CHRONIC HYPERTENSION PRODUCED BY CAROTID SINUS AND AORTIC-DEPRESSOR NERVE SECTION*

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HERING'S DEMONSTRATION[1] of acute hypertension in various animals, especially the rabbit, after bilateral section of the carotid sinus and aortic-depressor nerves, was followed by his inquiry into the possibility of producing chronic hypertension by the same means. The results of his investigation were only partially successful. His pupils, Koch and Mies,[2] in 1929, employing rabbits, with a slight variation in technic, reported more substantial hypertensive results, ranging from 125 to 178 Mm. of mercury over a period of months (maximum of 511 days). In 1931, Koch[3] observed the production of chronic hypertension of several months' duration by similar means in dogs. In the same year, Heymans and Bouckaert[4] published their first series of studies on chronic hypertension in dogs, reporting values as high as 250 Mm. of mercury. In 1933, Kremer, Wright and Scarff[5] confirmed Koch and Mies's observations in the rabbit, observing elevations of pressure between 120 and 190 Mm. of mercury; 80 per cent of the cases registered between 150 and 190 Mm. Dautrebande,[6] in 1934, recorded three dogs with pressures of 190 to 220 Mm. of mercury, in his studies on the pharmacologic and chemical properties of the carotid sinus nerve.

A reconsideration of Koch's earlier work led him and his co-worker, Mattonet[7] to recant his original claims of chronic duration of the hypertension obtained by carotid sinus and aortic-depressor denervation. Green, DeGroat and McDonald[8] also reported essentially negative results after section of these afferent pathways.

The writer began this investigation, in 1934, on dogs, resorting to the Hering technic as modified by Heymans.†

METHOD.—Twenty dogs were studied. Ether or intravenous nembutal (0.5 cc. of 6 per cent solution [Abbott] per kilo) were used for anesthesia. In 13 of these dogs bilateral denervation was accomplished in one stage, according to the Hering-Heymans technic. This consisted of excising both common carotid bifurcations with the intervening plexus constituting the carotid sinus nerve and by resecting one to two centimeters of the aortic-depressor nerve in the vagal sheath (Fig. 1). In one dog, the effect of unilateral excision of the carotid bifurcation and aortic-depressor nerve was studied.

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† This technic, and the results of Heymans' investigation, were personally observed, in his laboratory in Ghent, by the author over a period of a year.

In three dogs, "pure denervation" was attempted by leaving the carotid bifurcation intact, resecting the carotid sinus plexus with careful removal of all macroscopic evidence of nerve structures including the adventitia in this region, and by excision of the aortic-depressor nerve in the neck as described above.

Damage to the internal carotid artery during this procedure, in one dog, necessitated excision of the bifurcation after pure denervation of the other side. This dog developed hypertension and was grouped with the first series.

The anemic effect of excising the carotid bifurcations and leaving the aortic-

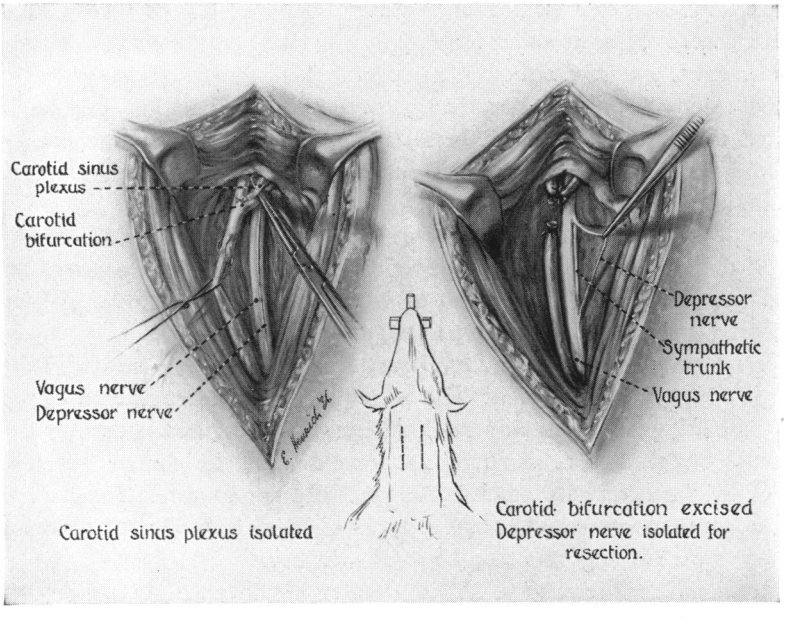

FIG. 1.—The Hering-Heymans method for carotid sinus exclusion and aortic-depressor nerve section.

depressor nerves intact was studied in one dog. It was further investigated by ligating the external and internal carotid arteries in two dogs. This procedure left the carotid sinus nerve plexus undisturbed.

