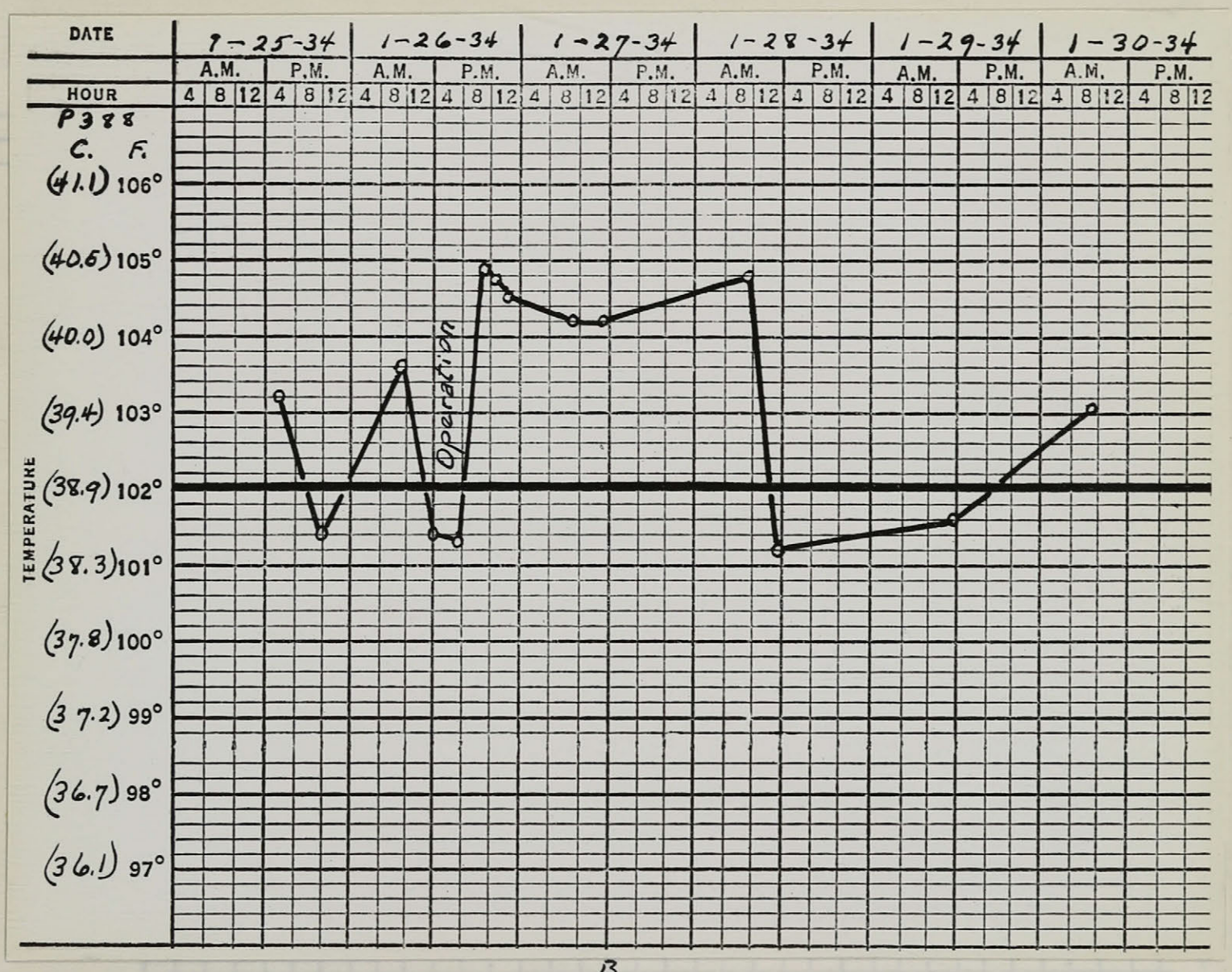
PM AM PM AM PM AM PM

12-6-33 