EXPERIMENTAL HYPERTENSION—OBSERVATIONS ON SUSTAINED ELEVATION OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN DOGS

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(Received for publication May 25, 1936)

The study of hypertension by animal experimentation has been hampered by the absence of satisfactory means of producing sustained elevations of blood pressure, and by the lack of accurate methods of recording systolic and diastolic blood pressures in the intact unanesthetized animal.

Recently, however, Goldblatt and his coworkers (1) have described an excellent method for the production of sustained increase in systolic blood pressure in dogs. Hypertension was produced by these authors by reducing the blood flow to the kidneys through the application of special silver clamps to both renal arteries; increases in systolic blood pressures, as recorded by the Van Leersum carotid loop method (2), were observed for as long as fifteen months after operation. Further, one of us, in a recent study (3), by using a syhygmographic blood pressure assembly originally described in principle by Erlanger (4) and later modified by Kolls (5), was able to record successfully systolic and diastolic hypertension in the unanesthetized dog. Although increases in systolic blood pressure have been reported, very few studies of diastolic blood pressures by acceptable methods are available in experimental hypertension, and even these are not of sufficiently long duration.

This communication presents studies on the effects of renal ischemia obtained by application of Goldblatt clamps, on the effects of ligation of the renal artery, and of partial nephrectomy on both the systolic and diastolic blood pressure in the unanesthetized dog. A further modification of the method utilized by Kolls and Cash (6) for measuring blood pressure in the unanesthetized dog is described.

Eight dogs, after suitable control periods, have been subjected to the following procedures: three animals have had Goldblatt clamps applied to the renal arteries, two have had partial nephrectomy, and three, ligation of the renal artery. Numerous observations on systolic and diastolic pressure have been made at appropriate intervals over periods of five to twenty-eight months. Seven additional animals have been subjected to renal ischemia of short duration produced by the application of Goldblatt clamps. In the prolonged experiments occasional blood nonprotein nitrogen, twenty-four hour water intake, urinary output, and determinations of the specific gravity of the urine have served to indicate major changes in renal function.

METHODS

Large and medium size dogs of mixed breeds have been used. They have been fed on prepared dog food (protein content approximately thirty per cent), supplemented by appropriate addition of cod liver oil from time to time. Water has not been limited to any specific amount except when the animals have been placed in metabolism cages for twenty-four hour studies of the urine at which time food was withheld and water measured and limited. Animals have been housed in individual cages and kept for weeks under laboratory conditions prior to the experimental period. The temperature of the room, in which blood pressure measurements were taken, varied between 70° and 78° F., except for somewhat higher temperatures obtaining at times during the summer months. The measurements of blood pressure were made on unanesthetized dogs by two observers.

Method of determination of blood pressure

The method which was utilized for measuring blood pressure employs the usual sphygmomanometer assembly with the special sphygmograph designed by Kolls (5). This apparatus has been tested repeatedly in the unanesthetized dog by Kolls and Cash (6) who proved the accuracy of the method by simultaneous direct measurement of systolic and diastolic pressures with the maximum-minimum valve, in dogs which received both morphia and ether anesthesia.

An additional modification to the apparatus has been made by us which has proved practical and satisfactory. Owing to the difficulty of obtaining and keeping fresh

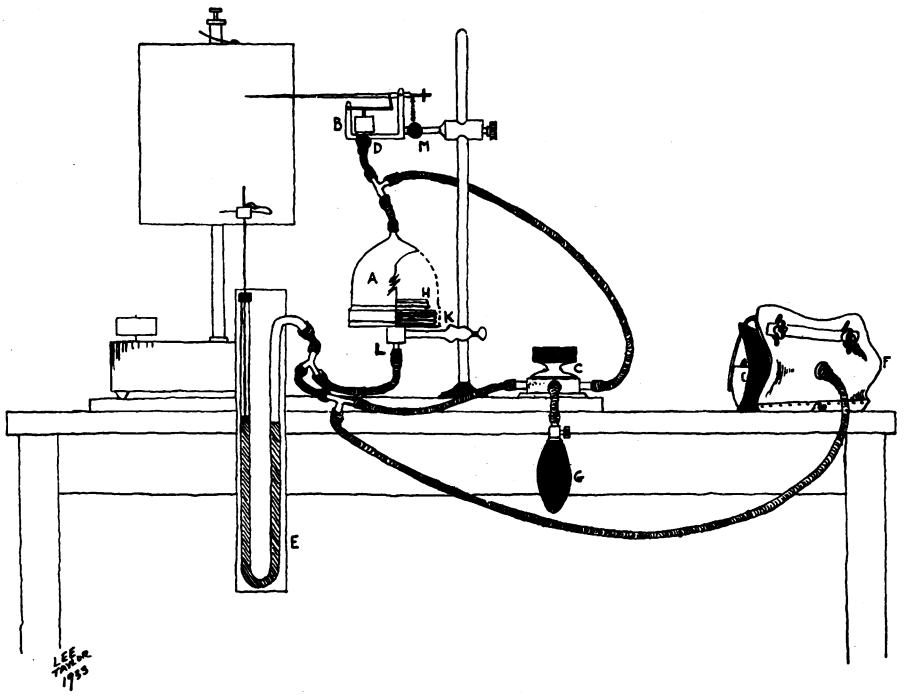

FIG. 1. ARRANGEMENT OF SPHYGMOMANOMETER ASSEMBLY.

A—Pressure bell; *B*—Kolls' sphygmograph; *C*—Three way valve; *D*—Escape valve of sphygmograph for adjustment of lever excursion; *E*—Mercury manometer; *F*—Metal and leather cuff containing rubber cuff for dog's leg; *G*—Bulb for inflation of cuff; *H*—Flange; *K*—Flanged base over which heavy rubber membrane is stretched; *L*—Outlet below rubber membrane connected with manometer cuff and three way valve; *M*—Screw adjusting lever against drum.

the original type of Erlanger bulb and to difficulties in recording low diastolic pressures with the more recent Erlanger and Meek sphygmoscope (7) we have substituted a pressure bell (*A*), Figure 1, measuring 8 cm. in diameter across the base over the flange (*H*) over which an unusually thick piece of automobile inner tubing (4.5 mm. thick) is tied with fine, strong cord. The bell is screwed on to the base (*K*), which is slightly raised above a lower outlet (*L*). This latter feature allows a delicate response to pulsations at extremely low diastolic levels, while at higher systolic levels the thick rubber diaphragm prevents overdistention into the bell toward the upper outlet. The measurements and shape of cuff (*F*), suitable for practically any dog, are essentially the same as those already described by Kolls.

The hair on the dog's leg should be kept closely clipped, the cuff accurately fitted as high as possible and maintained in this same position during the entire time of the tracing. As the pressure in the cuff is pumped up gradually, the dog may strain and tighten the leg muscles. Generally relaxation follows promptly and pressure may be recorded. Occasionally a very nervous animal may fail to respond to training.

Though this apparatus has proved highly satisfactory when properly used, we should like to point out that experience with its numerous idiosyncrasies is necessary to obtain consistently accurate results. Dust, variations in temperature, and necessarily frequent handling may result in slight binding of the delicate joints or jewel bearings of the compound lever. Light weight, highly glazed paper, when smoked, frequently develops small, rough areas which interfere with the action of the lever. Therefore, a heavy variety of unglazed paper, lightly smoked is to be recommended. The lever should barely touch the drum, otherwise the small pulsations of systolic pressure will not be shown by a sudden increase in amplitude or the reduction in amplitude at the diastolic level will not be clearly reflected. Very accurate adjustment of the pressure of the lever against the drum is readily accomplished by the screw (*M*). We have found it best to regulate this pressure so that the lever writes in slightly broken lines (Figure 2). We have also found that the bakelite cap (*B*) (Figure 1) sometimes contracts or expands sufficiently to cause binding upon the underlying gold plated cylinder. This can be readily corrected by polishing with emery powder, or even slight reaming out with a small, sharp scalpel. The final point at which serious difficulty may arise is in the three-way valve (*C*) which allows atmospheric pressure to be maintained in the bell above the rubber membrane both during inflation

