STUDIES ON THE ETIOLOGY OF RENAL HYPERTENSION*

ALFRED BLALOCK, M.D., AND SANFORD E. LEVY,† M.D.
NASHVILLE, TENN.
FROM THE DEPARTMENT OF SURGERY OF VANDERBILT UNIVERSITY, NASHVILLE, TENN.

IT HAS been known for many years that disorders of the kidneys are frequently associated with an elevation of the blood pressure. Hypertension is observed frequently in patients in whom there is long continued obstruction to the flow of urine from the kidney and the release of the obstruction usually results in a decline in the blood pressure. Fishberg[1] states that more than one-half of the patients with polycystic disease of the kidneys have a high blood pressure. Hypertension may be observed in patients with periarteritis nodosa, involving the kidney, with extensive destruction of the kidney by infection or amyloid disease or poisoning by mercury. More frequently, hypertension is encountered in patients with glomerulonephritis. Nephritic hypertension is far less frequent than so called essential hypertension. The recent experimental demonstration[2] of the fact that the artificial production of ischemia of the kidney may result in hypertension without a measurable decrease in renal function has served somewhat to break down the barrier that has separated renal and essential hypertension.

The experimental evidence that abnormalities of the kidneys may result in hypertension is convincing. A number of observers have produced hypertension by occluding the ureters. Included among these are: Rautenberg,[3] Hartwich,[4] and Harrison, Mason, Resnik and Rainey.[5] The latter authors found a well marked rise in blood pressure in nine of 13 experiments on dogs in which the ureters were ligated. Pässler and Heineke[6] were apparently the first to make an extensive study of the effects of removal of varying amounts of the kidneys on the blood pressure. Multiple operations in which, at each, the remaining portion of the kidney substance was reduced were carried out until hypertension resulted. Janeway[7] produced an elevation of the blood pressure of dogs by removal of one kidney and ligation of one branch of the opposite renal artery. Cash[8] caused a rise in both the systolic and diastolic pressures in dogs by excision of kidney tissue and ligation of renal vessels. Complete excision of one kidney did not cause a rise nor did the production of extensive renal necrosis result in hypertension. Subsequently, Cash[9] reported the results of experiments in which the renal tissue was reduced to 15 to 50 per cent of the original total and he stated: "In none of these experiments could evidence of renal insufficiency be obtained by examination of the blood for retention of urinary constituents; nor was there any striking alteration of the ability of the remaining functioning kidney tissue to excrete phenolsulphonephthalein."

* Aided by a Grant from the Division of Medical Sciences of the Rockefeller Foundation.

† National Research Fellow in the Medical Sciences.

A definite rise in both the systolic and diastolic pressure was found by Cash to follow bilateral ligation of the renal arteries. On the other hand, Backmann,[10] Cash,[9] Hartwich,[4] and Harrison, Mason, Resnik and Rainey[5] have stated that an elevation of the blood pressure does not usually follow bilateral nephrectomy. Cash[9] found also that complete occlusion of all the blood vessels and the ureters of both kidneys does not usually cause a rise in blood pressure.

Several other methods have been used experimentally in producing hypertension. These include the injection of nephrotoxic substances, the application of high voltage roentgen therapy to the kidneys and the production of chronic renal venous congestion. Hartman, Bolliger and Doub,[11] by the use of roentgen therapy, caused fibrosis and vascular sclerosis of the kidneys and an associated hypertension. Pedersen[12] produced hypertension in rabbits by partially occluding the renal vein and placing a membrane around the kidney in order to prevent the development of large venous collaterals.

The interest in experimental hypertension has been given a decided impetus by the development by Goldblatt, Lynch, Hanzal and Summerville[2] of a method by which a persistent elevation of the blood pressure can be produced with greater uniformity and ease than by any means heretofore reported. The method, in brief, consists of the production of renal ischemia by partially occluding the renal arteries by silver clamps. They state: "When the constriction of both main renal arteries is made only moderately severe in the beginning, the elevation of systolic blood pressure is unaccompanied by signs of materially decreased renal function. In this respect the hypertension in these animals resembles the hypertension which is associated with benign nephrosclerosis in man." Some of the animals were observed for more than a year. Postmortem examinations of several of the animals showed definite changes in glomeruli, parenchyma and vessels of the kidneys. They state: "Gross infarction of the kidney substance was not observed in these kidneys, and microscopically massive necrosis was not present. The changes in the tissues of the animals with persistent hypertension and without signs of uremia were therefore abiotrophic rather than necrobiotic. Thus, necrosis of kidney substance was not a necessary condition for the development of elevated blood pressure in these animals. It is to those abiotrophic changes in the kidneys that the elevation of blood pressure is probably attributable because it is well known that in acute experiments clamping even of both renal vessels has little or no immediate effect on blood pressure." Goldblatt and his associates determined the systolic blood pressure by the use of the van Leersum carotid loop method. Wood and Cash[13] have produced renal ischemia by the Goldblatt method and have determined the diastolic as well as the systolic pressure by the Erlanger-Kolls-Cash sphygmographic method. A sustained rise in both the systolic and diastolic levels was observed. An extremely interesting finding which has been recorded by Goldblatt *et al.*, and Wood and Cash is that severe constriction of only one main renal artery may lead to a significant rise

in the blood pressure. There is usually a return to the preocclusion level unless the opposite artery is constricted subsequently.

Much work has been performed in the last several years in an effort to explain the mechanism by which renal disorders result in hypertension. Prinzmetal and Wilson[14] noted that anesthetization of vasomotor nerves does not release the vascular hypertonicity in hypertension. Prinzmetal, Friedman and Rosenthal,[15] and Page[16] have been unable to demonstrate pressor substances in the blood of patients with nephritis and dogs with renal hypertension. Page[17] showed that the hypertension associated with renal ischemia is not prevented by renal denervation. Goldblatt, Gross and Hanzal[18] found that splanchnic section does not prevent the elevation of blood pressure produced by renal ischemia, and does not lower the pressure in dogs with experimental renal hypertension. Goldblatt and coworkers[2] produced hypertension in an animal in which the right suprarenal body had been removed, the left splanchnic nerves had been sectioned, the left suprarenal body had been denervated and its medulla had been destroyed. Page and Sweet[19] state concerning the effects of removal of the pituitary that: "Hypophysectomy in dogs with hypertension produced by renal ischemia reduces arterial pressure to about normal levels. It appears to reduce slightly the blood pressure of normal dogs. Preliminary hypophysectomy does not prevent the rise in blood pressure established by renal ischemia, but the rise tends to be transient."

Tigerstedt and Bergman[20] observed many years ago that saline extracts of the kidneys of rabbits produce a sustained rise in blood pressure when injected into other rabbits. Harrison, Blalock and Mason[21] found that saline extracts of an ischemic kidney usually cause a greater rise in blood pressure when injected into another dog than do extracts from the opposite normal kidney. These findings were confirmed concurrently by Prinzmetal and Friedman.[22]

Since hypertension can be produced by partial constriction of the arterial supply to one kidney, without interfering with the other, it seemed important to exclude a nervous mechanism as the agency by which it is produced. Since it is impossible to be certain that an organ which remains in situ has been completely denervated, it was decided that the kidney should be transplanted to another part of the body. Such experiments constituted the first part of our study and subsequently a variety of other procedures was carried out.