Identification of the aortic-depressor nerve is unquestionably the most difficult part of the denervation. In some cases it stands out as a definite, fine white strand at the level of the carotid bifurcation lying within the vagal sheath in the groove between the cervical sympathetic trunk medially and the vagus trunk laterally (Fig. 1). In doubtful cases, Kreidman's[9] method of identification of the nerve is very helpful. He observed that the nerve is formed by two or three fine strands at the junction of the superior laryngeal and vagus nerves which unite into a single strand and which continues its peripheral course as described above.

In several doubtful cases, stimulation of the cranial end of one of these strands was employed to observe cardiac slowing or hypotension but this test

could not be relied upon consistently. Its chief value lay in identifying the cervical sympathetic trunk which responds to stimulation by marked ipsilateral exophthalmos.

Blood pressure readings were accomplished by direct arterial puncture with a No. 19 or 20-gauge, intravenous needle with appropriate manometric connections for kymographic recording, 25 per cent magnesium sulphate being used as anticoagulant. The dogs were immobilized on their backs on an animal board and were observed for any unusual excitement during the process of blood pressure registration. In several cases the possible exciting effect of this procedure was studied by recording the heart rate by means of a modified Boas cardiotachometer before and during the blood pressure registration. Pressures were taken at about fortnightly intervals. One control blood pressure was usually taken, although in several dogs two to four readings were obtained when the initial pressure appeared unusually high. The dog's diet consisted of cooked meat, milk, bread and water. The animals were kept in cages and were exercised only by being allowed to run about the room once a day for a short time.

RESULTS.—*Control Blood Pressure and Heart Rates in Dogs:* In this series of dogs the predenervation blood pressures obtained by direct femoral arterial puncture varied from 100 to 162, averaging 130 Mm. of mercury. The heart rates ranged from 92 to 170, averaging 124.

Effect Upon the Heart Rate of Direct Puncture of the Femoral Artery for Blood Pressure Determination: The response of the heart rate to this procedure was used as an index of a possible exciting effect and consequently false hypertensive registration. In Dog 23, for example, the control heart rate as recorded by the Boas cardiotachometer was 115 per minute. Insertion of the needle into the artery caused absolutely no change in the heart rate while the blood pressure reading was 214 Mm. of mercury.

Criteria for Hypertension: While greater significance should be attached to relative changes in blood pressure, certain criteria are obviously necessary for gauging the results as a whole. On the basis of an average blood pressure of 130 Mm. of mercury, it was decided to establish 180 Mm. as a minimum hypertensive requisite. The required minimal duration was taken as six months. One dog (No. 15) was included with a hypertensive period of four and one-quarter months, however, because death occurred under an anesthetic prior to splanchnic section, after a consistently maintained average arterial tension of 213 Mm. of mercury.

Effect of Bilateral Carotid Bifurcation Excision and Aortic-Depressor Nerve Resection on Blood Pressure (Hering-Heymans Technic): Of the 13 dogs denervated by this method, seven developed definite chronic hypertension (Chart 1 and Table I). Four dogs showed only transient or no hypertension, and two died within four days after denervation.*

* Since submission of this article for publication three more dogs with hypertension have been added to this series, making a total of 10 chronic hypertensive dogs out of 16 attempts.

Marked elevation of arterial pressure was observed as early as two days after this type of denervation. Thus Dog 9, whose control pressure was 124 prior to denervation, showed an increase to 184 two days later. In Dog 7, the pressure rose from a control level of 158 to 190 on the third day. In general, the blood pressure became definitely elevated within two to three

