Nov. 1953.

8. Litchfield, J., and Wilcoxen, F., *J. Pharm. Exp. Therap.*, 1949, v95, 99.

9. Chinn, H. I., and Sheldon, G. L., unpublished data.

10. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P., *Arch. Internat. Pharmacodyn, Ther.*, 1953, v92, 305.

11. Boyd, E. M., Cassell, W. A., and Boyd, C. E., *Fed. Proc.*, 1953, v12, 303.

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Effect of Hypothalamic Lesions on Canine Neurogenic Arterial Hypertension.* (20923)

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That the hypothalamus plays a role in the regulation of the arterial tension has long been recognized, but it has also been known that it is not essential for the production of temporary hypertension by reflex or direct stimulation of the medulla oblongata. Its importance in the maintenance of chronic states of arterial hypertension has never been determined. The present study is concerned with the effect of lesions of the hypothalamus and its descending pathways upon chronic neurogenic hypertension in dogs. This type of hypertension is characterized by a marked increase in the cardiac output occasioned by the tachycardia which results when medullary cardiovascular centers are released from the inhibitory influence of stretch receptors in the carotid sinus and certain other arterial walls. According to some investigators, a polycythemia(3) and a peripheral vasoconstriction(1) are present as well. Nevertheless the present study concerns primarily the influence of the hypothalamus upon the raised central excitatory state of medullary cardiovascular centers which results subsequent to their release from peripheral inhibitory influences.

Methods. Twenty-four stock dogs were used in these experiments. They were rendered hypertensive by bilateral resection of the carotid sinuses, section of the vagosympathetic trunk on one side and a section of the aortic depressor nerve on the other. All

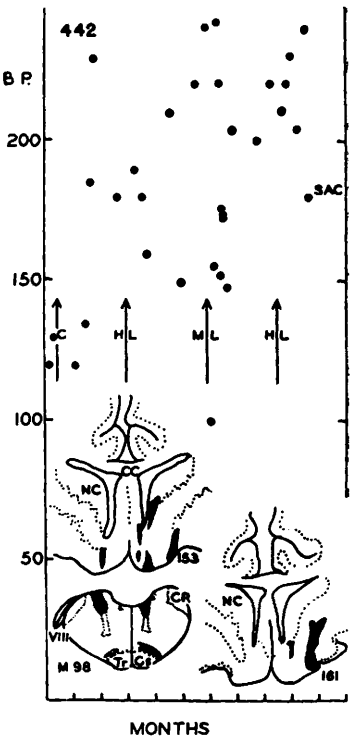

FIG. 1. (Dog 442). Indicates systolic blood pressures (ordinates) at intervals after excision of carotid sinus and partial vagectomy (C), and effect of bilateral hypothalamic lesions in septal region (Section 153), later medullary reticular lesions (Section 98) and finally larger lesions on the right side of anterior hypothalamus (Section 161). Although the pressures vary considerably, there was no consistent change following any of these procedures. Abbreviations used in the illustrations are as follows: C—moderator nerve section. CC—corpus callosum. CP—peduncularis cerebri. CR—corpus restiforme. HL—hypothalamic lesions. LG—corpus geniculatum laterale. M—corpus mammillare. MD—nucleus medialis dorsalis.

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ML—medullary lesions. NC—nucleus caudatus. NR—nucleus ruber. P—pulvinar. PC—commisura posterior. S—nucleus subthalamicus. Sac—sacrifice. Tr Cs—tractus corticospinalis. V—tractus spinalis nervi trigeminus. VIII—nervus acusticus. X—nucleus dorsalis vagi.

blood pressure determinations were made by percutaneous puncture of the femoral artery. When the hypertension was well established as determined by 3 or 4 systolic arterial pressures over 160 (usually 180-200 mm Hg), bilateral lesions were made in the hypothalamus or adjoining regions. These lesions were produced by inserting parallel needles, separated 4 mm and insulated except at the tips, through a midline burr hole into the hypothalamus. The position of the needles was controlled radiographically. An electrocautery current was passed for 30 seconds through each needle using a setting of 20 or 30 on the electrosurgical unit, which current would just coagulate the surface musculature. The resultant lesions varied somewhat in size, presumably due to escape of the current at points other than the tips of the electrodes. In early experiments an attempt was made to coagulate at points which gave pressor responses upon electrical stimulation but in later experiments, the lesions were made without prior stimulation in various parts of the hypothalamus and brain stem. All surgical procedures were carried out under general anesthesia and under aseptic conditions. Blood pressures were recorded for periods of 6-20 months after the production of neurogenic hypertension. In some experiments cortical ablations were made and if the elevated arterial pressure persisted after 6-12 months hypothalamic lesions were produced; finally lesions were placed in the brain stem of the still hypertensive dogs as shown in Table I. The animals were sacrificed under anesthesia and the brain, eyes, adrenals, kidneys, heart and thyroid removed for histological study. The brain was sectioned serially and stained for cells by Nissl's technic and for myelin by Weil's method.