12-7-33 12-8-33 12-9-33

Time

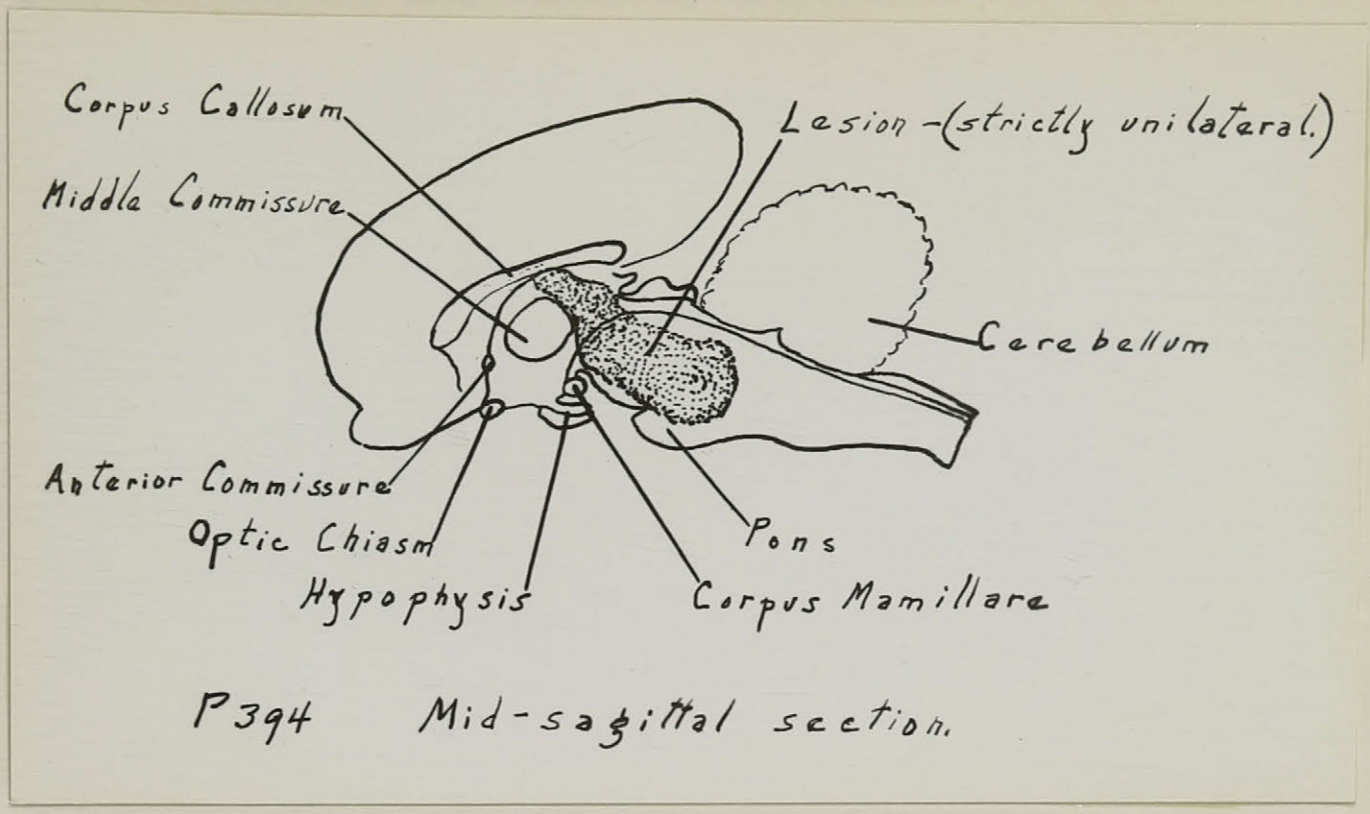


A.