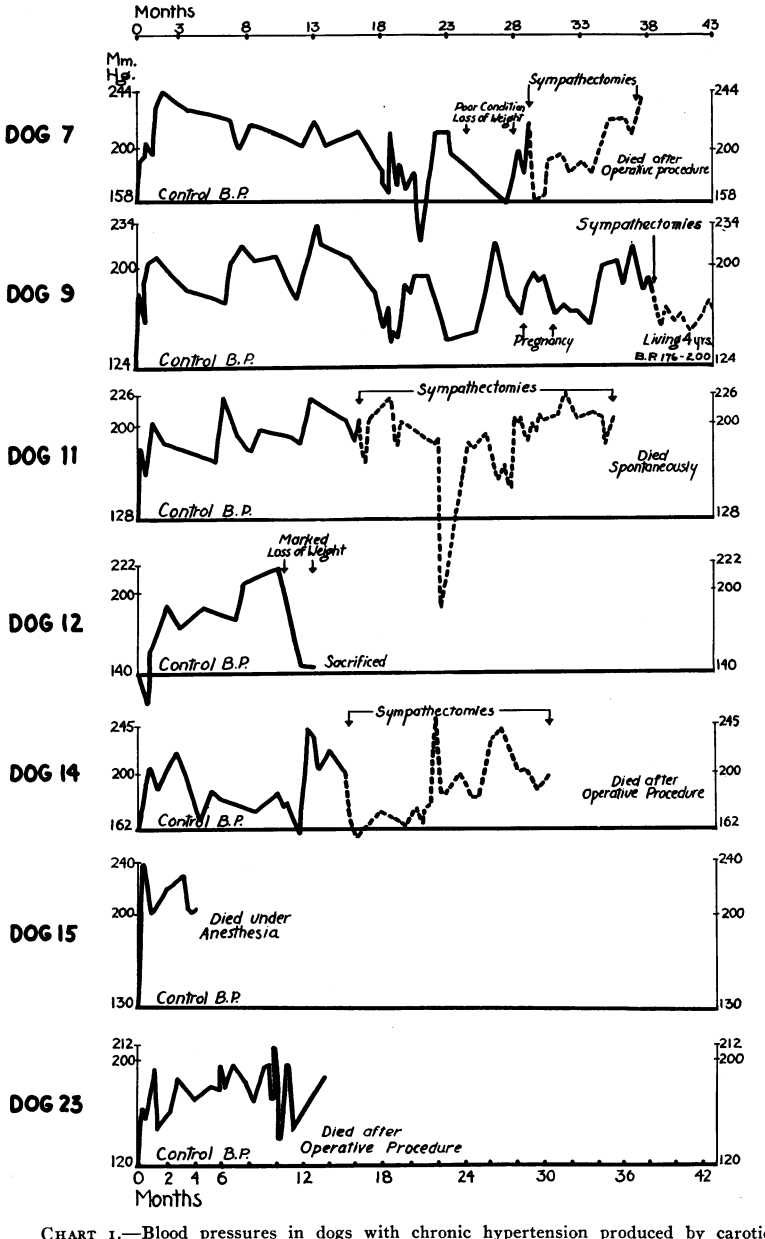

CHART 1.—Blood pressures in dogs with chronic hypertension produced by carotid sinus and aortic-depressor denervation. (Details of sympathetic procedures will appear in a subsequent communication.) Blood pressures brought up-to-date to show longevity of hypertension.

TABLE I

SUMMARY OF BLOOD PRESSURES AND HEART RATES IN DOGS WITH CHRONIC HYPERTENSION PRODUCED BY CAROTID SINUS AND AORTIC-DEPRESSOR DENERVATION

Dog No.	Sex	Control B.P. and H.R.	Maximum B.P. Corresponding H.R.	Minimum B.P. Corresponding H.R.	No. B.P. Determinations	Per Cent B.P. Readings over 180 Mm.	Final B.P. and H.R.	Duration of Hypertension in Months
7	M.	B.P. 158 Mm. H.R. 155	B.P. 244 Mm. H.R. 174	B.P. 156 Mm. H.R. 150	52	67	B.P. 240 Mm. H.R. 96	38—Operative procedure fatal
9	F.	B.P. 124 Mm. H.R. 140	B.P. 234 Mm. H.R. 228	B.P. 140 Mm. H.R. 150	50	60	B.P. 190 Mm. H.R. 192	39—Living*
11	M.	B.P. 128 Mm. H.R. 170	B.P. 226 Mm. H.R. 222	B.P. 112 Mm. H.R. 136	53	74	B.P. 202 Mm. H.R. 146	36—Died spontaneously
12	F.	B.P. 140 Mm. H.R. 110	B.P. 222 Mm. H.R. 228	B.P. 114 Mm. H.R. 180	11	55	B.P. 146 Mm. H.R. 132	10—Sacrificed at 13 months. Condition poor. B.P. low
14	M.	B.P. 162 Mm. H.R. 136	B.P. 245 Mm. H.R. 156	B.P. 154 Mm. H.R. 138	38	68	B.P. 202 Mm. H.R. 150	30¼—Operative procedure fatal
15	M.	B.P. 130 Mm. H.R. 96	B.P. 244 Mm. H.R. 216	B.P. 197 Mm. H.R. 186	7	100	B.P. 204 Mm. H.R. 186	4¼—Died of anesthesia
23	M.	B.P. 120 Mm. H.R. 94	B.P. 212 Mm. H.R. 77	B.P. 142 Mm. H.R. 83	26	54	B.P. 190 Mm. H.R. 96	13½—Operative procedure fatal