METHODS.—Large and medium size dogs have been used. They were fed chow which was supplemented by meat four times weekly. Water was not restricted. The animals were housed in individual cages.

The blood pressure was determined without anesthesia. A method which was utilized in all experiments consisted of introducing into the femoral artery, without making an incision, a No. 20 gauge needle which was connected to a mercury manometer. The pressure obtained in this manner corresponds fairly closely to the mean of the systolic and diastolic levels. By this method, there is very little variation in the blood pressure of normal dogs from day to day. In addition to the needle puncture method, the blood pressure of many of the dogs was determined by the van Leersum carotid loop method. Pres-

sures by the latter technic were usually determined daily for several weeks or longer preceding the operative procedures. Greater daily variations in pressure were obtained by the use of the carotid loop. The production of hypertension was usually associated with a greater rise in the pressure as determined by the loop method than by the arterial puncture procedure.

All operations which involved the exposure of the kidney or its vessels when they were in or near their normal positions were carried out under general anesthesia. Inhalation ether was used in some instances and nembutal in others. When the position of the kidney had been altered so that it was placed just beneath the skin, local anesthesia was employed in the various procedures. No evidence of pain was observed. Aseptic technic was employed in all operations.

Hypertension was produced by a number of different methods but that most commonly employed consisted of the use of the Goldblatt clamp* with which the degree of constriction of the renal artery can be varied and controlled. In some instances the clamp was applied to the renal artery of a kidney which was in its normal position, in others to the artery of a kidney which was explanted in the flank and in still others to the carotid artery leading to a kidney which had been transplanted to the neck. As has been stated, the main idea of transplantation to the neck was to be certain that complete denervation had been effected. Another reason was that it seemed to be desirable to be able to increase or decrease the amount of constriction without using general anesthesia. This can be effected without discomfort under local anesthesia when the kidney has been placed previously beneath the skin. Furthermore, the superficial position of the kidney permits of its removal under local anesthesia if it seems desirable to do so. The avoidance of general anesthesia places greater significance upon results which are obtained within the first few hours following any of these procedures. For the same reason the kidney or kidneys were explanted to the flanks in many of the experiments.

Hypertension was produced in some experiments by occlusion and division of one or both ureters. In some instances the kidney was left in its normal position while in others it was explanted to the flank. An elevation of the blood pressure was produced in a few experiments by ligation and division of the main renal arteries. Before we were aware of the Goldblatt method, hypertension was produced in several animals by gradually occluding the main renal arteries by lead bands and the arteries were subsequently ligated and divided. After the blood pressure returned to the control level following the application of a clamp to the renal artery of one kidney, the opposite normal kidney was removed in some animals and the blood pressure was followed.

The method which was used in explanting the kidney consisted simply of exposing and delivering the organ through an incision in the flank. The kidney was placed in a pocket beneath the skin. The deeper structures were loosely approximated around the pedicle. The skin incision was closed with-

* Silver clamps and instruments for their application were obtained through the courtesy of Dr. Harry Goldblatt, Cleveland, Ohio.

out drainage. Transplantation of the kidney was performed by the Carrel method. The renal artery was anastamosed to the carotid, the renal vein to the external jugular vein and the ureter was brought out through a small opening in the skin. The kidney was placed in the neck in a pocket beneath the skin.

The explantation method may be open to criticism on the grounds that this procedure alone is in some instances followed by a temporary rise in blood pressure. However, it seems likely that it is due to ischemia or at least to the same cause which results in a rise in pressure following the application of a Goldblatt clamp to the artery. The rise in pressure which may follow explantation of the kidney is usually not very great and is of short duration. Except for those experiments in which a clamp was applied to the artery at the time of the explantation of the kidney, the pressure was allowed to return to the control level before other procedures were carried out.

The methods, other than those that have been described, varied in the different types of experiments and they will be described in detail along with the results of the individual groups.

RESULTS.—(1) *Remaining Kidney Explanted to Flank—Effects of Removal under Local Anesthesia. Does an alteration in the blood pressure occur?* Ten experiments of this type were performed. As has been stated, the kidney was explanted to the flank in order that the effects of the operative procedure necessary for its removal might be reduced to a minimum. All animals except two lived four days or longer following the removal of the remaining kidney. The longest interval separating the operation and death was seven days. No significant alteration in the blood pressure was encountered in nine of the ten animals. Two of these showed a slight elevation and two a slight decline in the pressure. The remaining animal showed a rise in pressure of approximately 40 Mm. Hg. However, this dog was restless and was always shivering at the time of the determinations.

In summary, the removal of the remaining explanted kidney under local anesthesia usually caused little if any alteration in the blood pressure. The findings indicate that the maintenance of a normal blood pressure is not dependent upon the presence of kidney tissue and that the complete absence of renal tissue does not usually result in an elevation in the blood pressure.

(2) *The Effects on the Blood Pressure of the Removal of an Ischemic Explanted Kidney in Dogs with (A) Two Kidneys and (B) One Kidney. Does a fall in blood pressure occur? How long does it take the blood pressure to decline to normal level?*—Nine experiments of this type were performed. The effects on the blood pressure of unilateral renal ischemia and of subsequent removal of the kidney were studied in all experiments. In four of them, similar observations were carried out on the remaining kidney. In all instances, the blood pressure rose following the application of a Goldblatt clamp to a kidney which was explanted at the same time. The maximum rise varied from 20 to 66 Mm. Hg. when ischemia of the first kidney was produced and 28 to 88 Mm. Hg. with ischemia of the remaining kidney. General

anesthesia was administered during the explantation of the kidney and the application of the clamp. For this reason the blood pressure was not determined in most experiments during the early postoperative period. However, a definite elevation of the pressure was observed in one experiment five hours following the operation and in another at seven hours. The pressure in all instances was definitely elevated the day following the production of ischemia but the maximum rise usually occurred several days later.

Following the removal of the ischemic explanted kidney without general anesthesia, the blood pressure usually began to decline in an hour or two and in most instances approached closely the control level in six to 12 hours. It

TABLE I

EFFECTS OF REMOVAL OF ISCHEMIC EXPLANTED KIDNEY

	Arterial Blood Pressure, Mm. Hg.									
Dog No.	Control	One Day After Applying Clamp	Just Before Removal Kidney	7 Hours After Removal	3 Days After Removal	Control on Second Kidney	One Day After Applying Clamp	Just Before Removal Kidney	7 Hours After Removal	Days After Removal
1.....	134 (142)*	163 (170)	172 (180)	127 (150)	146 (144)	134 (138)	162 (230) 7 hrs.	177 (230)	123 (154)	137 (154) 1 day
2.....	107 (144)*	144 (166) 16 hrs.	153 (210)	119 (162)	127 (160)	120 (142)	175 (230) 5 hrs. 163	Died		
3.....	123	136	180	139 10 hrs. 123	117	112	174	160	137	147 3 days
4.....	140	157	173	143	137	143	177	198	148	129 1 day
5.....	120	139	163	125	147	128	148	158	137 3 hrs.	128 2 days
6.....	135	137	166	140 10 hrs. 121	137					
7.....	126	143	165	116	128	130	142			
8.....	118	136	150	137 13 hrs. 127	134					
9.....	150	163	170	163	148					

*The figures in parentheses in Experiments 1 and 2 are the pressures as determined by carotid loop method.

seemed quite definite in most instances that the rise in pressure following the production of ischemia was slower than the decline after the removal of the kidney. Following the removal of the second kidney, the animals did not usually live as long as did those reported in Group I in which the effects of the removal of normal kidneys were reported. Mild renal insufficiency had probably developed following the partial constriction of the renal artery in the former group.