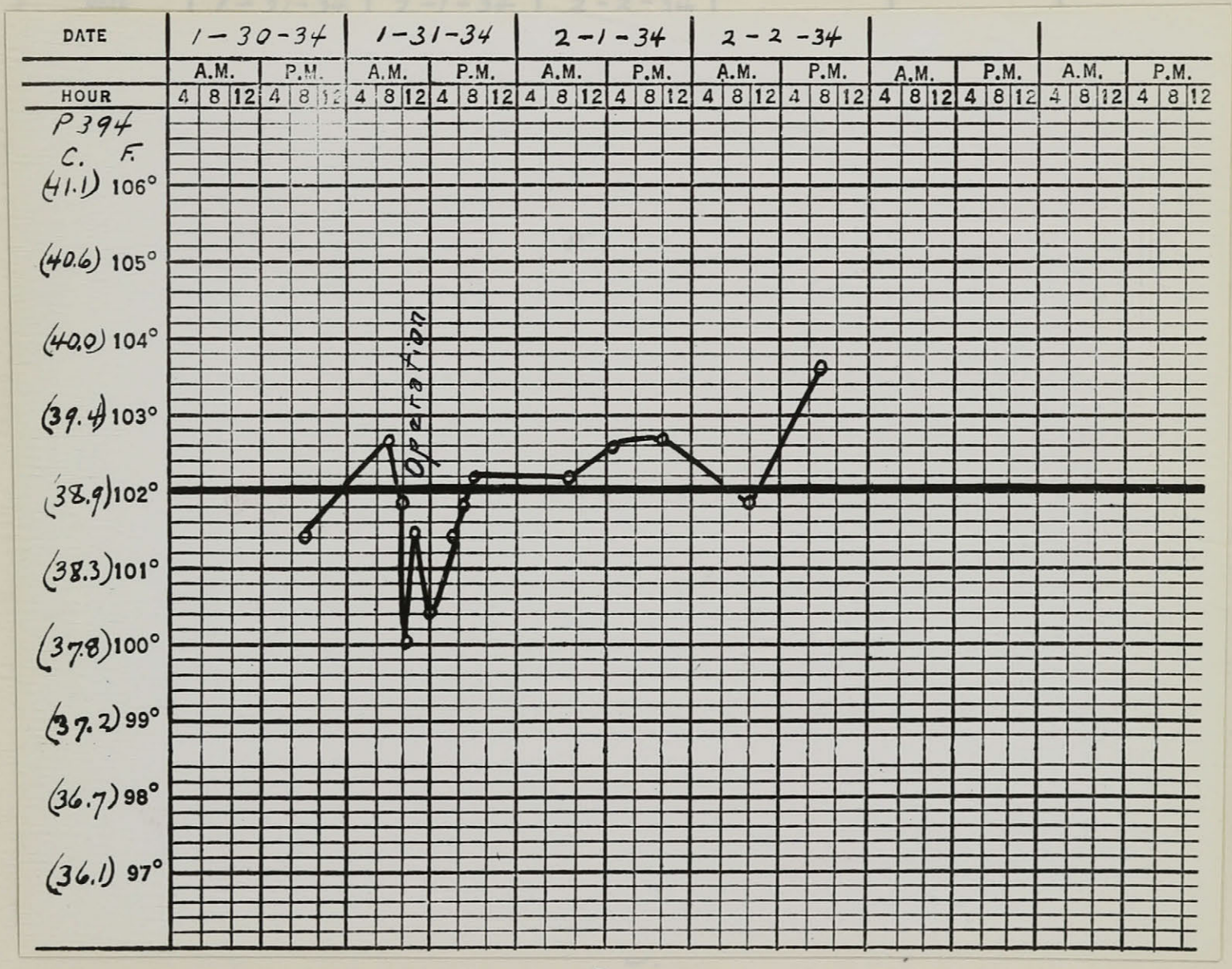


B.

FIG. 6, A - Photograph of a coronal section at the level of the corpora mamillaria showing a discrete unilateral lesion. (Frozen section stained with thionin).
B - Temperature chart before and after production of this lesion.