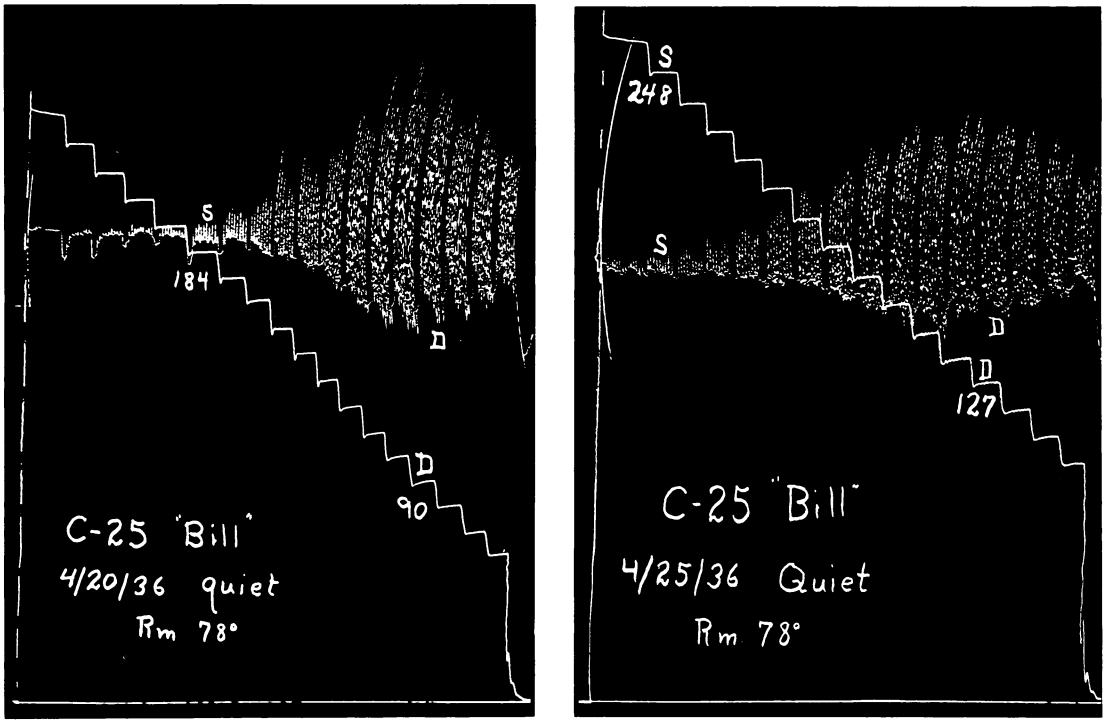

FIG. 2. TYPICAL SPHYGMOGRAPHIC RECORD OF BLOOD PRESSURE ON DOG C–25.

Tracing April 20, 1936, taken five months after application of Goldblatt clamp to right renal artery. Tracing April 25, 1936, taken taken three days after application of Goldblatt clamp to left renal artery. *S*—Systolic, *D*—Diastolic blood pressure level.

and deflation of the cuff. The grease with which the valve is kept sealed frequently is inadequate for the purpose or partially obstructs one of the openings and prevents the ready adjustment of pressure within the bell on the two sides of the rubber membrane. Any interference with this mechanism will, of course, produce bizarre paroxysms of the lever. All values on the tracings have been charted even from the first day of training, unless some obvious mechanical error occurred. Generally speaking, we have found greater variation in the systolic pressures, while diastolic readings are less labile.

Two sphygmographic records are shown in Figure 2. The first sudden increase in amplitude of the sphygmoscopic lever, with slight spreading of the limbs, represents the systolic pressure and sudden decrease of amplitude, the diastolic. Opinion as to appearance of systolic excursions may occasionally vary slightly (8 to 10 mm.) but the diastolic readings are nearly always sharp and unmistakable. Four or five pressures, both systolic and diastolic, have been recorded on one ordinary smoked kymograph paper, fixed and filed as a record.

EFFECT OF RENAL ISCHEMIA (GOLDBLATT CLAMP) ON BLOOD PRESSURE

Goldblatt and his coworkers (1) found that constriction of one renal artery almost invariably produced hypertension with a gradual return toward the normal level while constriction of both renal arteries led to a sustained increase in blood pressure. Animals were observed for as long as fifteen months after operation.

Our own experience with this method [1] is reported in the following experiments.

Experiment 1, Dog C–1 (Figure 3). Goldblatt clamps —both renal arteries. Male, hound, weight 40 pounds. Preoperative observations of blood pressure were made in Dog C–1 from September 19, 1933, until November 28, 1933, when, following the usual retroperitoneal approach, a Goldblatt silver clamp was applied to the right renal artery. The clamp was tightened one and three-quarter turns, or three quarter turns back from complete obliteration. A prompt recovery with no rise in blood pressure ensued.

On January 3, 1934, a Goldblatt clamp was applied to the left renal artery. This time the clamp was tightened two and one-quarter turns, almost obliterating the left renal artery; faint pulsations could still be felt, however,

[1] Silver clamps and instruments for their application were obtained through courtesy of Dr. Harry Goldblatt, Cleveland, Ohio.

on the renal side of clamp. A sharp rise in blood pressure, particularly diastolic, followed (Figure 3).

Striking polyuria and marked nitrogen retention also occurred, blood nonprotein nitrogen rising to 182 mgm. per 100 cc. just before death. Animal lost appetite, weight and strength, and died February 3, 1934. Autopsy confirmed position of clamps.

During the four months prior to constriction of the renal artery the blood pressures in this animal showed a mean systolic value of approximately 170 mm. Hg with a steadier diastolic level with a mean of approximately 70 mm. Hg. Constriction of the right renal artery caused little change, but subsequent constriction of the left renal artery brought about a sharp rise of blood pressure to a mean systolic of 200 mm. Hg and a mean diastolic of 110 mm. Hg. That the reduction of blood flow to the kidney was severe enough to cause marked renal insufficiency is attested by the rising nonprotein nitrogen in the blood, increased urinary output over water intake in twenty-four hour tests, falling urinary specific gravity, cachexia, and death of the animal.