* Died at 48½ months after operative procedure, with final blood pressure of 186 Mm. Hg.

weeks after denervation. These findings are in agreement with those observed in the rabbit by Kremer, Wright and Scarff.[5] The maximum reading obtained was 245 Mm. of mercury in Dog 14.

Effect of Unilateral Carotid Bifurcation Excision and Aortic-Depressor Nerve Resection on the Blood Pressure: Unilateral (left) excision of the carotid bifurcation and depressor nerve in the neck in one dog resulted in hypertension (210-190 Mm. of mercury) of seven and one-half months' duration, with return to about normal after this interval.

Fluctuations of Blood Pressure and Known Factors Associated with Such Fluctuations: Fluctuations in arterial tension were observed in the rabbit by Koch and Mies, and by Kremer, Wright and Scarff, and also in the dog by Heymans and Bouckaert.[10] In Dogs 11 and 15, the blood pressure readings showed practically no fluctuations (Chart 1 and Table I). Known factors associated with fluctuations may be stated as follows:

(a) *Regeneration or Incomplete Denervation.* In two dogs, which failed to develop definite chronic hypertension after the Hering-Heymans operation, experiments were carried out to examine evidence of the aortic-depressor nerves due to regeneration or incomplete removal. The possible presence of the aortic-depressor nerves was determined by section of the vagi, below the

region of resection and by cephalad faradic stimulation at this point. In one of these dogs (No. 19), bilateral vagotomy caused the blood pressure to rise temporarily from 150 to 216 Mm. of mercury, in another dog (No. 16), there was a slight rise from 114 to 140 Mm. In the latter dog there was evidence of a depressor reaction (118 to 74 Mm.) upon faradic stimulation of the left vagus.

(b) *Debility and Loss of Weight.* Dog 12 began to lose weight from severe cachexia 10 months after denervation. During the ensuing three months the blood pressure dropped to 146 after a persistent level of 182 to 222 Mm. of mercury. Recovery seemed unlikely and the dog was sacrificed.

Dog 7 also became cachectic 14 months after denervation with a drop to normal over a period of six months, after which, however, the blood pressure rose concomitantly with clinical improvement.

(c) *Pregnancy.* Dog 9 became pregnant 29 months after denervation. Prior to this time the blood pressure curve was quite variable with an upward trend before pregnancy so that the effect of the latter was difficult to evaluate. The blood pressure, however, rose further from 186 to 196 and dropped abruptly to 160, 10 days before termination of pregnancy (Chart 1). This part of the blood pressure readings can, in fact, be duplicated in other sections of the curve where spontaneous elevations and depressions were even more marked. The significant feature would appear to be absence of a striking hypertensive effect of pregnancy.

Duration of Hypertension: The shortest duration in this hypertensive series was four and one-quarter months (Dog No. 15), death occurring accidentally under anesthesia prior to an operative procedure. The longest survival was in Dog 9, with a hypertensive duration of three years and three months. (This dog is still alive after unilateral thoraco-abdominal sympathectomy with a final blood pressure of 200 Mm. of mercury, four years after denervation.)

Heart Rate: In general, denervation was followed by a marked and sustained augmentation of the heart rate. In practically all the dogs the acceleration varied almost directly with the blood pressure (Table I). In four dogs (Nos. 9, 11, 12 and 15) the maximum blood pressure readings showed correspondingly maximum heart rates. In three dogs (Nos. 7, 14 and 23) this relationship did not hold.

Dog 9 illustrates the parallelism with a maximum blood pressure of 234 Mm. of mercury and corresponding maximum heart rate of 228 per minute (Chart 2). Dog 7 shows the dissociation of these two factors with a blood pressure of 220 Mm. of mercury and heart rate of 130 per minute (Chart 2).