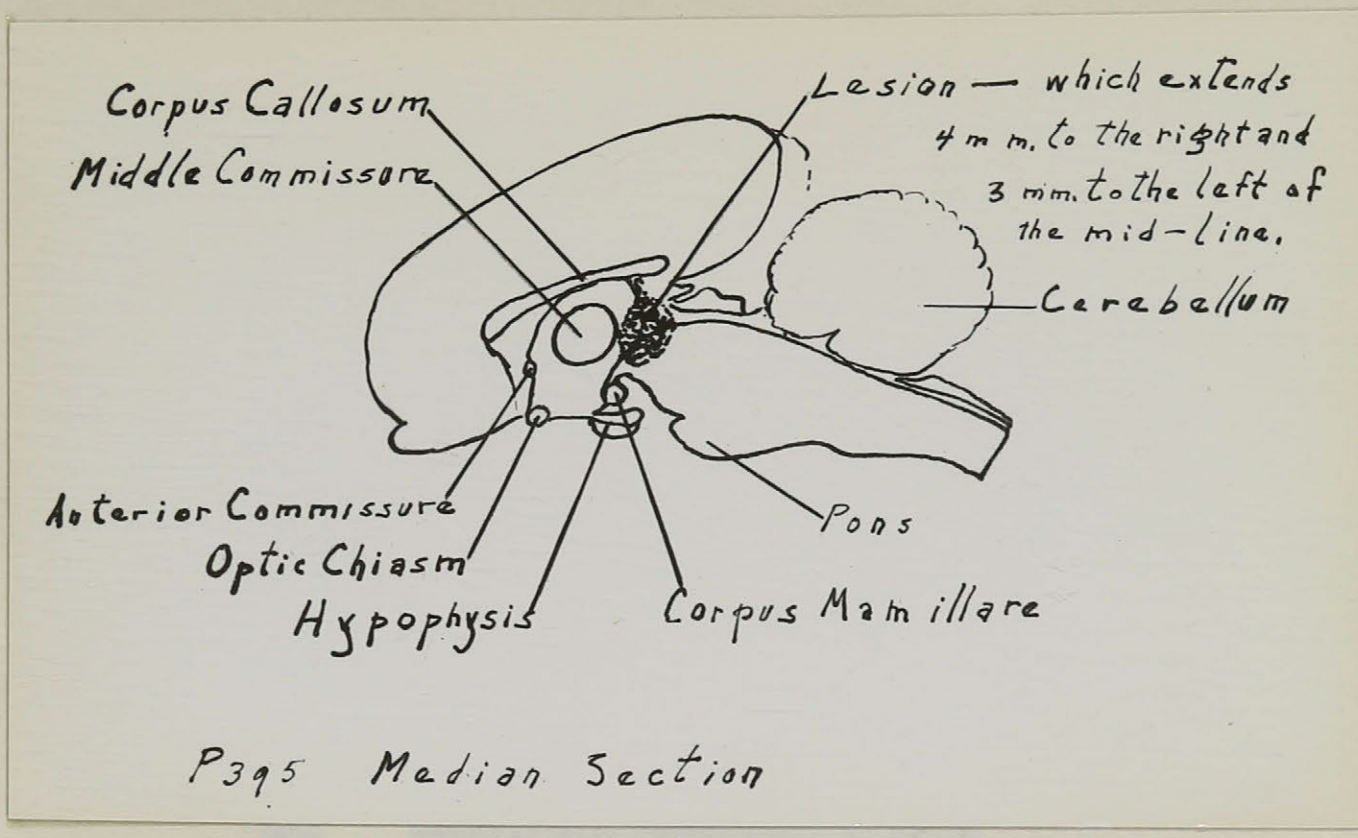


A.