Some of the results of these experiments are given in Table I. The findings in one experiment are shown graphically in Chart I.

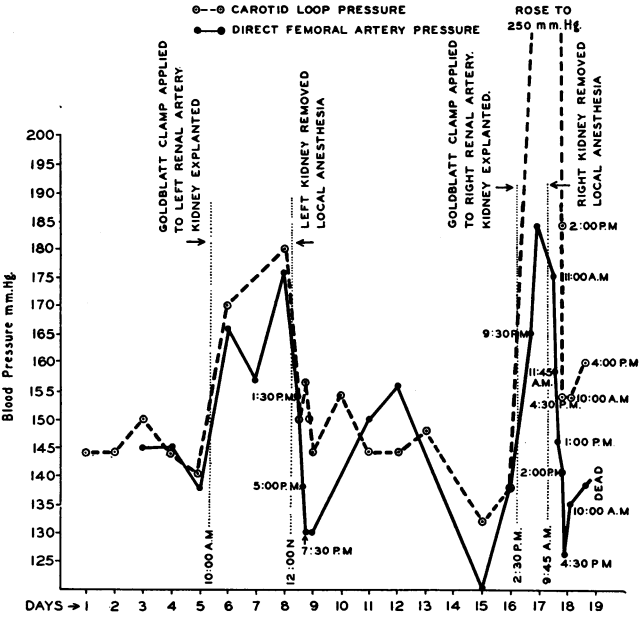

CHART I.—The effect on the blood pressure of the removal of an ischemic explanted kidney, a normal kidney being present, and subsequently the removal of a single remaining ischemic kidney. Local anesthesia employed in removal. After sharp rises in blood pressure following constriction of the renal artery plus explantation, the pressure approached normal within seven and one-half hours after removing the first kidney, and in six and three-quarters hours following removal of the remaining kidney. It will be noted that after constricting the artery to the second kidney, the rise in blood pressure was more marked and that the loop pressure was elevated out of proportion to the femoral pressure.

In summary, the application of a Goldblatt clamp to the renal artery of one of the two kidneys, which is at the same time explanted to the flank, results in a rise in blood pressure which usually reaches its maximum in several days. However, the pressure usually begins to rise a few hours after the production of ischemia. The removal of the kidney under local anesthesia is usually followed in approximately ten hours by a return of the pressure to the control level. Similar findings were obtained when the same procedures were carried out on the opposite remaining kidney.

(3) *The Effects of Removal of a Kidney after Hydronephrosis and a Rise in Blood Pressure Have Followed Ureteral Occlusion. Does a decline in the*

blood pressure take place?—Four experiments of this type were performed. In three of these, one of the kidneys had been removed at a previous operation. At the second operation, the remaining kidney was explanted and the ureter was ligated and divided. The elevation in pressure was not as great as in the studies in which ischemia was produced by applying a clamp. The pressure rose approximately 30 Mm. Hg. in each experiment and it returned to approximately the normal level six hours following the removal of the kidney under local anesthesia. Following this latter procedure, one of the animals lived three days, one 5.5 days and the other seven days. The pressure rose somewhat subsequently in the latter animal.

One experiment was carried out in which the ureter of one of the two kidneys was ligated and divided, the kidney being left in its normal position. A moderate elevation in the blood pressure occurred several days later and the pressure returned to the control level within 24 hours following nephrectomy under general anesthesia.

In summary, the rise in blood pressure which may be associated with occlusion of a ureter is abolished by removal of the kidney. The pressure usually returns to normal in approximately six hours.

(4) *The Effects of Various Degrees of Occlusion of the Arterial Supply of the Kidneys. Under what conditions does a rise in pressure occur?*

(A) Ligation and Division of the Entire Pedicle Except the Vein. Explantation of the Kidney. Effect on Blood Pressure.—Six experiments were performed in which one of the two kidneys was freed from the surrounding structures, the entire pedicle except for the vein was doubly ligated and divided, and the kidney was placed beneath the skin in the flank. Since the kidney was freed from the surrounding structures and since the ureter as well as the arteries was divided, the kidney was entirely deprived of arterial supply. The opposite kidney was not disturbed. A significant rise in the blood pressure was not observed in any of the six experiments. The greatest increase in pressure was 15 Mm. Hg. This occurred in only one experiment and it was sustained for two days.

(B) Ligation and Division of the Entire Pedicle Except the Vein. Incisions Made in Cortex and Kidney Placed in Peritoneal Cavity.—These experiments were similar to the preceding series except that the kidney was placed in the peritoneal cavity instead of the flank and incisions were made into the cortex. Cash[9] observed a rise in blood pressure in one animal in which a kidney which was deprived of its blood supply was accidentally injured.

Four experiments were performed on dogs with only one kidney in which the procedure outlined was carried out. Three of the animals had no rise in blood pressure while it rose 25 Mm. Hg. in the fourth. Two of the animals lived two days each and two lived three days.

In three experiments, the same procedure was performed on one of the kidneys of dogs with two kidneys. None of these animals showed any appreciable alteration in the blood pressure.

(C) Ligation and Division of the Pedicle Except for the Vein and Ureter.—In all instances except two, the kidney or kidneys were explanted. In half of the experiments, the vessels were divided at the time that the kidney was explanted. In the remainder, an untied ligature was left around the vessels and they were divided subsequently under local anesthesia. The results did not seem to be affected by the time at which the occlusion was produced.

Five experiments were performed in which both kidneys were freed from surrounding structures and explanted and in which the pedicle except for the vein and ureter was divided. An elevation in pressure ranging from 16 to 40 Mm. Hg. occurred in four of the experiments and no rise was detected in the other.

In four experiments on animals with two kidneys, one of the kidneys was explanted and the arterial supply was divided. An increase in pressure of 30 Mm. Hg. occurred in one, an increase of 20 Mm. Hg. in another and no change in the pressure took place in the remaining two.

In four experiments on animals with only one kidney, explantation and division of the arterial supply were carried out. Three showed a rise in blood pressure of 20, 25 and 38 Mm. Hg. respectively.

In two experiments, the kidneys were left in situ, and the pedicle except for the vein and ureter was divided. The arterial blood pressure increased 10 Mm. Hg. in one and 35 Mm. Hg. in the other. In one experiment on a dog with two kidneys, the structures in the pedicle of one kidney except for the vein and ureter were divided and the kidney was explanted. Following a rise in the blood pressure, the kidney was removed under local anesthesia and the pressure declined. Subsequently, the arteries to the remaining kidney, except those in the ureter, were divided. The results of this experiment are given in Chart 2.

Most of these experiments differed from those described in Series A only in that the ureter was not divided in the present group. Elevations in the blood pressure were encountered much more frequently in this latter study. There was definite evidence in a number of them that the kidney was receiving an appreciable quantity of blood through the ureteral arteries. The results indicate that the pressure is more apt to rise if a small quantity of blood is reaching the kidney than if it is receiving no blood.