Results. Of the 24 dogs utilized in these experiments, 14 survived sufficiently long to give significant results. The majority of dogs in which subsequent larger brain stem lesions were made did not survive the procedure for

TABLE I. Results of Hypothalamic Lesions.

B. P. (avg) before	Mo after hypothalamic lesion	Site of hypothalamic lesion	Result: B. P. range	Result: Avg	Remarks
150	12	Dorsal to optic chiasm (N. med. preoptic)	150-190	175	Hypothalamic lesions made first
200	6	R.—ant. paravent.	170-220	200	Preliminary bilateral frontal lobectomy
		L.—ant. limb. int. cap. at optic chiasm			
210	8	Prob. posterior hypothalamus*	160-230	220	Preliminary lesions of orbital gyri bilaterally
190	8	Hippocampus above mesencephalon	170-220	190	Preliminary bilateral occipital lobectomy; later medullary lesions
205	9	*	160-230	205	Preliminary bilateral orbital gyrectomy
190	10	Para-aqueductal	150-200	170	Preliminary bilateral cingular gyrectomy
200	1 (died)	N. lat. preopt. at post. optic chiasm	185-230	200	Preliminary bilateral ablation of motor cortex; died 1 mo P. O.
160	5	N. reuniens at post. optic chiasm	140-200	160	Preliminary bilateral frontal lobectomy
210	4	Prob. post. chiasmal	190-230	205	X-ray localization lesions only; brain too decomposed for study
200	7	Septal areas ant. to optic chiasm	150-240	195	2 pairs hypothalamic lesions, 1 pair medullary
190	6	N. post. hypothal. at N. subthal.	160-240	180	Medullary lesions caused death in 1 wk
185	3	N. interpeduncul.	100-240	220	Died after 2nd series hypothal. lesions
		N. tr. peduncul. trans.			
200	6	R.—N. mam. & N. interped.	150-240	185	Medullary lesions and second large post. hypothal. lesions
		L.—N. interpeduncul.			
150	3	R.—N. interpeduncul.	130-210	175	Died after 2nd series hypothal. lesions
		L.—N. mam. & N. interped.			

*Lesions not clearly defined in sections available.

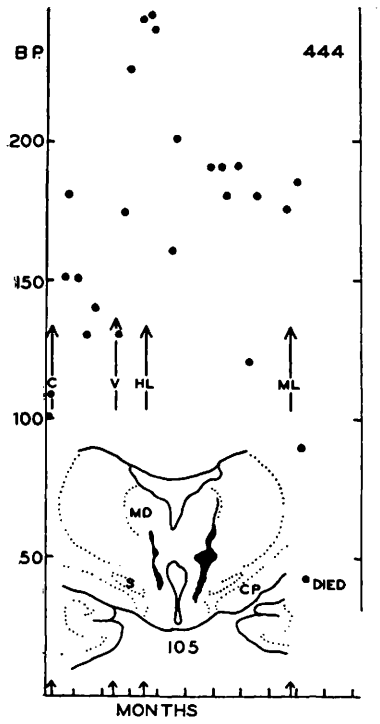

FIG. 2. (Dog 444). Indicates systolic blood pressures at intervals after induction of neurogenic hypertension (C) by carotid sinusectomy and partial vagectomy (repeated because of failure to maintain a hypertension (V)) and effect of bilateral hypothalamic lesions at level of subthalamic nuclei, and finally large lesions of the rostral pons from which the animal succumbed within a week.

more than a few hours or several days.

The site and the number of the electrocautery lesions and the brain stem incisions together with their resultant effect upon the neurogenic hypertension are listed in Table I. Most of the hypothalamic lesions were situated in its posterior extent in order to interrupt as many descending fiber tracts as possible, but neither anterior (Fig. 1) nor posterior (Fig. 2 and 3) electrocautery lesions, compatible with survival of the dog, resulted in a persistent fall in the arterial hypertension.

Incisions were made in the reticular substance of the medulla near the level of the lateral recess in 3 dogs with well developed neurogenic hypertension. One of these dogs died on the fourth postoperative day after having regained a blood pressure level of 170 mm Hg. The other 2 dogs had a marked but transient fall in their blood pressures (Fig. 2). By the end of the second postoperative week their hypertension had returned, and it persisted for the following 3 months period of observation. In a fourth dog (H24), small bilateral, transverse incisions in the region of the cephalic extent of the dorsal motor nucleus of the vagus nerve failed to prevent the development of chronic neurogenic hypertension. In the sections made of the eyes, adrenals, kidneys, heart and thyroid no abnormality was seen.