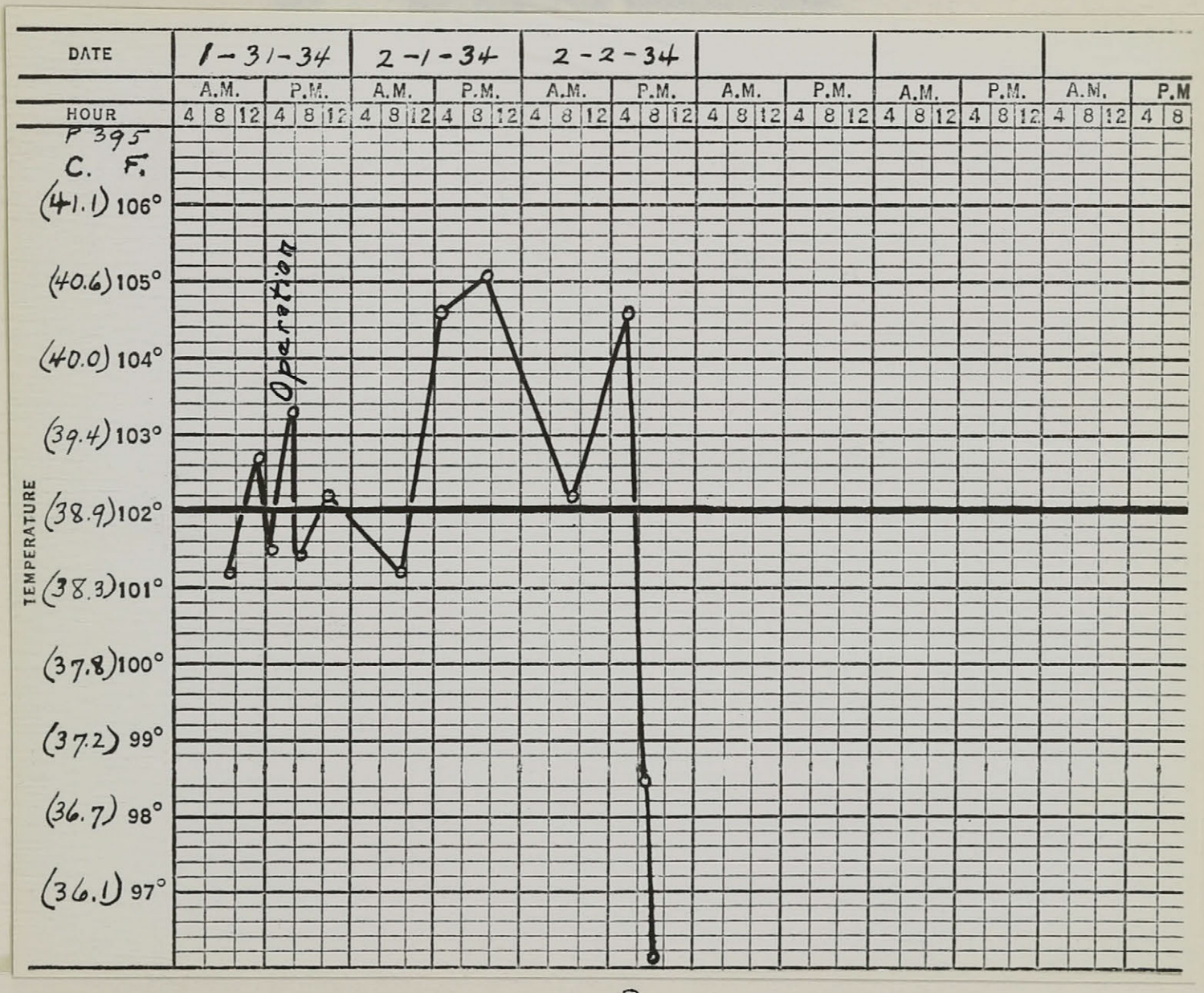


B.

FIG. 7, A - Sketch showing the location of a unilateral lesion in the brain, which did not cause any significant alteration from the normal body temperature.
B - Chart of temperature before and after this lesion was produced.



A.



B.

FIG. 8, A - Sketch showing location of a bilateral lesion in the posterion hypothalamus.
B - The rectal temperature which followed the production of this lesion.