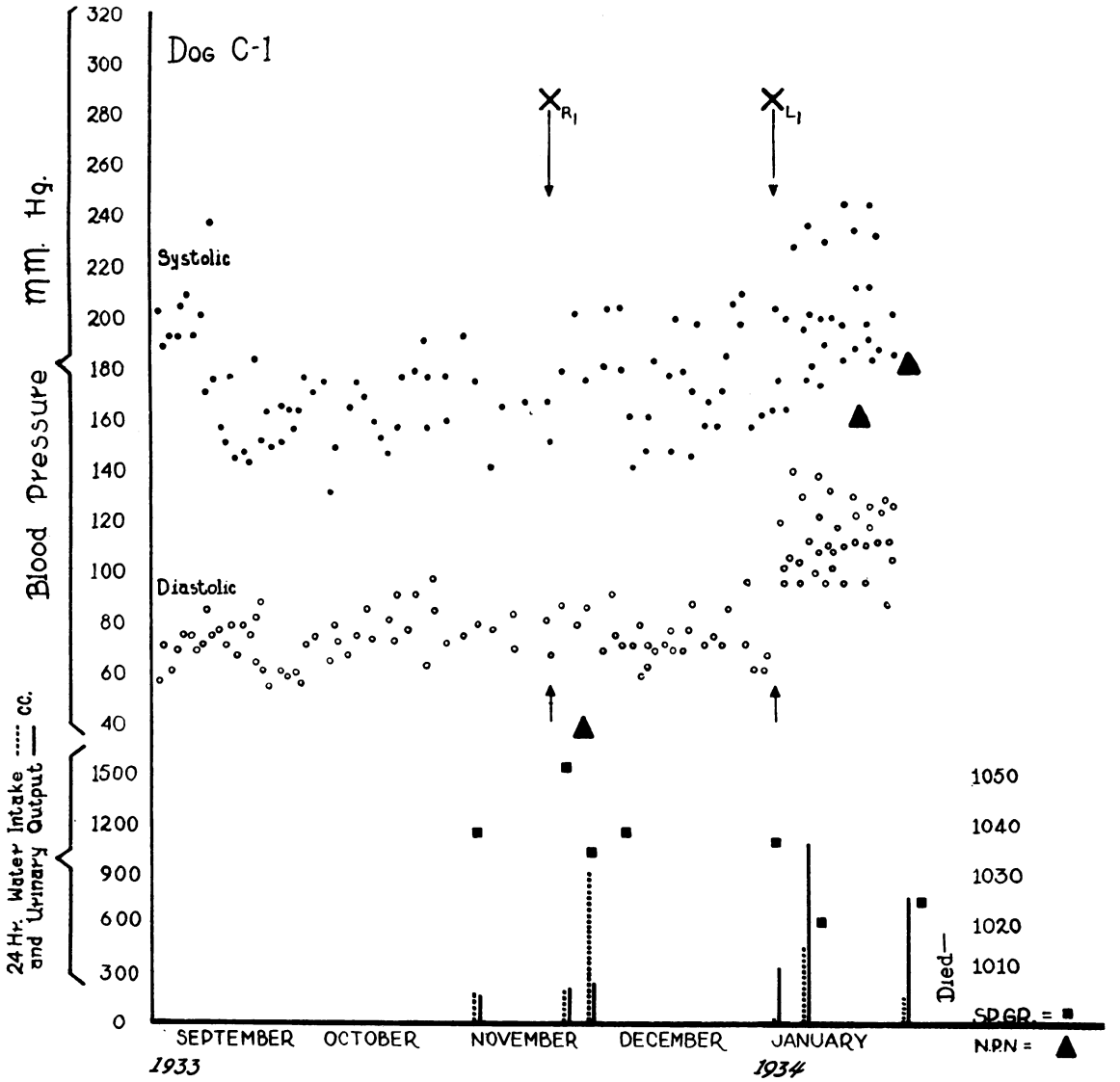

FIG. 3. GOLDBLATT CLAMPS ON RIGHT RENAL ARTERY, XR_1 MODERATE CONSTRICTION, AND LEFT RENAL ARTERY, XL_1 MARKED CONSTRICTION.

In this and subsequent charts black dots represent systolic and open circles diastolic pressure; triangles, blood nonprotein nitrogen expressed in mgm. per 100 cc.; squares urinary specific gravity; interrupted lines (- - - -) twenty-four hour water intake; and solid line (———) twenty-four hour urinary output; arrows, time of operative procedure.

While this discussion does not plan to deal with the pathological findings it is interesting to note that the differential ventricular dissection of this dog's heart showed a L/R ratio of 2.125 (left ventricular weight 59.4 grams, right ventricular weight 27.95 grams), a figure obtained after the method of Herrmann (8) and well above his maximum normal ratio of 1.773 based upon differential dissection of 200 hearts from normal dogs. Our own experience with the differential ventricular dissection of normal dogs has always fallen within Herrmann's L/R ratio extremes of a minimum of 1.153 and a maximum of 1.773.

The following experiment illustrates the effect of slight to moderate reduction of blood flow through the renal arteries.

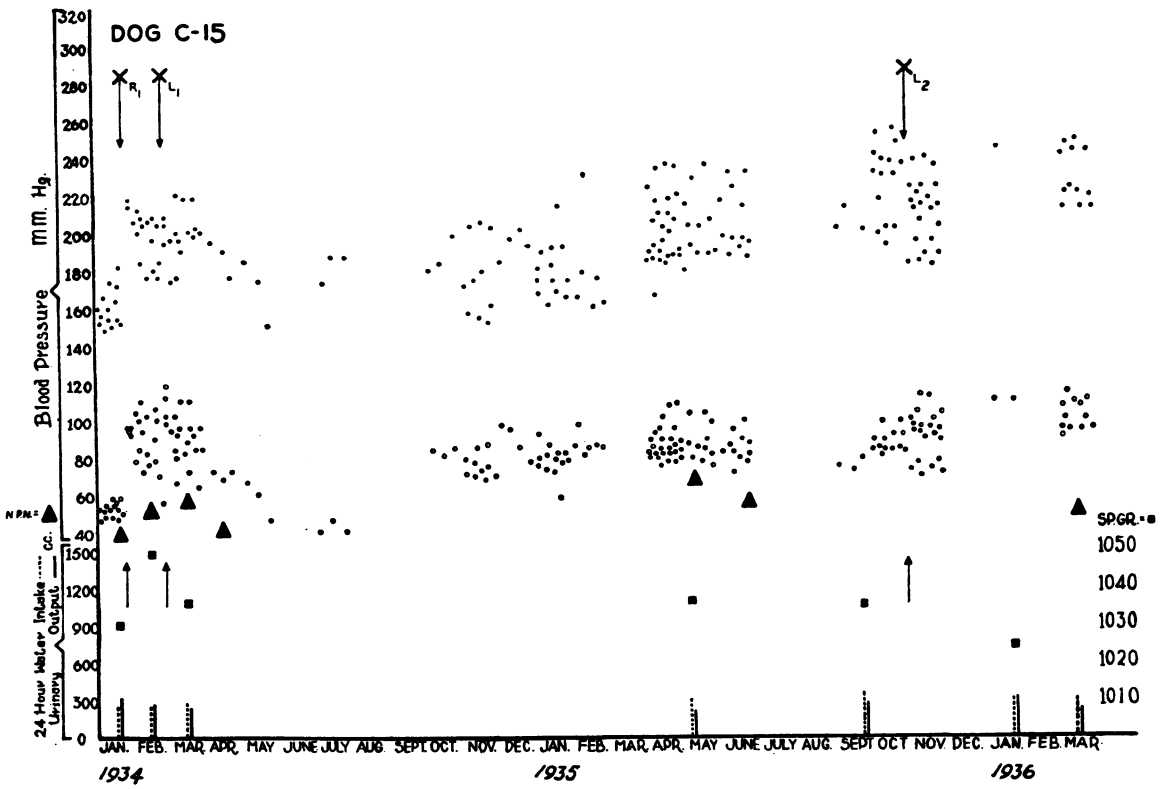

FIG. 4. GOLDBLATT CLAMPS, XR_1 MODERATE CONSTRICTION RIGHT RENAL ARTERY, XL_1 SLIGHT CONSTRICTION LEFT RENAL ARTERY, XL_2 ADDITIONAL AND MARKED CONSTRICTION OF LEFT RENAL ARTERY.

Experiment 2, Dog C–15 (*Figure 4*). Goldblatt clamps—both renal arteries. Male, mongrel, weight 21.5 pounds. Control observation for preoperative levels of blood pressure were made in this animal from January 11 to January 25, 1934. The diastolic pressure was low and unusually stable during the control period. On January 25, following the usual retroperitoneal approach, a Goldblatt clamp was applied on the right renal artery, tightened to the point of complete obliteration, and then loosened one-half turn, allowing a small amount of blood to pass through the artery to the kidney. The blood pressure, particularly the diastolic, rose sharply, and then returned gradually toward more normal levels. A Goldblatt clamp was then applied to the left renal artery on February 27, 1934. Another slight rise of blood pressure was obtained; this was followed in time by a temporary fall but later a definitely elevated mean diastolic pressure. On November 8, 1935, a third operation exposed the silver clamp on the left renal artery, and this was tightened an additional two turns, almost obliterating the artery. The animal has remained in relatively good health. The absence of renal insufficiency is probably due to the fact that the renal arteries are small and the degree of clamping indicated is not as effective as in larger dogs. Present weight is 22.5 pounds.

This dog, with less severe constriction of the renal arteries, has shown slight but definite hypertension but no diminished renal function. During the control period prior to operation the mean systolic pressure was approximately 160 mm. Hg, and the diastolic 52 mm. Hg. For months following moderate constriction of the renal arteries the systolic pressure approximated a mean of 185 mm. Hg and the diastolic a mean of 80 mm. Hg. Variations occurred but the tendency, except on two occasions, has been toward the maintenance of relatively higher diastolic pressure. This slight but definite rise in blood