Discussion. This study would seem to indicate that the heightened activity of medullary cardiovascular centers which is occasioned by their release from the inhibitory influence of the moderator nerves is not permanently influenced to a significant degree by lesions of the hypothalamus and its descending pathways compatible with the survival of

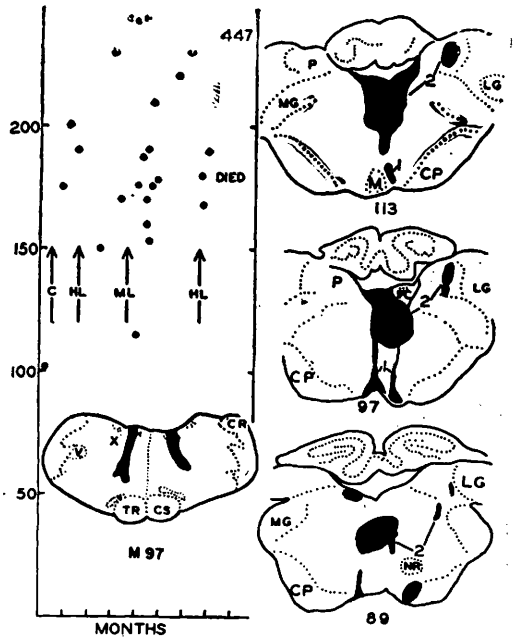

FIG. 3. (Dog 447). Indicates systolic blood pressures at intervals after induction of neurogenic hypertension (C) and effect of hypothalamic lesions destroying right mammillary body and damaging left retro-mammillary area (lesions marked 1 in sections 113 and 97), then bilateral lesions of medullary reticular areas (Section M97) and finally a large lesion of floor of aqueduct of Sylvius (lesions marked 2 in sections 113, 97 and 89). In spite of the extent of these lesions, and the eventual virtual destruction of the periaqueductal gray matter, blood pressure remained high until the animal's death 10 days after the last operation.

the dogs. It appears that the main source of nervous energy concerned with the maintenance of the hypertension induced by section of the moderator nerves is derived from medullary cardiovascular centers. Our results suggest that the most important chronic inhibitory influence upon these centers is the moderator nerve system, for although certain autonomic zones of the cerebral cortex, hypothalamus, and the upper brain stem are capable of vasomotor effects when excited electrically, their elimination to a greater or lesser extent does not necessarily modify the activity of the medullary cardiovascular centers in dogs with neurogenic hypertension. In fact, the pressor and depressor responses elicited from these higher levels of the central nervous system are as marked in hypertensive as in normotensive animals(2). These observations have led us to the conclusion that the neurogenic function of cardiovascular "centers" situated cephalad to those in the medulla is directed toward a modulation of the existing cardiovascular status for temporary needs without regard for the prevailing blood pressure level or pulse rate. Thus our concept of the neurogenic control of the arterial tension is that the moderator nerve system acting at the medullary level is the most important homeostatic influence upon the blood pressure and that higher levels of the central nervous system produce essentially temporary modulating influences upon these vital centers. This does not deny that such temporary cardiovascular effects repeatedly induced might not result in a state of chronic hypertension in some indirect fashion such as by altering renal hemodynamics, but it seems to us unlikely that a purely neurogenic type of chronic hypertension would frequently exist without a disturbance of cardiovascular regulatory functions at the medullary level.

Summary. Chronic neurogenic hypertension in dogs induced by moderator nerve section producing an increase in the central excitatory state of the medullary cardiovascular centers, is not permanently influenced to a significant degree by lesions of the hypothalamus or its descending pathways compatible with survival of the animals. It is suggested that the most important neurogenic homeostatic influence upon the arterial tension is exerted by the moderator nerves at the medullary level and that higher levels of the central nervous system act as temporary modulating influences in response to momentary needs rather than as chronic adjusters of the arterial tension.

1. Heymans, C., *Compt. rend. Soc. de Biol.*, 1931, v107, 1293.

2. McQueen, J. D., and Walker, A. E., *Arch. Neurol. and Psychiat.*, 1952, v67, 833.

3. Schafer, P. W., PROC. SOC. EXP. BIOL. AND MED., 1942, v49, 327.

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In vitro Induction of Cartilage in Mouse Somite Mesoderm by Embryonic Spinal Cord. (20924)

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Evidence has been accumulating that the origin of axial cartilage in fish(1), amphibia (2), and the chick(3) is dependent upon association of somite mesoderm with spinal cord. An inductive influence of some kind between the 2 tissues has been postulated. Inductive tissue interaction in mammals recently has been described in simple 2-component systems *in vitro*(4), offering opportunity for analysis of mechanism(5). The present experiments were designed to determine whether inductive effects between spinal cord and somites could be demonstrated under similar conditions. For this purpose clusters of somites from 9-day mouse embryos were cultured in the presence or absence of