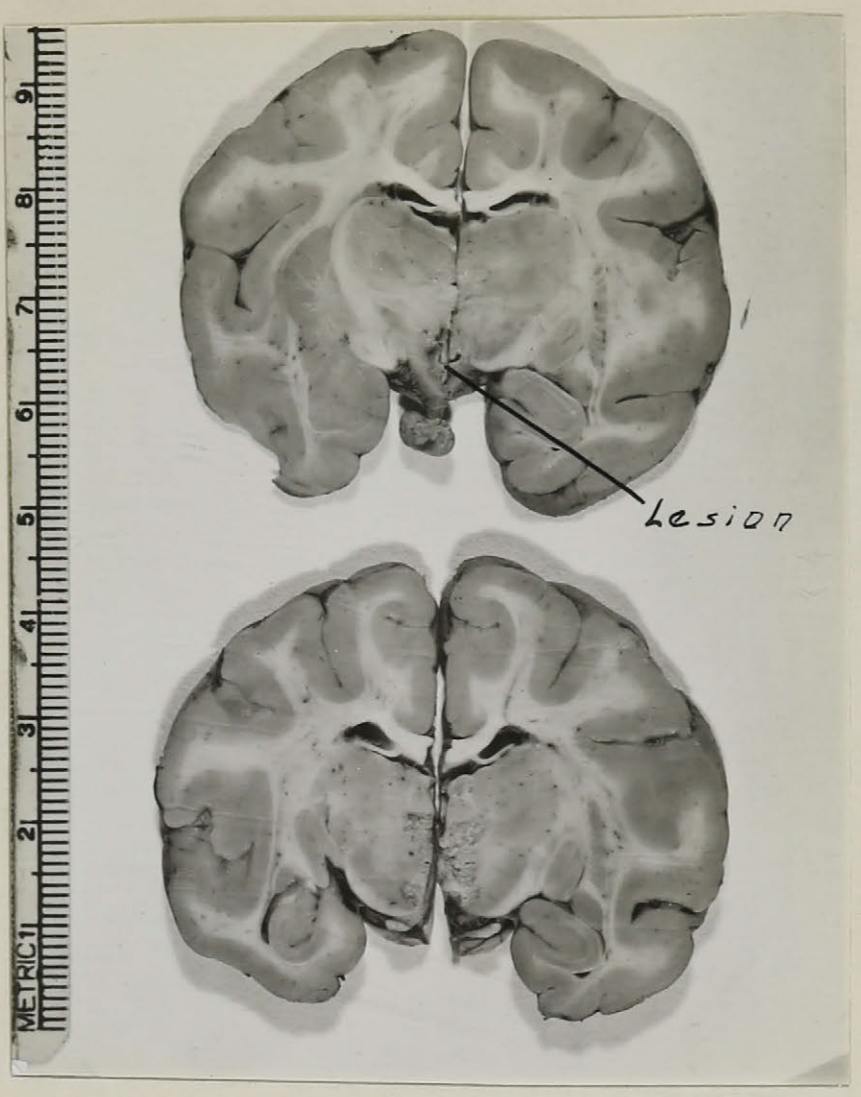
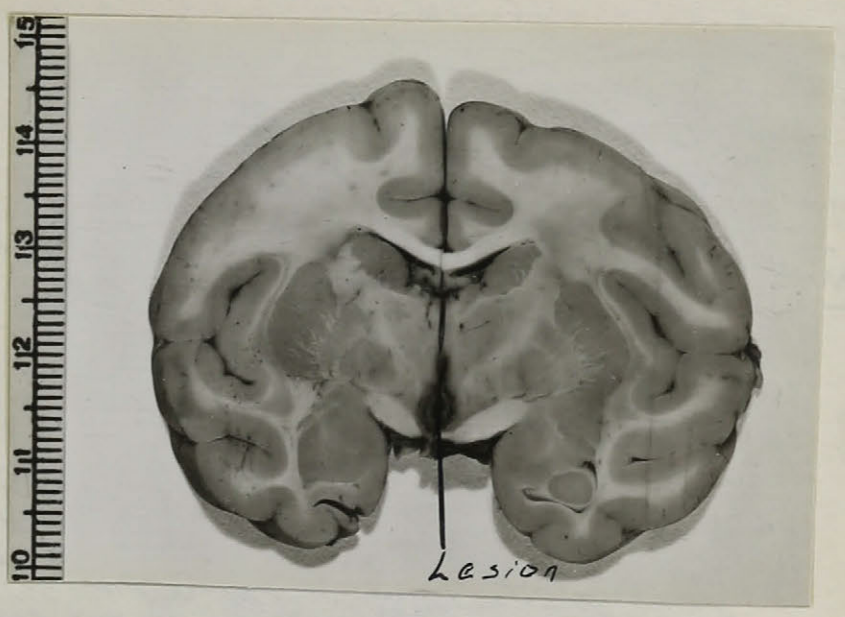