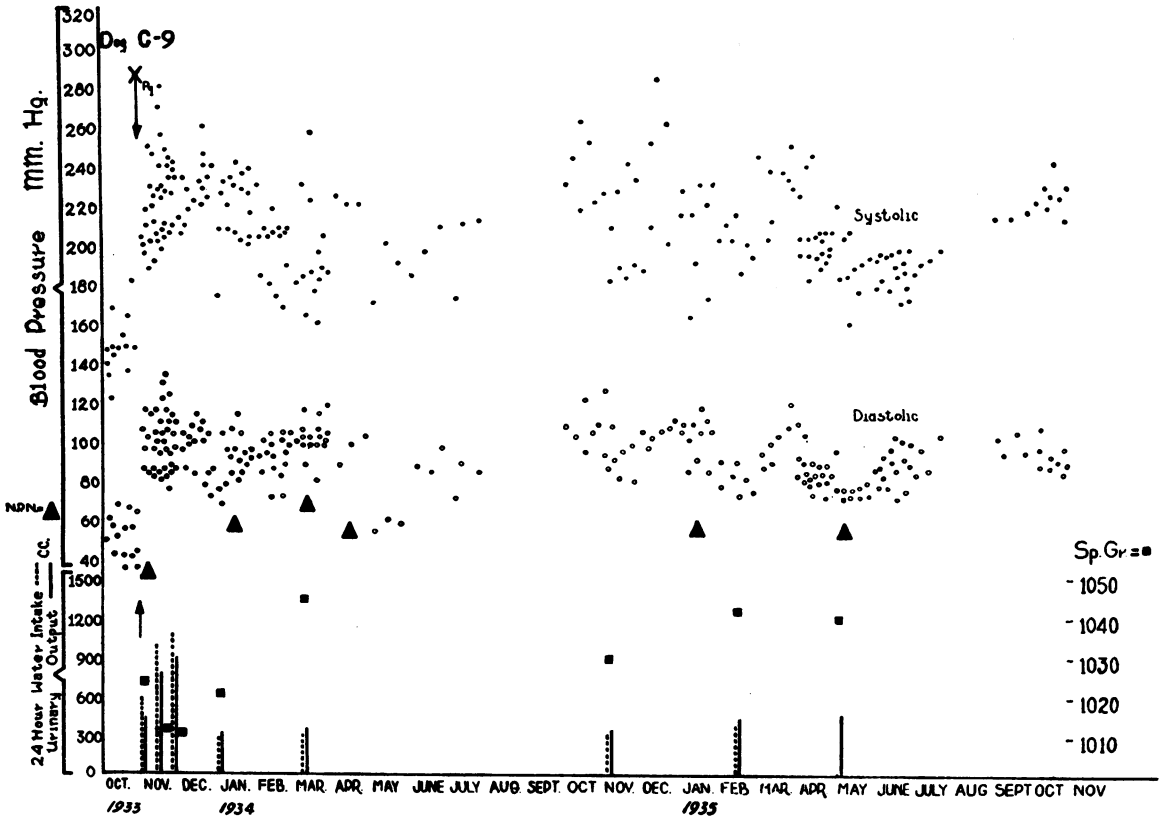

FIG. 5. GOLDBLATT CLAMP, XR_1 MARKED CONSTRICTION OF RIGHT RENAL ARTERY.

pressure, while within the limits of normal blood pressure for some animals, apparently represents mild hypertension for this dog with a greater degree of diastolic pressure developing after the third operation (Figure 4).

The third animal in this series has proved of unusual interest.

Experiment 3, Dog C-9 (*Figure 5*). Goldblatt clamp —right renal artery. Male, hound, 27 pounds. Control readings of the blood pressure were observed in Dog C-9 from October 12, to November 2, 1933. The animal was somewhat nervous, requiring patience and care during the recording of each set of blood pressures. On November 2, 1933, a Goldblatt clamp was applied to the right renal artery and tightened two and one-eighth turns, causing marked partial obliteration of the artery. There was a sharp rise in blood pressure, both systolic and diastolic, with a very gradual return toward the normal. As the pressures remained definitely above the original levels no second operation has been attempted. No nitrogen retention, polyuria, cachexia or renal insufficiency has occurred. The animal is in good condition; weighs 37.5 pounds, 24 months after operation.

Goldblatt and his coworkers noted a moderate rise in blood pressure following constriction of one renal artery but went on to complete their experiment with reduction of blood flow in both vessels. The behavior of arterial pressure following constriction of the right renal artery in Dog C-9 of our series led us to omit application of a second clamp. A mean systolic blood pressure of 148 mm. Hg and a mean diastolic of 54 mm. Hg in the control period was followed immediately after application of a clamp to one renal artery by a mean systolic of well above 200 mm. Hg and a diastolic well above 90 mm. Hg. Elevated values have persisted for two years.

Experiment 4 (*Figure 6*). Goldblatt clamps—one renal artery. Dogs C-9, C-18, C-24, C-25, C-29, C-30, C-31 and C-34. The unusual behavior of Dog C-9 and the fact that Goldblatt and his coworkers constricted the right renal artery first, with more striking results, led us to investigate blood pressure changes following approximately equal constriction of right and left renal arteries. Goldblatt clamps were applied in the usual fashion to the right renal artery of four dogs, the clamps tightened to complete obliteration and then loosened one-half turn. A similar procedure was carried out on three additional dogs using the left renal artery. Blood pressures were recorded several days before and after each experiment and significant rises occurred in all animals (Figure 6) save the last (C-30). Finally, thinking that trauma or edema might affect the renal pedicle, we applied a clamp to the right renal artery of one dog (C-30), tightened and immediately removed the clamp. Severe constriction of either the right or left renal artery frequently leads to a significant rise

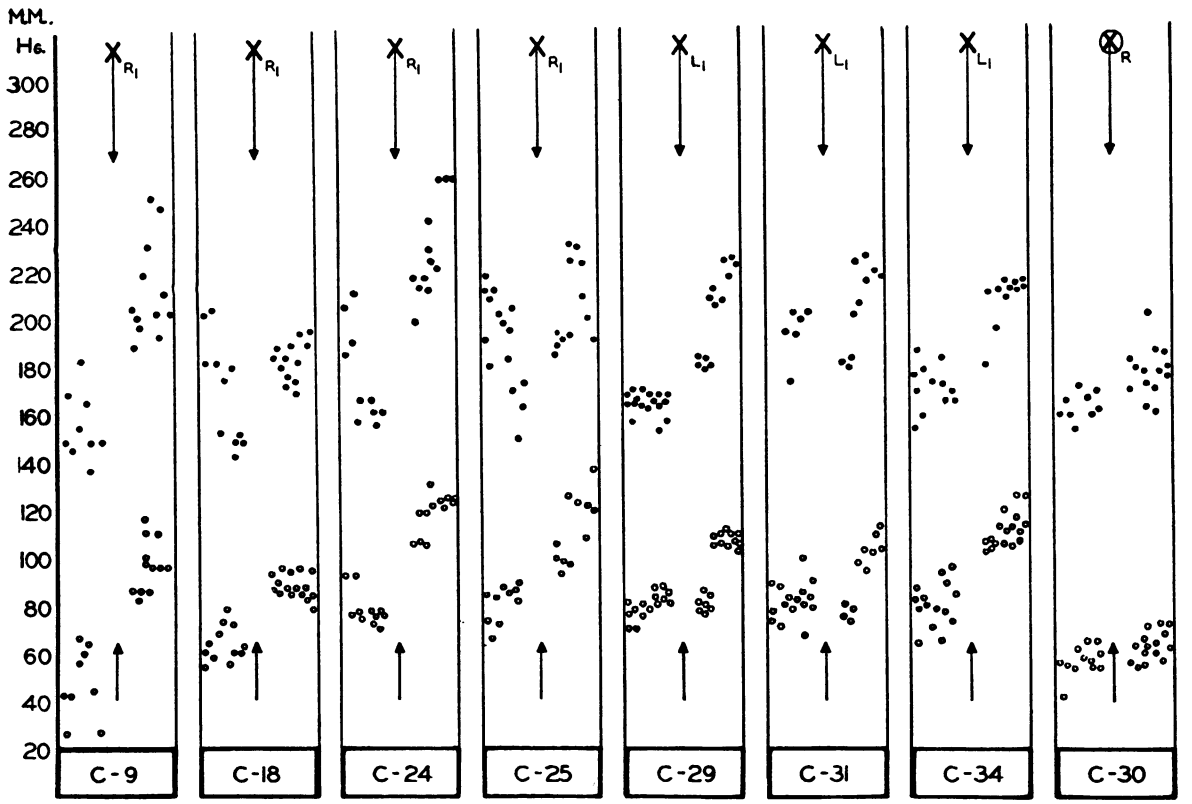

FIG. 6. GOLDBLATT CLAMPS, BLOOD PRESSURE BEFORE AND AFTER APPLICATION OF CLAMPS TO RIGHT RENAL ARTERY (XR_1) OF FOUR DOGS AND TO LEFT RENAL ARTERY (XL_1) OF THREE DOGS, ALL SEVEN CLAMPS ADJUSTED TO PRODUCE APPROXIMATELY SAME DEGREE OF MODERATELY SEVERE CONSTRICTION.