That adrenal secretion plays a definite rôle in the tachycardia in some of these animals, and a contributory rôle in others, was shown by diminution in the heart rate after bilateral adrenal inactivation or unilateral removal and contralateral inactivation. These findings will be discussed in detail in a subsequent communication.

Blood Counts, Cell Volume, Blood Gases, Blood and Urine Chemistry:

Blood counts, cell volume, oxygen and carbon dioxide content and capacity of the blood were within normal limits. Examination of carbohydrate, protein, fat, chloride and calcium content of the blood revealed no deviation from the normal. Uranalysis was also not remarkable except for a slight amount of sugar and moderate albumen.

Effect of Denervation of the Carotid Sinus Leaving the Bifurcation and Branches Intact with Excision of the Aortic-Depressor Nerve in the Neck—"Pure Denervation": This procedure was employed in three dogs, all of which failed to develop definite hypertension. Thus Dog 16, the control pressure of which was 117 Mm. of mercury, showed an increase of tension to 162 in two

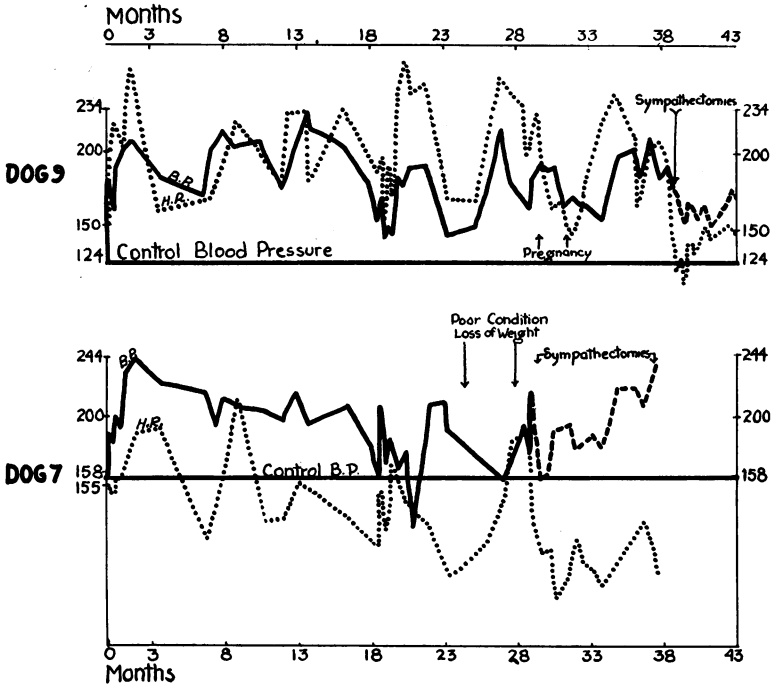

CHART 2.—Blood pressures and corresponding heart rates in dogs with chronic hypertension produced by carotid sinus and aortic-depressor denervation.

weeks followed by a drop to the control level and a later return to 154 Mm. of mercury two months after denervation. It is of interest that subsequent bilateral excision of the carotid bifurcations also failed to induce hypertension.

Dog 17, starting with a blood pressure of 146 Mm. of mercury, responded to pure denervation by a gradual rise to 172, four months after denervation, but returned to 143 Mm. eight months after denervation.

Dog 18 showed a rise from a control pressure of 144 Mm. of mercury to 166, three days after denervation and a decline to 154 Mm. at the end of one month. Excision of both carotid bifurcations subsequently failed to produce hypertension.

Effect upon Blood Pressure of Excision of the Carotid Bifurcation and of

Ligation of the Branches of the Carotid Bifurcation: In Dog 19, the control blood pressure of which was 116 Mm. of mercury, the carotid bifurcations were excised in one stage. The maximum pressure observed after this procedure was 146 Mm. of mercury six weeks later. Seven and one-half months later it was 108 Mm. of mercury. It is of interest that bilateral depressor nerve section at this time also failed to produce hypertension. The highest pressure recorded was 144 Mm. of mercury, six weeks after this section.

In two dogs, the branches of the carotid bifurcation were ligated. The results in these dogs were as follows: In Dog 20 the blood pressure rose sharply from a control level of 150 to 197 Mm. of mercury in the first week, after which it showed variations and a gradual return to 158 Mm. of mercury in four months. Dog 29 showed a rise from a control pressure of 142 to 179 Mm. of mercury; this level has been maintained to date over a period of three and one-half months. Thus the anemic effect of exclusion of the carotid bifurcation or its branches with respect to the blood pressure response is a variable one. When the effect is hypertensive it was not permanent except in one dog which was only recently operated upon.