(D) Effects of Ligation and Division of Main Renal Artery to Each Kidney. Kidneys Left in Situ.—The renal artery was exposed extraperitoneally through the flank in the same manner as is used in the application of a Goldblatt clamp. The main artery on each side was doubly ligated and divided, the pedicle and the capsular vessels were not disturbed otherwise. Seven experiments of this type were performed. Most of the animals died on the fourth day following this procedure. All of the animals had at least a slight elevation in the blood pressure. This varied in six of them from 15 to 50 Mm. Hg.

(E) Progressive Occlusion of Renal Arteries. Destruction of Capsular Circulation.—Two experiments of this type were performed. The renal

arteries were partially constricted by lead cuffs, as we were not at that time acquainted with the use of the Goldblatt clamp. In addition, the capsule of the kidneys was stripped away. At a later time, the constriction was made more severe, and subsequently, the main arteries were doubly ligated and divided at the site of the lead cuffs. The blood pressure rose 50 Mm. Hg. in one animal and 65 Mm. Hg. in the other. The animals showed no clinical evidence of renal insufficiency despite the fact that the renal arteries were completely occluded and the capsular circulation was destroyed. Collateral circulation through the pedicle undoubtedly supplied the requirements of the

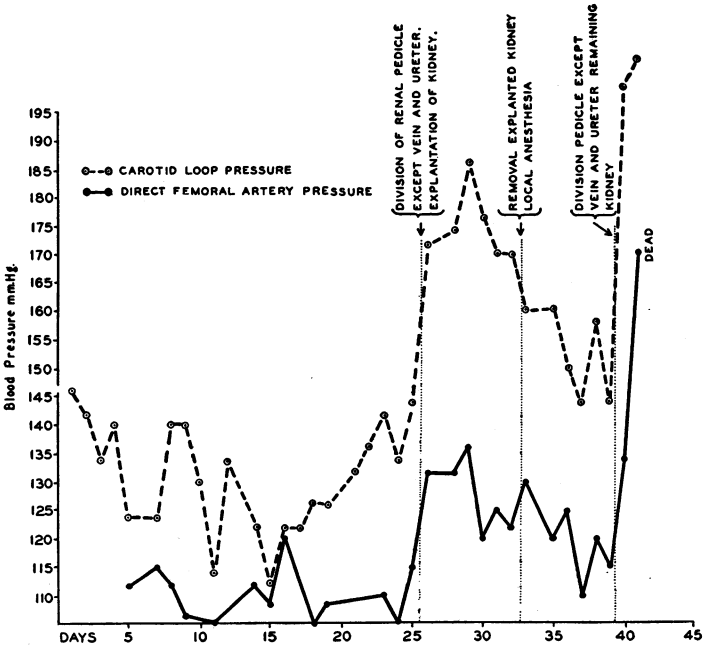

CHART 2.—The effect on the blood pressure of dividing the renal pedicle of one kidney except the vein and ureter, a normal kidney being present, and subsequently repeating the procedure on the single remaining kidney. After removing the first kidney, the blood pressure approached the control level. It is noted that the rise in blood pressure following the above procedure on the remaining kidney was more marked than when the opposite normal kidney was present; also that in general the carotid loop pressures were elevated more than femoral pressures.

kidneys. The animals were sacrificed after being observed for a year and the complete occlusion of the main vessels was verified. In this connection, it is of interest that the Goldblatt clamp frequently produces complete occlusion and at times division of the renal artery, even when the constriction produced by it was not extremely severe at the beginning.

(F) Partial Constriction of Renal Artery. Destruction of Remainder of Arterial Supply. Effect on Blood Pressure.—Five experiments were performed in which the renal artery to one of the two kidneys was partially constricted by a Goldblatt clamp and an attempt was made to destroy the remainder of the arterial supply to the kidney. These experiments were the

reverse of those in the last series in which the main artery was eventually completely occluded and the collaterals through the pedicle were not divided. The structures in the renal pedicle, except the main artery, vein and ureter, were doubly ligated and divided and the kidney was freed from the surrounding structure. As stated, this was effected on only one side and the kidney was not explanted. A temporary rise in pressure, persisting for from four to 13 days, occurred in four of the five experiments. The increases were 20, 30, 30 and 33 Mm. Hg. respectively.

In summary of this entire group of experiments, the effects on the arterial blood pressure of various degrees of occlusion of the arterial supply to the kidney have been studied. The procedures have included: (1) Complete obstruction of the arterial supply including that through the ureters; (2) obstruction of the supply except that through the ureters; (3) ligation and division of the renal arteries; (4) progressive occlusion of the renal arteries which was later made complete without interference with collateral vessels; and (5) partial occlusion of a main renal artery combined with division of the rest of the arterial supply. Significant increases in blood pressure have been noted in all groups of experiments except those in which the entire arterial supply to the kidney including that through the ureters and elsewhere has been abolished.

(5) *Goldblatt Clamp on Renal Artery of One Kidney, Normal Blood Pressure, Effects of Removal of Opposite Normal Kidney. Does a rise in blood pressure occur?*—Eight experiments of this type were performed. A Goldblatt clamp was applied to the renal artery of one kidney and a moderate degree of constriction was produced. The kidney was left in situ in two experiments and was explanted in six. A moderate elevation in the blood pressure usually followed the constriction of the artery. After the blood pressure returned to the control level, the opposite normal kidney was removed. This was followed by no alteration in the blood pressure in two experiments and by a rise in the remaining six. The maximum elevations in pressure in these experiments were 18, 26, 32, 35, 40 and 42 Mm. Hg. respectively.

These experiments were performed in an effort to determine whether or not the normal kidney influences alterations in the pressure which are associated with the partial constriction of the blood supply to the opposite kidney. The results indicate that it does.

In one experiment which does not belong strictly to this group, one of the kidneys was completely denervated by transplanting it to the neck. The carotid artery which supplied blood to the transplanted kidney was partially constricted by a Goldblatt clamp. The blood pressure rose 28 Mm. Hg. within 24 hours. The constriction of the carotid artery was lessened and the blood pressure declined 40 Mm. Hg. in the succeeding 24 hours. The normal non-transplanted kidney was then removed and the blood pressure gradually rose 40 Mm. Hg. during the succeeding seven hours.