Dog C–30 had clamp applied to right renal artery ($(X)R$) and removed at same operation.

of both systolic and diastolic pressures and does not occur following operative manipulation of the renal pedicle.

EFFECT OF REDUCTION OF RENAL TISSUE ON BLOOD PRESSURE

Numerous investigators have studied blood pressure in animals following the reduction of functional kidney tissue. Of the earlier experiments, those of Pässler and Heineke (9) are the most convincing. These workers reduced the kidney substance of eighteen dogs by successive operations. Seven of these dogs survived four weeks without extreme wasting. In five dogs blood pressure studies, with femoral artery readings, were made before operation, and again eight days and several weeks after the last operation. These five dogs showed an average increase in blood pressure of 21.5 mm. Hg. When too much kidney tissue was removed, according to the authors, cachexia followed with a falling blood pressure. In spite of the relatively short duration of the experiments, for all seven dogs the average proportionate weight of left to right ventricle showed an increase over the normal of 28.5 per cent. Polyuria was said to have developed regularly prior to the blood pressure rise. The widely quoted studies of Rose Bradford (10), while of limited value from the standpoint of the study of hypertension, were sufficiently extensive to approximate subtotal nephrectomy for dogs. A seventy-five per cent reduction of kidney substance almost invariably led to asthenia and death of the dog in one to six weeks. Although Pearce (11) and his coworkers have been able to remove at times seventy-five per cent of renal tissue in dogs with survival, both workers have established that about one-third of the kidney substance is necessary for relatively healthy survival. Janeway (12) in a number of dogs, ex-

cised one kidney and ligated the arterial branches to the other close to the hilus, leaving infarcted renal tissue in situ. One of these dogs survived thirty-nine days after operation and showed a rise of systolic blood pressure from an average of 106 mm. Hg to 127 mm. Hg during the first twenty-one days; later the blood pressure fell, and the dog became cachectic. Only approximate systolic figures were taken by the use of a Riva-Rocci cuff on the foreleg, palpation of the artery serving as a criterion for the estimation of pressure.

Relatively recent observations on blood pressure following reduction of renal substance have been more convincing. Cash (3), using the Kolls sphygmograph, showed rises of both systolic and diastolic blood pressures in dogs after extensive ligation of renal arteries as well as following subtotal nephrectomy. These changes in pressure occurred independently of renal insufficiency and were not accompanied by changes in blood volume. The significance of these experiments was materially lessened by the short periods of observation in many instances. The elevations in pressure were interpreted as depending on two main factors, namely, a marked reduction of the normal kidney substance, plus the presence within the body of degenerating renal tissue due to inadequate blood supply. Subsequently Cash (13) observed that the blood pressure of dogs fell rapidly after bilateral nephrectomy, though a marked rise, persisting until death, occurred after complete ligation of both renal arteries. This observation was originally considered a support to the idea of a pressor substance liberated from degenerating renal tissue.

Hartman, Bolliger and Doub (14), finding renal tissue sensitive to x-ray, irradiated kidneys of large young dogs. This produced definite and marked renal insufficiency in some animals. They recorded both systolic and diastolic hypertension in several animals by the auscultatory method of Allen (15).

More recently, Chanutin and Ferris (16) have demonstrated the occurrence of hypertension and cardiac hypertrophy in rats following partial nephrectomy. They used an intra-carotid direct method for determining blood pressure with the animal under light anesthesia, partially obviating the objection to a single terminal reading by the study of a large number of animals at various periods after subtotal nephrectomy. Wood and Ethridge (17) repeated a portion of this experiment on a similar series of rats, confirming entirely the occurrence of hypertension and also describing fatty changes in the afferent arterioles of animals surviving operation for relatively long periods.

Mark (18, 19) and Mark and Geisendörfer (20), using an auscultatory method (15, 21), recorded only negligible rises of systolic and diastolic blood pressure after marked reduction of 75 per cent of kidney tissue by excision and ligation of branches of the renal artery in dogs fed on a low protein diet. When an excessive amount of protein was given to these same dogs, a prompt rise in blood pressure followed but subsided to normal upon return to a diet low in protein. Numerous other observations concerning the metabolism, renal function and pathological anatomy of their experimental animals were made.

Contrary observations have been offered by Jensen and Apfelbach (22) who produced renal insufficiency in dogs by injecting charcoal particles in the renal artery but failed to observe arterial hypertension over a period from one week to a year. They measured blood pressure by repeated femoral puncture without anesthesia.

While the foregoing evidence favors the occurrence of hypertension following the reduction of renal tissue, obviously long time experiments with frequent observations on systolic and diastolic blood pressure on the unanesthetized dog have considerable place in further discussion. Such experiments are reported below.

Experiment 5, Dog C–11 (*Figure 7*). Partial nephrectomy. Male, mongrel, 36 pounds. This animal was under control observation from October 12 to November 7, 1933. On November 7, following retroperitoneal approach and exposure, the left kidney was exposed, a clamp placed across the lower pole, mattress sutures put in, and 10 grams of this kidney removed. Following this there was no appreciable change in blood pressure. On November 14, 1933, the remaining normal kidney was removed (weight 39 grams). The dog made an uneventful recovery, and in the following months the blood pressure showed a very slight and gradual elevation. The animal has remained in apparently good

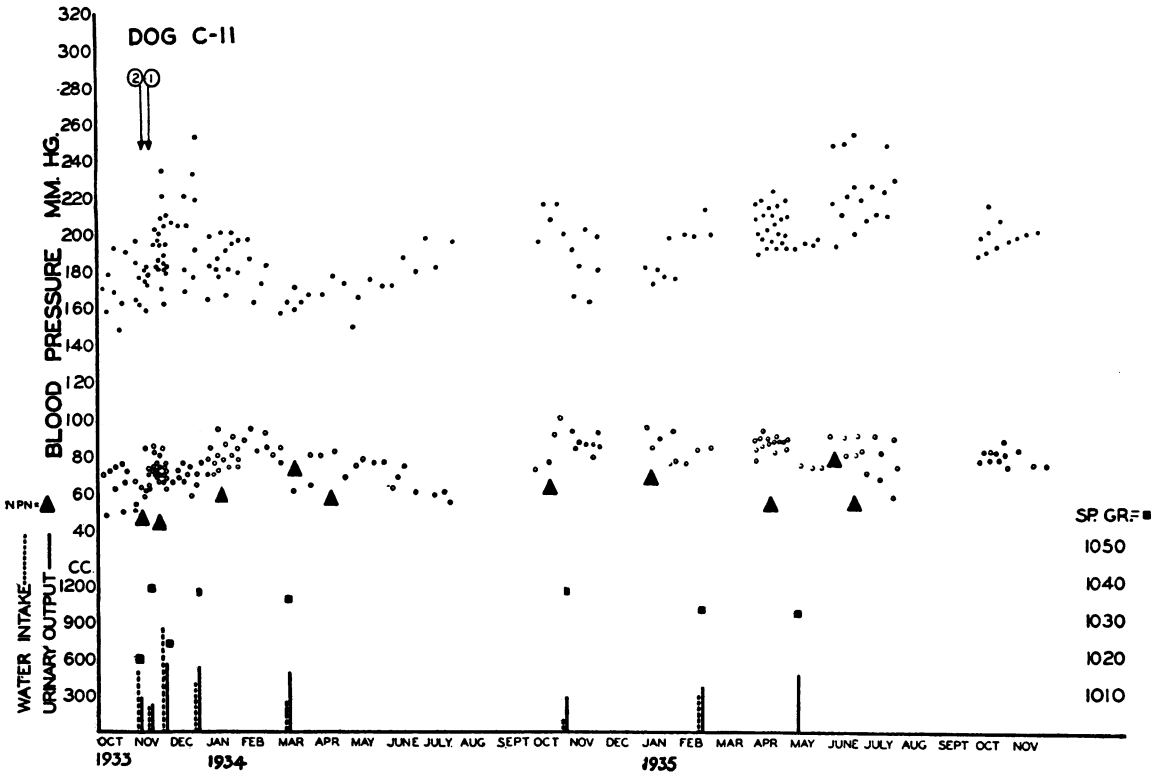

FIG. 7. PARTIAL NEPHRECTOMY, REMOVAL OF APPROXIMATELY SIXTY-FIVE PER CENT OF RENAL TISSUE. ②—Removal of portion of left kidney. ①—Removal of right kidney.

health, has no appreciable renal insufficiency, but his weight has decreased to 24 pounds.