FIG. 9 Mid-sagittal and coronal sections of the brain of a monkey showing hypothalamic lesions which produced an absolute poikilothermia.



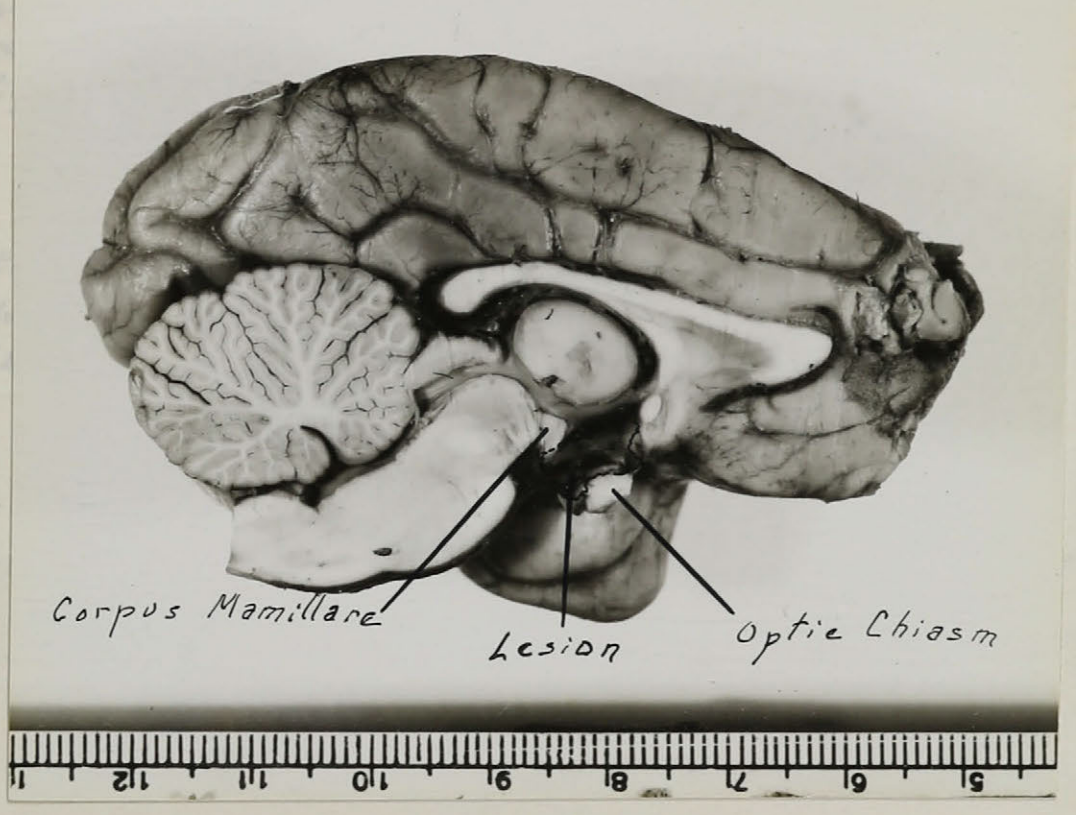


FIG. 10 Mid-sagittal and coronal sections of the brain of a monkey which had a normal temperature curve after operation. (Note the difference in extent of this lesion and that in FIG. 9, where the monkey was poikilothermic).