(6) *Transplantation of One Kidney to the Neck, Opposite Kidney Re-*

moved. Effects of Reduction of Blood Supply to Transplanted Kidney on the Blood Pressure. Effects of Removal of Transplanted Kidney.—Four experiments of this type were performed. The main purpose of these studies was to test the effect of certain procedures when no doubt existed as to whether or not the kidney had been completely denervated. Following an interval of seven to ten days after the transplantation of one kidney, the other kidney was removed. On the twelfth to eighteenth day after the transplantation, partial occlusion of the carotid artery supplying the transplant was produced by the use of a Goldblatt clamp. This was followed within 24 hours in three of the four

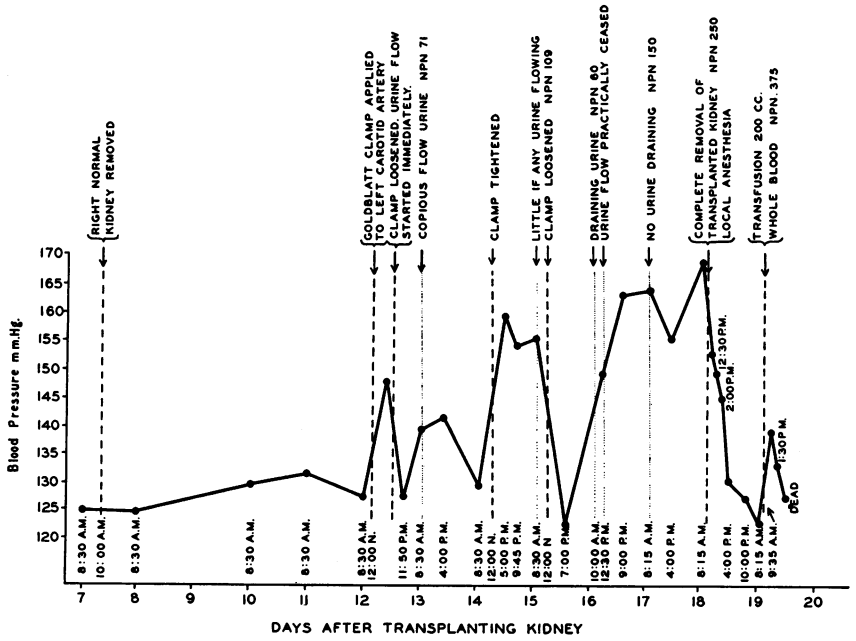

CHART 3.—Blood pressures of a dog with one kidney transplanted to the neck, the other kidney removed. The effects on the blood pressure of loosening and tightening a Goldblatt clamp applied to the carotid artery supplying the completely denervated kidney are illustrated. The blood pressure rose spontaneously on the sixteenth day, probably due to a clot at the site of the clamp. A decline in the blood pressure to normal in six and one-half hours followed the removal of the transplanted kidney.

animals by a rise in blood pressure of 16 to 29 Mm. Hg. as measured by direct femoral artery puncture. An elevation in pressure in the fourth animal was noted when the constriction was increased. The maximum increases in the blood pressure above the control levels in the four animals were 32, 40, 47 and 56 Mm. Hg. In one experiment in which the clamp was loosened after an elevation had occurred, the blood pressure returned to normal in seven hours. The blood pressure subsequently rose spontaneously to a higher level, probably due to a small clot in the artery. Removal under local anesthesia of the kidney of this animal, when the blood pressure was 45 Mm. Hg. above the control level, resulted in a gradual decline and a return to the normal in six and one-half hours. The rise in blood pressure was associated in all instances with a marked reduction in the flow of urine. Release of the constriction in

one animal, after an elevation in the pressure had occurred, resulted in a copious flow of urine. The results of one of the four experiments are pictured graphically in Chart 3.

In summary, an elevation in blood pressure was produced by partial constriction of the blood supply to the remaining kidney which had been completely denervated by transplantation to the neck. Release of the constriction or removal of the kidney resulted in a decline in the blood pressure to the normal level.

(7) *Transplantation of One Kidney to the Neck, Opposite Kidney Left in Situ. Effects of Reduction of Blood Supply to Transplanted Kidney on the Blood Pressure.*—These experiments were essentially the same as those in the preceding group except that the normal kidney was not removed. Five experiments of this type were performed. The maximum rise in blood pressure which followed the reduction in the blood supply to the transplant varied from 25 to 50 Mm. Hg. in the different experiments. In one instance, the pressure returned to the control level ten hours following the release of the constriction. In another, it declined to the control figure eight hours following the removal of the transplanted kidney. In one experiment in which the kidney received its arterial supply through a carotid artery that had been placed previously in a tube of skin, external constriction of the loop was followed by edema and superficial necrosis of the skin, and the femoral arterial pressure showed a rise of 50 Mm. Hg. When the edema subsided, the pressure returned to normal. In another experiment in which a Goldblatt clamp was used to constrict a carotid artery proximal to a van Leersum loop which contained the carotid artery supplying the transplant, the pressure in the loop as determined by needle puncture was 85 Mm. Hg. as compared with 146 Mm. Hg. in the femoral artery. Subsequent removal of the transplanted kidney resulted in a fall in the general blood pressure to normal in three hours. These observations are shown graphically in Chart 4.

(8) *Production of Hypertension by Partial Constriction of Renal Arteries to Both Kidneys Which Were Explanted. Effects on Blood Pressure of Homotransplantation of Kidney.*—Two experiments were performed in which hypertension was produced by partially constricting the arterial supply of both kidneys which were explanted. After a marked rise in pressure had taken place, one of the kidneys was removed from a normal second dog and was transplanted to the neck of the animal with hypertension. The homotransplanted kidney apparently functioned well for five days in one of the experiments and for six days in the other, but the hypertension persisted.

(9) *The Effects of Adrenalectomy on the Production of and the Persistence of Hypertension.*—Goldblatt, in unpublished observations, has found that bilateral adrenalectomy abolishes experimental hypertension. We have repeated the experiments under slightly different conditions. Five experiments were performed in which at the first operation one of the adrenal glands was removed, the corresponding kidney was explanted and its artery was partially occluded by a Goldblatt clamp. While the pressure was still elevated follow-

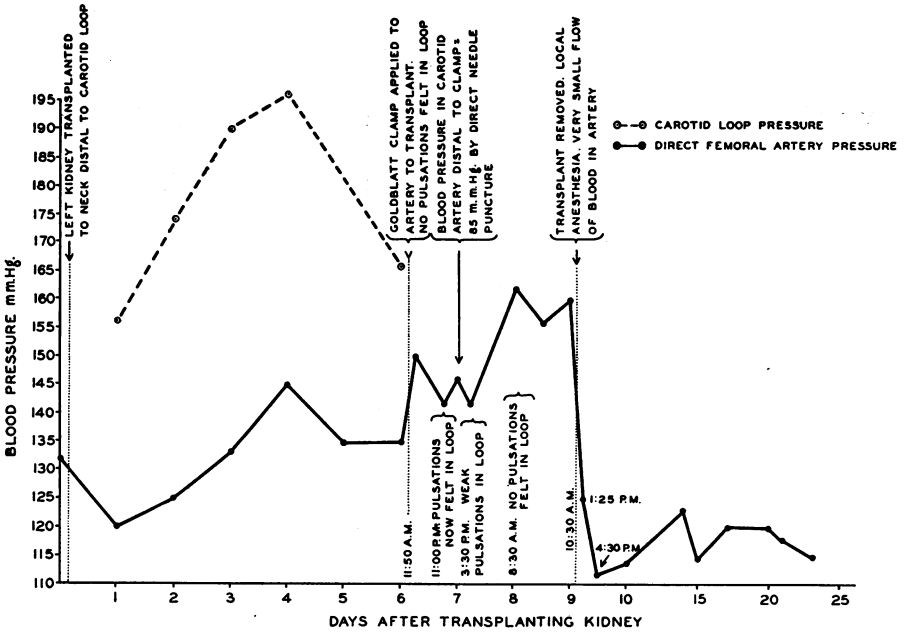

CHART 4.—Blood pressures of a dog with one kidney transplanted to the neck distal to a carotid loop, the opposite kidney left in situ. The effect on the blood pressure of constricting the carotid artery supplying the denervated kidney is shown. The blood pressure in the carotid artery distal to the constricting clamp was found to be 85 Mm. Hg. by direct needle puncture. At the same time the femoral artery pressure was 146 Mm. Hg. The blood pressure fell to normal in six hours after the transplant was removed.