DISCUSSION.—The recantation of Koch,[7] and the negative results of Green, DeGroat and McDonald[8] have raised serious doubts as to the accuracy of the findings of the workers who have reported chronic hypertension by carotid sinus and aortic-depressor denervation.

Examination of Koch and Mattonet's[7] results on four dogs, all of which failed to maintain their original hypertension, shows that at least two manifested evidence of depressor nerve activity by a rise in pressure (125 to 185 Mm.) after bilateral vagotomy in the terminal experiment. The other two dogs showed slight rises in pressure after the same procedure. In the face of these indications of incomplete denervation or regeneration, their work cannot be considered conclusive.

The possibility of incomplete denervation or regeneration might also be considered in the technic employed by Green, DeGroat and McDonald.[8] In order to assure complete chronic denervation of the carotid sinus nerve, excision of either arterial branch of the carotid bifurcation or the bifurcation itself has been practiced by most workers. The technic of Green and his coworkers leaves the bifurcation and its branches intact. Employing a similar technic, referred to above as "pure denervation," the writer was unable to produce definite hypertension in three dogs, and in this respect is in agreement with these workers but failure to obtain hypertension was ascribed to incomplete denervation. Our control experiments on the anemic effect of carotid bifurcation excision and of ligation of the branches of the bifurcation, although variable, appeared to rule out anemia as a factor in this hypertension. It is impossible to say, however, whether this degree of anemia might not sensitize the effect of carotid sinus and aortic-depressor denervation.

On the other hand, terminal studies carried out in two of our four failures, operated upon by the Hering-Heymans' technic, showed evidence of some

degree of depressor nerve response upon stimulating the cranial end of the cut vagus nerve. It cannot be stated that the amount of depressor activity observed was sufficient to account for the lack of hypertension. It is conceivable that other afferent pathways were operating in these dogs to neutralize the hypertensive effect of the denervation.

Fluctuations in blood pressure readings have already been described by previous workers. In three of the seven hypertensive dogs the fluctuations were marked, reaching normal values frequently over a period of weeks. As discussed in the results, inanition was undoubtedly the cause of this remission in two dogs, while in the third no apparent cause could be found. In two of these dogs hypertension was reestablished. Insistence on a sustained high arterial tension, although met with in two of our dogs, is an exacting demand in the light of clinical hypertensive experience.

The absence of abnormal chemical changes in the blood carbohydrate, protein, fat, chloride, calcium, oxygen and carbon dioxide argues against the possibility of chemohumoral basis for the hypertension produced by this method. The lack of disturbance in the cell volume rules out blood viscosity as a factor. On the other hand the investigations of Hering,[1] Koch and Mies,[2] Heymans and Bouckaert,[11] and Nowak[12] show that the hypertension resulting from carotid sinus and aortic-depressor denervation is chiefly neuroconstrictive.

SUMMARY

(1) Chronic hypertension was produced in ten dogs by carotid bifurcation excision and cervical aortic-depressor nerve resection.

(2) The maximum duration of hypertension was three years and four months.

(3) Fluctuations in arterial tension were observed in the majority of these dogs. Inanition was definitely responsible for marked remission of hypertension in two dogs.

(4) Failure to produce chronic hypertension by this method occurred in four dogs. In two of these animals, in which terminal experiments were carried out, there was evidence of some degree of aortic-depressor nerve activity.

(5) The anemic effect of excising the carotid bifurcations are discussed.

(6) "Pure denervation," preserving the vessels of the carotid bifurcation, failed to produce lasting hypertension in three dogs.

(7) Unilateral (left) denervation produced hypertension in one dog of seven and one-half months' duration, with final return to normal level.

(8) Pregnancy did not alter appreciably the course of hypertension in one dog.

(9) Persistent tachycardia was a common finding after denervation. Its degree varied directly with the blood pressure readings in most instances. Maximum blood pressure readings were correlated with maximum heart rates in about one-half the cases.

(10) There were no changes in the blood carbohydrates, proteins, fats, chlorides, calcium, oxygen, carbon dioxide, cell volume and red cell counts.

(11) Urinalyses were also essentially normal.

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