In this animal approximately sixty-five per cent of renal tissue has been removed, allowing for partial destruction of tissue along suture lines. The approximate systolic mean blood pressure before operation was 174 mm. Hg and the diastolic mean 62 mm. Hg. In the twenty-five months following the second operation the systolic mean has varied from 161 mm. Hg to 226 mm. Hg, with a tendency to remain above 190 mm. Hg during the last ten months. Following operation, the diastolic mean has varied from 57 mm. Hg to 86 mm. Hg with a tendency to remain above 72 mm. Hg during the last twelve months. The absence of severe renal insufficiency is indicated by the relatively slight elevation of nonprotein nitrogen and relatively normal urinary specific gravity.

Experiment 6, Dog C–2 (*Figure 8*). Partial ligation of renal artery and partial nephrectomy. Male, mongrel, 30 pounds. Dog C–2 was under control observation from October 18, 1933, to December 7, 1933. On the latter date, the posterior branch of the left renal artery was ligated and one pole of the kidney removed (16 grams). The dog recovered promptly without complications. Eight days later, December 15, 1933, the remaining normal kidney was removed (weight 34 grams).

Following this the animal showed definite polyuria and nitrogen retention, the nonprotein nitrogen mounting to 160 mgm. per 100 cc. blood, later returning to values from 62 to 73 mgm. per 100 cc. blood. The dog has recovered and remains in apparently good health. His present weight is 29.5 pounds.

Approximately 75 per cent of renal tissue was removed in this animal. Nitrogen retention occurred after the second operation, with marked polyuria. Although the condition of the animal has greatly improved during subsequent months, polyuria persists with a falling urinary specific gravity. Most striking have been the wide fluctuations of systolic pressure and the relatively steady diastolic blood pressure; although a slight definite trend upward occurs in each, the most impressive change has taken place in the diastolic pressure. The mean systolic blood pressure before operation was 169 mm. Hg and the mean diastolic 78 mm. Hg. After the second operation the mean systolic pressure rose to remain consistently above 185 mm. Hg, with the exception of one of the last ten months, while the diastolic mean remained above 90 mm. Hg, and generally above 100 mm. Hg, for the same period.

Experiment 7, Dog C–6 (*Figure 9*). Partial ligation of renal artery without removal of renal tissue. Male, terrier, 25 pounds. Dog C–6 was observed during a control period from October 12, 1933, to January 16, 1934. On the latter date, the left renal artery was well exposed and showed the usual anterior and posterior

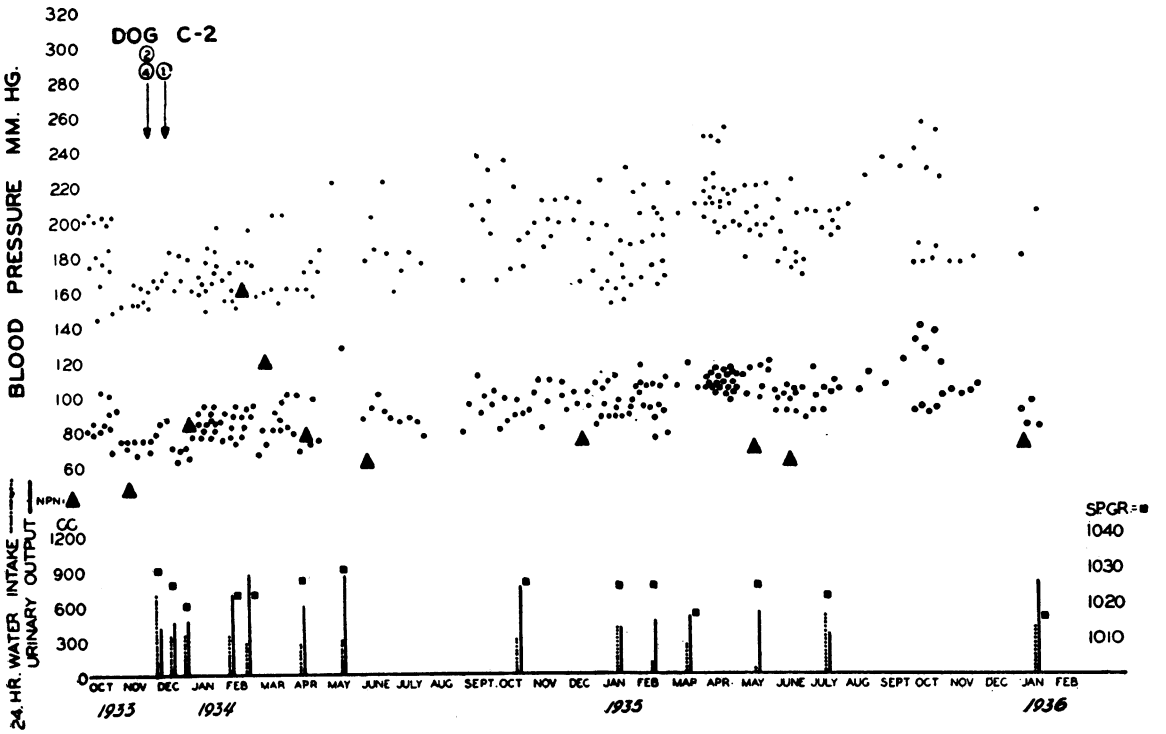

FIG. 8. PARTIAL LIGATION OF RENAL ARTERY AND PARTIAL NEPHRECTOMY.

④—Ligation of posterior branch of left renal artery. ②—Removal of portion of left kidney. ①—Removal of right kidney.

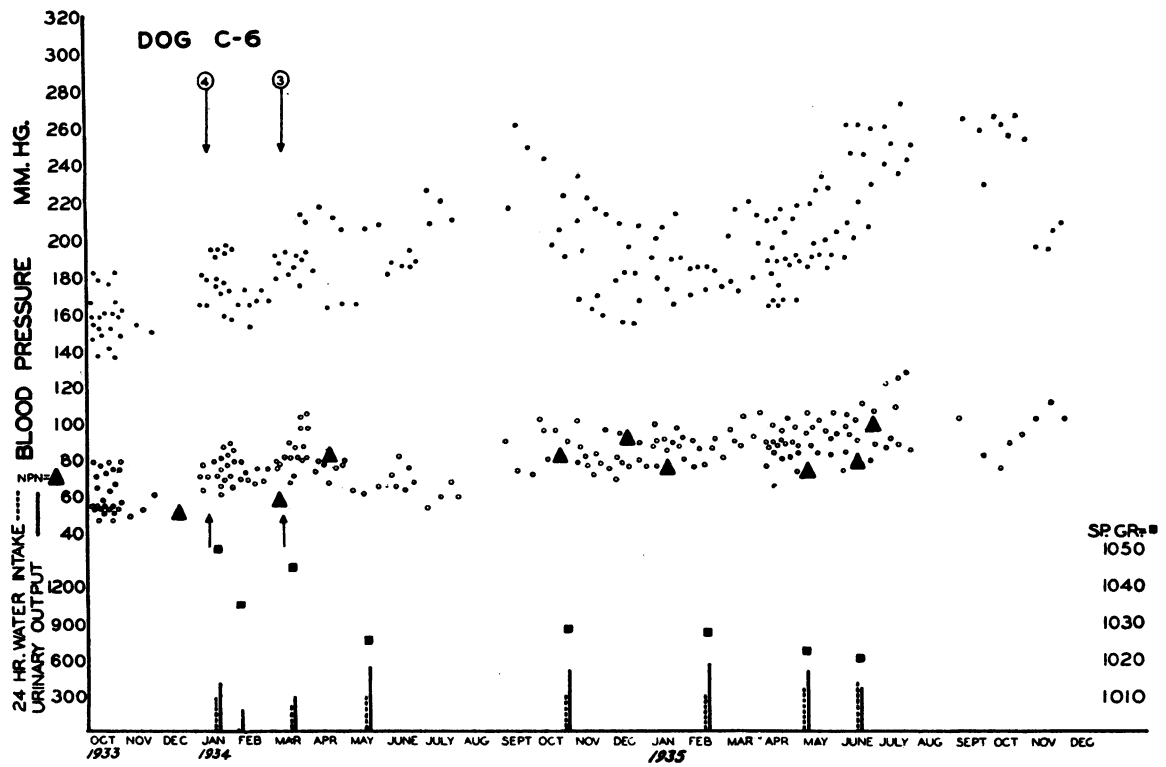

FIG. 9. PARTIAL LIGATION OF RENAL ARTERY, LEFT ④, AND COMPLETE LIGATION OF RENAL ARTERY, RIGHT ③.

branches. Close to the hilum of the kidney the posterior branch further divided into two small arteries. The anterior and one small division of the posterior branch were ligated, leaving only one small division of the posterior branch intact. Following this there was little change in the blood pressure level.