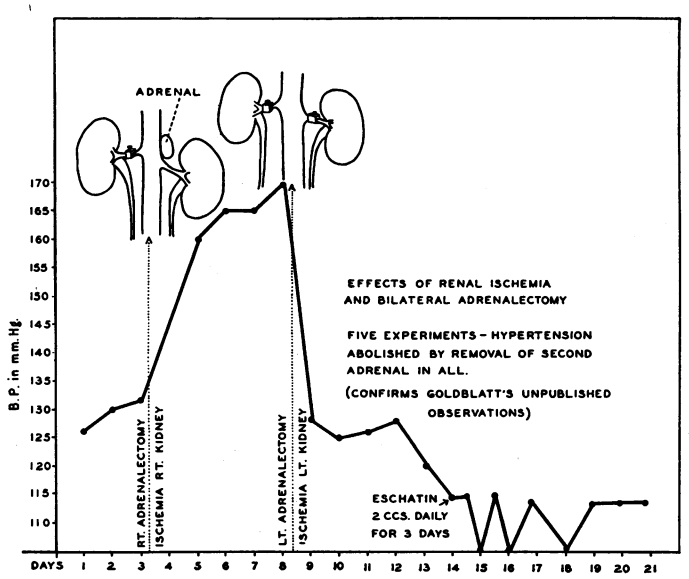

CHART 5.—Showing the effects on the blood pressure of bilateral adrenalectomy and renal ischemia.

ing this operation, the same procedure was carried out on the opposite side. The blood pressure was usually determined 16 hours subsequently and it was found in all instances to have returned to the control level. In the two instances in which it was determined five hours after the removal of the second adrenal, it had returned to normal. The animals were given sodium chloride, sodium citrate and glucose and were placed on a low protein diet. No elevation of the blood pressure occurred at any time following the removal of the second suprarenal gland. Three of the animals lived nine days or longer. The findings in one experiment are shown in Chart 5.

(10) *Effects on Experimental Hypertension of Subdiaphragmatic Splanchnic Nerve Section, Removal of Celiac and Upper Lumbar Ganglia and Partial*

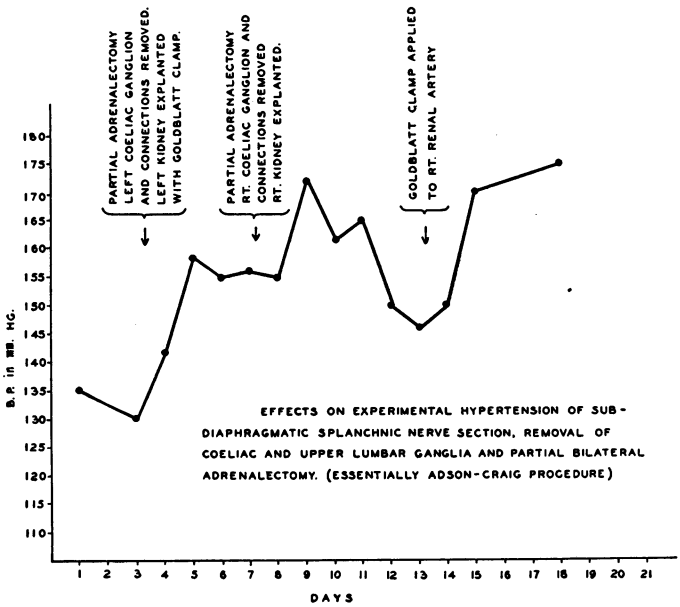

CHART 6.—Showing the effects on experimental hypertension due to results of renal ischemia of subdiaphragmatic splanchnic nerve section, removal of celiac and upper lumbar ganglia, and partial bilateral adrenalectomy.

Bilateral Adrenalectomy (essentially the Adson-Craig[23] procedure).—In three experiments, the effects on the production of hypertension of subdiaphragmatic nerve section, of removal of the celiac and upper lumbar ganglia and of partial bilateral adrenalectomy were studied. The procedure was similar to that described by Adson, Craig and Brown.[23] At the first operation, the procedure indicated was performed on the right side and the right kidney was explanted and its artery was partially occluded. A number of days later, a similar operation was performed on the left side. A definite elevation in the blood pressure occurred in the three experiments in which this was done. The maximum increases in pressure by the needle stick method were 41, 45 and 57 Mm. Hg. The results in one experiment are shown in Chart 6.

Discussion.—As has been stated, the determination of the blood pressure by puncture of the femoral artery with a needle was used in all experiments, and in addition, the carotid loop method was employed in several experiments in each group. The latter method frequently gave greater daily variations in pressure in both normal and hypertensive dogs. The alterations in pressure which were associated with the various procedures were somewhat greater when determined by the carotid loop method. If this procedure had been used throughout, it is likely that the changes in pressure in our experiments would have been more marked. As to the relative merits of the two methods, we are not competent to judge, but due to the smaller daily variations in pressure by the needle puncture method, we have more confidence in the correctness of the alterations which were detected by its use.

All of the methods for producing hypertension used in this investigation are supposedly associated with at least a temporary reduction in the arterial supply to the kidney. The total renal blood flow has not been determined following partial constriction of the main artery, total occlusion of the artery, *etc.*, but it seems certain that the flow is reduced, at least temporarily, until some of the collateral channels enlarge. Levy, Mason, Harrison and Blalock[24] have shown that ureteral occlusion is followed by a decrease in the total renal blood flow. The effects on the blood pressure of ureteral occlusion and of constriction of renal vessels are similar.

The most satisfactory method that has been developed for the production of renal hypertension is that of Goldblatt and his coworkers, which consists of partial constriction of the renal artery. We have used this method as well as several others in this study. A modification of the Goldblatt method which consists of explanting a kidney as well as constricting the renal artery has produced much more consistent elevations in pressure in our experience than any other procedure. A possible objection to explantation of the kidney is the fact that this procedure alone is very frequently followed by an elevation in the pressure for several days. However, it seems likely that this rise in pressure is dependent upon the same cause which is responsible for the elevation associated with the application of the Goldblatt clamp. At any rate, in the control studies on the effect of removal of a normal kidney under local anesthesia, sufficient time, following the explantation, was allowed for the pressure to return to the preoperative level. The explantation method has seemed to us to offer many advantages. Since general anesthesia is not necessary in the removal of an explanted kidney, the blood pressure determinations which are made during the first few hours following nephrectomy are probably of greater significance.

In this connection, it is of interest that none of our animals (Group 1) in which the remaining normal explanted kidney was removed developed a marked hypotension and only one had a significant rise in blood pressure. Harrison *et al.*[5] reported the development of marked hypotension in six of 12 animals in which bilateral nephrectomy was performed under general anesthesia. They state: "The occurrence of hypotension in most animals following

bilateral nephrectomy and in an occasional animal after ligation of both ureters can possibly be accounted for on the basis of postoperative shock and dehydration from vomiting and diarrhea. Whether the absence of renal tissue tends per se to reduce the blood pressure is still an unsettled question." Our experiments indicate very strongly that the presence of normal renal tissue is not necessary for the maintenance of a normal blood pressure, at least for the few days that dogs live after having been deprived of both kidneys.