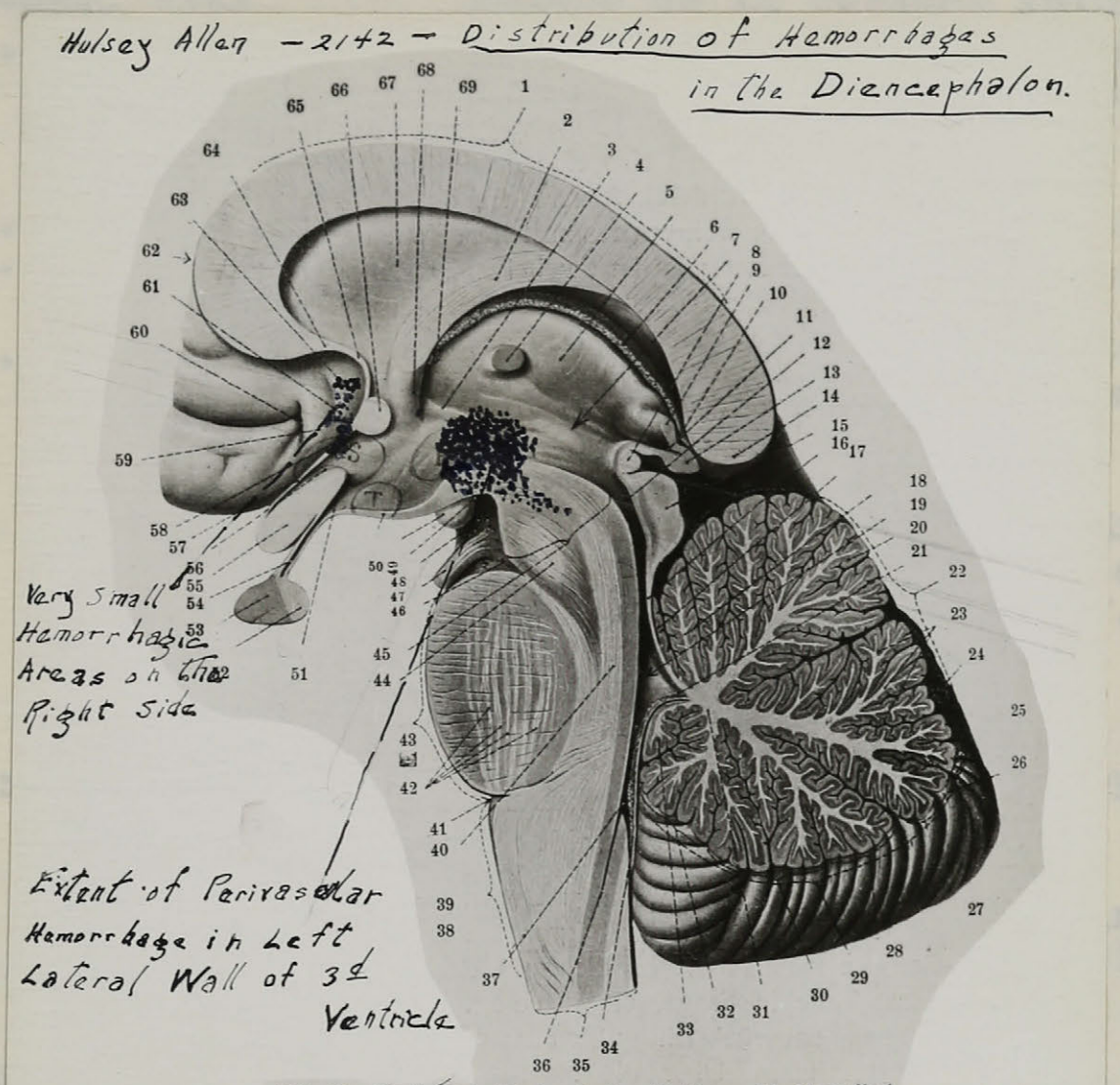


Abb. 2. Medianschnitt durch das Gehirn. III. Ventrikel.
(Nach einer Abbildung aus Sobotta, Atlas der Anatomie.)

FIG. 11 Mid-sagittal section of the diencephalon showing the distribution of hemorrhage in a case of head trauma which was followed by hyperthermia.

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