On March 14, 1934, the arterial supply to the right kidney was exposed in the usual fashion and the ligature placed around the anterior and posterior branches, obliterating the blood supply to this kidney, and leaving the dog with approximately 25 per cent of his original renal tissue.

Following these procedures there was slight but definite nitrogen retention, and very slight but definite gradual increase in the diastolic pressure. The weight of the animal at present is 26.5 pounds.

The reduction of kidney substance in this experiment approaches the desired result. A low grade renal insufficiency has been produced as shown by a slight but definite nitrogen retention in the blood, polyuria, and a gradually decreasing specific gravity of the urine, in twenty-four hour tests. A slow but definite rise in diastolic and systolic blood pressure has been recorded (Figure 9). Fluctuations of systolic blood pressure occur in wide swings but a general upward trend occurs from the preoperative mean systolic level of 164 mm. Hg and mean diastolic of 61 mm. Hg. Definite rises of both systolic and diastolic pressure occurred after each operation, and in the twenty-one months following the second operation the monthly systolic mean has ranged from 176 to 256 mm. Hg. The less variable diastolic pressure has also shown a steady rise with a monthly diastolic mean of 59 to 103 mm. Hg.

Experiment 8, Dog C–3 (*Figure 10*). Partial ligation of renal artery without removal of renal tissue. Male, shepherd, 40 pounds. Control blood pressure readings were made in Dog C–3 from October 4, 1933, to December 5, 1933. On the last date, following the usual retroperitoneal approach, the right renal artery was exposed and ligated, cutting off all blood supply to the kidney. No kidney tissue was removed. No change in blood pressure followed this operation. On December 12, 1933, the artery to the left kidney was exposed and found to have the usual anterior and posterior branches. The posterior branch was ligated.

The animal remains in good condition without definite nitrogen retention, weight 40 pounds.

A variation in method here seemed to influence the blood pressure response rather definitely. Contrary to the usual procedure of removing intact kidney at the second operation, thereby allowing edema and injury from trauma to subside in the small remaining stump, the right renal artery was completely ligated at the first operation and partial ligations of left renal artery

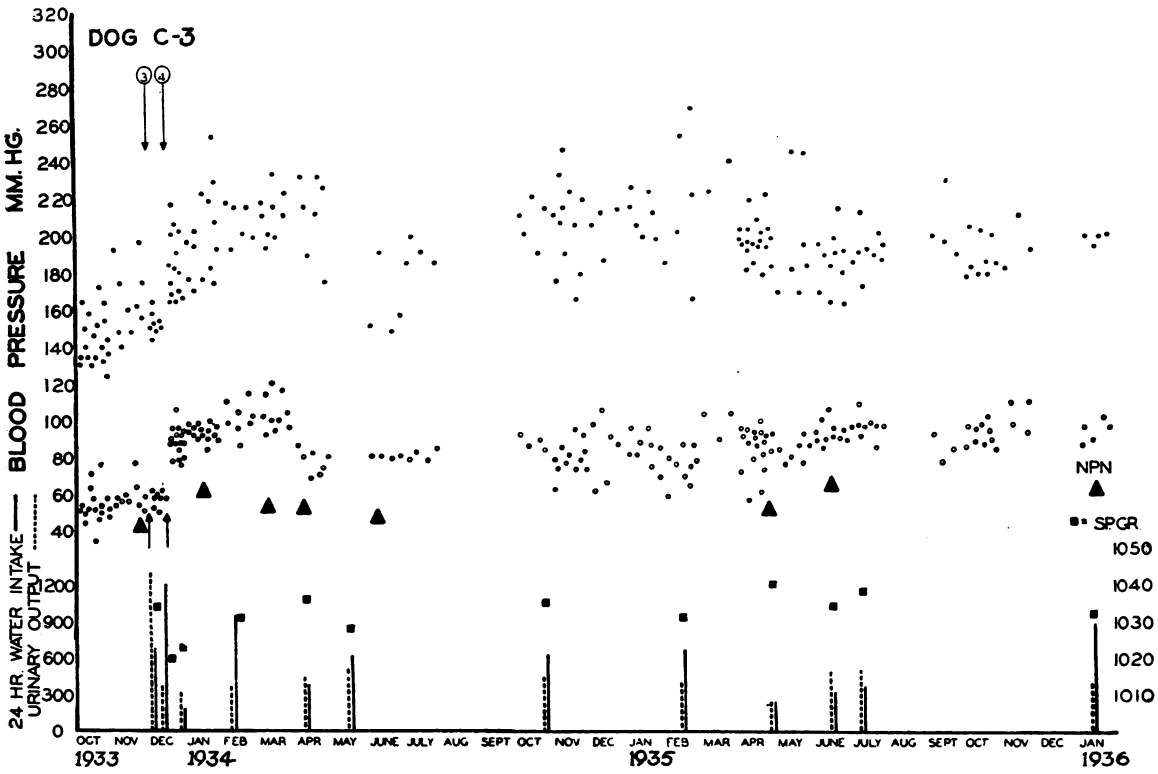

FIG. 10. PARTIAL LIGATION OF RENAL ARTERY WITHOUT REMOVAL OF RENAL TISSUE, COMPLETE LIGATION OF RIGHT RENAL ARTERY ③ AND LIGATION OF POSTERIOR BRANCH OF LEFT RENAL ARTERY ④.

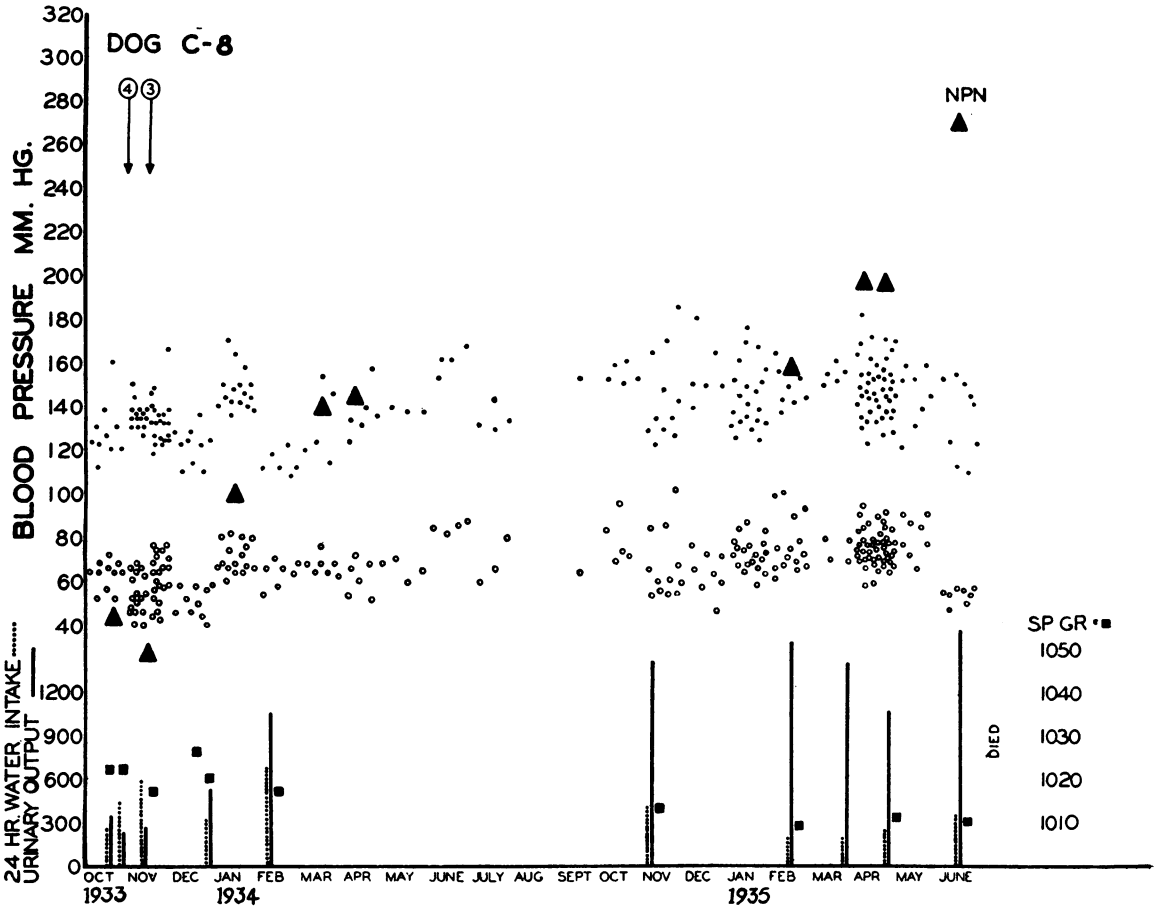

FIG. 11. PARTIAL LIGATION OF RENAL ARTERY WITHOUT REMOVAL OF RENAL TISSUE.
④ Ligation of posterior branches of left renal artery, and ③ ligation of right renal artery.