Only one of our animals in which the remaining normal kidney was removed showed a significant elevation in the blood pressure and this animal did not appear to be relaxed and was shivering at the time of the determinations. The mechanism responsible for the rise in pressure which occurs in an occasional animal following the removal of all renal tissue is not entirely clear. Harrison *et al.*[5] state that it appears to be dependent on the central effects of deficiency of calcium ions and is brought about by the retention of phosphate and possibly also of oxalate and other substances which form un-ionized calcium salts. They further state: "The absence of an elevation of blood pressure in most nephrectomized animals in spite of marked phosphate retention can be accounted for by the simultaneous accumulation in the body of phenol-like substances which have been shown experimentally to prevent the pressor effects of phosphate."

Of greater interest in our studies were the effects of the removal of an explanted kidney, the artery of which had been partially occluded by a Goldblatt clamp with a resultant rise in the blood pressure. The superficial position of the kidney permits its painless removal without general anesthesia. By determining the blood pressure at approximately hourly intervals following the nephrectomy, a slowly progressive decline was observed with a return to the control level usually in six to ten hours. The presence or absence of the other kidney did not seem to affect the results. Almost identical findings were obtained when a hydronephrotic kidney was removed under local anesthesia. The mechanism of elevation of the blood pressure of these animals has not been elucidated but it is clear that it is abolished by removal of the kidney and that it takes a number of hours for the pressure to return to the control level.

The results of the experiments in which the effects of varying degrees of occlusion of the arterial supply to the kidney or kidneys were studied are of interest. The impairment to the renal arterial circulation produced in the different experiments included: (a) Total occlusion of all arterial supply; (b) occlusion, except for that through the ureteral vessels; (c) partial occlusion of main renal artery (Goldblatt method); (d) total occlusion of main renal artery; (e) total occlusion of main renal artery and capsular vessels; and (f) partial occlusion of the main renal artery and total occlusion of the rest of the arterial supply. An elevation in the blood pressure resulted in a high percentage of all types of experiments except those in which the kidney was entirely deprived of all blood supply. The results indicate that a diminu-

tion rather than an absence of blood supply is the important factor in the production of this type of hypertension.

It was noted in a good many of our experiments that the Goldblatt clamp eventually completely occluded the renal artery, even though the constriction was only moderately severe in the beginning, and in some instances the artery was found to be completely divided at exploration or autopsy. In this connection, it is of interest that two of our animals remained in good condition following gradually produced complete occlusion of both main renal arteries with their subsequent division and destruction of the capsular blood supply. All of the arterial blood supply to the kidneys entered through collateral vessels in the pedicle. Both of these animals developed hypertension, and were sacrificed after having been observed for one year.

An interesting, unanswered question has to do with why the blood pressure usually returns to normal following a temporary elevation for a number of days as a result of partially constricting the renal artery of one of the two kidneys. It is possible that the normal kidney takes over some of the excretory function of the ischemic one, with a resulting decline in pressure. It is unlikely that this is the explanation for it is well known that unilateral nephrectomy rarely results in an elevation in the blood pressure. It is possible that the collateral channels to the ischemic kidney increase in size and that the pressure returns to normal as the renal blood flow approaches the preoperative level. Another possibility is that the normal kidney may in some way destroy the effects of a pressor substance, if the evidence to the effect that such is formed in the ischemic kidney is correct. The experiments, in which the normal kidney was removed after the blood pressure returned to normal following the production of ischemia of the opposite kidney, were performed in an effort to throw some light on this question. A definite rise in pressure was noted in three-fourths of the experiments in which this was done. The reason for this is not apparent. Even though an elevation in the blood pressure usually follows the partial occlusion of the renal artery of one of the two kidneys or the occlusion of one of the ureters, a more marked and more lasting elevation in pressure results when the same procedures are performed on animals with only one kidney. There seems to be little doubt but that the normal kidney in some manner influences the effects of ischemia of the opposite kidney.

Additional experiments should be performed in which the pressure in the renal artery between the point of constriction and the kidney is determined. In the single experiment on a transplanted kidney in which this was done, the pressure was approximately one-half of that in the femoral artery. In another experiment on a dog with a single explanted ischemic kidney, the arterial pressure in the renal artery distal to the constriction was 85 Mm. Hg., while the femoral pressure was 170 Mm. Hg. If corroborated, they show that the production of general hypertension by the Goldblatt method is associated with renal hypotension.

In regard to the mechanism of renal hypertension, Wood and Cash[13]

state: "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 or excision of splanchnic nerves. However, a number of our own dogs 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." It was with a similar thought in mind that our experiments in which the kidney was transplanted were performed, for it is the only way that one can be positive that the kidney has been completely denervated. As has been stated, a definite elevation in the blood pressure was associated with partial occlusion of the arterial supply to a kidney transplanted to the neck. The elevation disappeared when the occlusion was released or the kidney was removed. The elevations in pressure were more marked in the animals in which the normal nontransplanted kidney was removed. The experiments show conclusively that this type of hypertension may be produced when the ischemic kidney is totally devoid of nervous connections and when the opposite kidney is undisturbed.

As has been stated, Harrison, Blalock and Mason,[21] and Prinzmetal and Friedman[22] have presented evidence that extracts of ischemic kidneys contain a greater amount of pressor substances than normal kidneys. Whether these pressor substances are actually the cause of this type of hypertension is not yet certain. The possibility that the hypertension is dependent upon a diminution in the rate of formation of depressor substances has not been excluded. Page and Sweet[19] showed that hypophysectomy, in dogs with hypertension produced by renal ischemia, is followed by a reduction in the arterial pressure to the normal level. Goldblatt[25] has recently made the same observation in regard to bilateral adrenalectomy and he noted further that as long as even a small portion of the adrenal cortex remains in the body, hypertension can be produced by renal ischemia. We have confirmed Goldblatt's observations on dogs with ischemia of bilaterally explanted kidneys. Goldblatt and his associates[2] have mentioned a number of possible mechanisms whereby the blood pressure may be raised as a result of renal ischemia: (a) "Afferent impulses from the affected nerve endings in the ischemic kidneys to the sympathetic ganglia or vasomotor center may result in general vasoconstriction and consequent elevation of blood pressure." Our studies on the denervated transplanted kidneys are evidence against this possibility: (b) "Afferent impulses from the ischemic kidneys may, in some way, bring about increased output of some internal secretion which, by peripheral or central action, may effect general vasoconstriction, and thus raise the blood pressure." Again, the experiments in which the kidney was transplanted are believed to rule out the possible effects of afferent impulses. Finally: (c) "There may be an accumulation or new formation of some substance, or there may occur a disturbance of chemical equilibrium between substances present in the blood which may effect a pressor action like that of a hormone." This latter possibility seems decidedly to be the most likely one. Since the presence of the

adrenals and pituitary is necessary for the production of this type of hypertension, it is possible that the rise in pressure is due to the formation within the kidney of a substance which brings about an increased output of some internal secretion which in turn results in vasoconstriction. It seems likely that the action is peripheral since Prinzmetal and Wilson[14] found that anesthetization of vasomotor nerves does not release the vascular hypertonicity in renal hypertension. This has been confirmed by Pickering.[26] On the other hand, Dock and Rytand[27] abolished hypertension of renal origin in rats by destroying the central nervous system.