branches were done at the second operation, no tissue being removed at any time. A sharp and prompt rise of blood pressure followed the second operation, as shown in Figure 10. The mean blood pressures prior to the second operation were approximately 154 mm. Hg systolic and 57 mm. Hg diastolic, whereas immediately after operation and for three and one-half months thereafter the monthly mean systolic blood pressure rose to 183 to 210 mm. Hg and the diastolic to 77 to 101 mm. Hg. The pressures then decreased to somewhat lower levels but definite hypertension has continued to the present time.

Definite polyuria and fall in urinary specific gravity followed the second operation. The disappearance of the polyuria and the apparent ability of the kidney to concentrate during the hot summer months of June and July, 1935, argues for a hypertrophy of the renal stump and some recovery of function. This animal, with the exception of a short period after the second operation, has remained lively and vigorous.

Experiment 9, Dog C–8 (Figure 11). Partial ligation of renal artery without removal of renal tissue. Male, mongrel, 31 pounds. Dog C–8 was observed from October 12 to October 31, 1933, when the anterior and posterior branches of the left renal artery were exposed. The latter was found to have two divisions and these were ligated. The animal recovered promptly without elevation of blood pressure. On November 9, 1933, the main artery of the right kidney was exposed and ligated. No kidney tissue was removed at either of the above operations.

The animal remained lively for a while, but the blood nonprotein nitrogen gradually mounted from a preoperative level of 44 mgm. per 100 cc. to 275 mgm. per 100 cc. just before death. Polyuria occurred to an extreme degree, urinary output being four times as great as water intake in several tests. The appetite became poor and the weight gradually decreased to 27.5 pounds just prior to death. Death occurred on June 14, 1935.

Following the second operation, the remaining renal tissue (about twenty-five per cent of the total) showed inadequate renal function as evidenced by a steadily rising nonprotein nitrogen in the blood, marked polyuria and falling urinary specific gravity, and the animal finally died with the typical uremic triad of symptoms: nitrogen

retention, polyuria, wasting and a terminal fall in blood pressure. Notwithstanding this marked grade of renal insufficiency, only a very slight rise in diastolic blood pressure took place in the ensuing months. That the slight rise of diastolic blood pressure was significant is suggested by the differential ventricular dissection of this dog's heart at autopsy. The L/R ratio of 2.009 (left ventricular weight 42.00 grams, right ventricular weight (20.90 grams) is sufficiently above the extreme normal figure of Herrmann (8) to offer additional evidence that low grade hypertension may lead to left ventricular hypertrophy.

COMMENT

The foregoing experiments record the blood pressure findings in dogs subjected to interference with renal substance or circulation for short and long periods. Much could have been done to smooth out the variations in the blood pressure curves reported if the figures for a single day had been reduced to a single mean value. However, the use of all individual values regardless of variations from the apparent levels at the time, has brought out beautifully the value of trends, particularly in the diastolic blood pressure. The relative stability of the diastolic pressure is especially well illustrated by Dog C–1 (Figure 3). This animal was particularly quiet, showing no effect of excitement except in the first few days of training. The diastolic rise following production of renal ischemia was much more pronounced than the systolic. Renal insufficiency, hypertension and left ventricular hypertrophy in this animal were unmistakably present.

That a slight diastolic trend upward from the preoperative level may represent definite hypertension seems to be indicated by a study of Dog C–8 (Figure 11). Following marked reduction of renal tissue, definite renal insufficiency promptly followed, lasted for eighteen months, and finally ended in typical uremic death. While the blood pressure changes following operation in this animal were not marked, we believe an upward trend in diastolic pressure was definite, except in the last few days during uremia. A small but definite left ventricular hypertrophy attested to the probability of hypertension. The method, therefore, appears valuable for the measurement of small as well as marked changes in blood pressure.

The contention of some observers, notably Jensen and Apfelbach (22) that unanesthetized dogs should be retrained after any temporary omission of observations of blood pressure is certainly true. However, in our experiments, hypertension was considered present only when values exceeded the pressures of the early training period. The trends became quite convincing when it was seen that the blood pressure was rising in spite of the fact that the animal was becoming progressively better trained. Here again, lack of training is generally reflected more violently in the systolic than diastolic pressures (Figures 5, 9, 10). More important, however, is the natural reaction of the dog. For example, Dogs C–1 (Figure 3) and C–8 (Figure 11) proved to be unusually quiet from the beginning, and omission of all studies during the eleventh month in Dog C–8 was followed by a slight elevation of systolic but no change of diastolic values. On the other hand, Dog C–9 (Figure 5), following a two month vacation (eleventh and twelfth months), definitely needed retraining as shown by a sharp elevation of systolic pressure; there was, however, much less disturbance of diastolic pressure. The dog should be comfortably warm to avoid fluctuations of blood pressure. We have therefore been careful to avoid low room temperatures when recording blood pressures. The trends of blood pressure in our animals generally seemed to be lower in summer.

Our observations indicate that varying degrees of hypertension follow reduction of renal tissue by the methods outlined above. Exact knowledge as to why this occurs is lacking, for the rise in blood pressure is not proportionate to the degree of renal insufficiency, nor does marked hypertension necessarily accompany even the severest renal insufficiency (Dog C–8, Figure 11). Conversely, hypertension may be produced experimentally in dogs by renal ischemia without material decrease in renal function (Goldblatt et al. (1)). The conclusion apparently follows that although hypertension is in some way related to the reduction or alteration of renal tissue it is largely independent of renal function.

The approach to the problem of experimental hypertension has been greatly facilitated by the renal artery clamp method of Goldblatt et al. (1). Reduction of renal tissue by arterial ligation or partial nephrectomy may or may not bring about

hypertension. The renal ischemia method invariably does lead to elevation of the blood pressure. However, much remains to be explained concerning the physiology of renal ischemia hypertension. Apparently the occurrence of renal ischemia hypertension is not prevented by renal denervation (24) or excision of splanchnic nerves (23). However, a number of our own dogs (Figure 6) as well as some of the animals of Goldblatt and his coworkers exhibited hypertension following the partial clamping of one renal artery. This phenomenon is lacking a patent explanation if a nervous mechanism is excluded. Further study of the rise in blood pressure following ischemia of one kidney would seem to be indicated. As Goldblatt et al. (1) have already suggested, an indirect humoral mechanism may be possible, but no good evidence of this is so far available.

SUMMARY AND CONCLUSIONS

1. A modification in the sphygmographic assembly of Kolls which has proven highly satisfactory for recording both the systolic and diastolic blood pressure of unanesthetized dogs has been reported.

2. Studies of the blood pressure and gross renal function of eight dogs subjected to various degrees of renal ischemia, to subtotal nephrectomy and to ligation of renal arteries are submitted. Elevations of both systolic and diastolic blood pressure have been observed for periods of from two and one-half to twenty-four months.

3. Seven additional short time experiments in dogs demonstrated that severe constriction of one renal artery, either the right or the left, leads to a significant rise of both systolic and diastolic blood pressures.

4. Of several methods hitherto used to produce sustained arterial hypertension in dogs, renal ischemia, as accomplished by the Goldblatt clamp, has proven to be the most reliable and effective procedure.

5. No explanation of the exact mechanism by which these rises in blood pressure occurred is offered but it is our belief that hypertension following subtotal nephrectomy, ligation of renal arteries, as well as renal ischemia, probably results from the same fundamental cause.

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