Fishberg[1] states: "Hypertension, like fever, is merely a symptom and not a disease; sometimes hypertension is produced by renal disease, but more often it is not." This was written before the work of Goldblatt and his associates appeared, but it still seems certain that all instances of hypertension are not renal in origin. For this reason and others, it is unwise to draw conclusions concerning the treatment of patients with hypertension from the experimental work that has been performed. Since hypertension can be produced by causing ischemia of the denervated transplanted kidney and since reflexes from the kidney cannot be concerned under these conditions, our results indicate that one cannot expect to relieve hypertension of this type by cutting the afferent nervous pathways from the kidneys. This confirms the findings of Page and Heuer[28] in man. As regards the more popular procedure of cutting efferent pathways, the finding, by Prinzmetal and Wilson,[14] that anesthetization of the vasomotor nerves does not release the vascular hypertonicity in renal hypertension, and particularly the observations of Goldblatt, and Gross and Hanzal,[18] that splanchnic section does not prevent the elevation of blood pressure produced by renal ischemia and does not lower the pressure in experimental renal hypertension, show very clearly that this type of hypertension is not dependent upon the integrity of these nervous pathways. Furthermore, we have found that subdiaphragmatic section of the splanchnic nerves, removal of the celiac and upper lumbar ganglia and partial bilateral adrenalectomy do not abolish experimental hypertension due to renal ischemia.

SUMMARY

A number of different types of experiments have been performed in an effort to determine the mechanism by which renal ischemia results in hypertension. The following are some of the results.

(1) When the remaining normal kidney is explanted in the flank and the blood pressure is normal, removal of this kidney under local anesthesia results in little if any alteration in the blood pressure.

(2) When hypertension is produced by partial occlusion of the renal artery of an explanted kidney, the removal of the kidney under local anesthesia usually results in a slow decline in the blood pressure, with a return to normal in six to ten hours. The rise in pressure is usually slower than the decline. Similar results were obtained in animals with only one kidney and in animals with a normal kidney in addition to the ischemic explanted one.

(3) The rise in pressure which may be associated with occlusion of a ureter is abolished by the removal of the kidney, the pressure returning to normal in approximately six hours.

(4) Various degrees of impairment of the renal arterial circulation were produced. These include: (a) Total occlusion of all arterial supply; (b) total occlusion except for that through the ureteral vessels; (c) partial occlusion of main renal artery (Goldblatt method); (d) total occlusion of main renal artery; (e) total occlusion of main renal artery and capsular vessels; and (f) partial occlusion of the main renal artery and total occlusion of the remaining arterial supply. A significant elevation in blood pressure occurred in a high percentage of all types of experiments, except those in which kidney was entirely deprived of all blood supply, including that through the ureteral vessels.

(5) When the blood pressure returned to normal following partial constriction of the artery to one kidney, removal of the opposite normal kidney usually resulted in a rise in the pressure..

(6) Partial constriction of the blood supply to the single remaining kidney which had been completely denervated by transplantation to the neck resulted in a rise in the blood pressure. Release of the constriction or removal of the kidney under local anesthesia resulted in a decline in the pressure to the normal level.

(7) Similar results were obtained with the transplanted ischemic kidney when the opposite normal kidney was not removed.

(8) Homotransplantation of a kidney to dogs with ischemia of both kidneys and hypertension did not cause a decline in the blood pressure.

(9) The observations of Goldblatt to the effect that bilateral adrenalectomy abolishes experimental renal hypertension have been confirmed.

(10) Subdiaphragmatic section of the splanchnic nerves, removal of the celiac and upper lumbar ganglia and partial bilateral adrenalectomy do not abolish or prevent hypertension due to renal ischemia.

The possible significance of these results has been discussed.

REFERENCES

[1] Fishberg, A. M.: Hypertension and Nephritis. 3rd ed., 225, Philadelphia, 1934.

[2] Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. 1. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia. Jour. Exper. Med., **59**, 347, 1934.

[3] Rautenberg, E.: Erzeungung chronischer Nierenerkrankungen mit folgender Blutdrucksteigerung und Arteriosklerose. Deutsch. med. Wchnschr., **36**, 551, 1910.

[4] Hartwich, A.: Der Blutdruck bei experimenteller Urämie und partieller Nierenausscheidung. Ztschr. f. d. ges. exp. Med., **69**, 462, 1930.

[5] Harrison, T. R., Mason, M. F., Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency. Trans. Assn. Am. Phys., **51**, 280, 1936.

[6] Pässler and Heineke: Versuche zur Pathologie des Morbus Brightii. Verhandl. d. deutsch. path. Gessellsch., **9**, 99, 1905.

[7] Janeway, T. C.: Note on the Blood Pressure Changes Following Reduction of the Renal Arterial Circulation. Proc. Soc. Exper. Biol. & Med., **6**, 109, 1909.

[8] Cash, J. R.: A Preliminary Study of the Blood Pressure Following Reduction of Renal Substance with a Note on Simultaneous Changes in Blood Chemistry and Blood Volume. Bull. Johns Hopkins Hosp., **35**, 168, 1924.

[9] Cash, J. R.: Further Studies of Arterial Hypertension. Proc. Soc. Exper. Biol. & Med., **23**, 609, 1906.

[10] Backmann, E. L.: Einige Versuche über das Verhalten der Blutdruckes nach Nierenentfernung und Nierenverklimerung. Ztschr. f. d. ges. exp. Med., **4**, 63, 1916.

[11] Hartman, F. W., Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Radiation. Am. Jour. Med. Sci., **172**, 487, 1926.

[12] Pedersen, A. H.: A Method of Producing Experimental Chronic Hypertension in the Rabbit. Arch. Path., **3**, 912, 1927.

[13] Wood, J. E., and Cash, J. R.: Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressures in Dogs. Jour. Clin. Invest., **15**, 543, 1936.

[14] Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System. Jour. Clin. Invest., **15**, 63, 1936.

[15] Prinzmetal, M., Friedman, B., and Rosenthal, N.: Nature of Peripheral Resistance in Arterial Hypertension. Proc. Soc. Exper. Biol. & Med., **34**, 545, 1936.

[16] Page, I. H.: Vasopressor Action of Extracts of Plasma of Normal Dogs and Dogs with Experimentally Produced Hypertension. Proc. Soc. Exper. Biol. & Med., **35**, 112, 1936.

[17] Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension. Am. Jour. Physiol., **112**, 116, 1935.

[18] Goldblatt, H., Gross, J., and Hanzal, R. F.: Splanchnic Section in Experimental Hypertension. Am. Jour. Path., **12**, 760, 1936.

[19] Page, I. H., and Sweet, J. E.: Extirpation of Pituitary Gland on Arterial Blood Pressure of Dogs with Experimental Hypertension. Proc. Soc. Exper. Biol. & Med., **34**, 260, 1936.

[20] Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf. Skand. Arch. f. Phys., **8**, 223, 1898.

[21] Harrison, T. R., Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension. Proc. Soc. Exper. Biol. & Med., **35**, 38, 1936.

[22] Prinzmetal, M., and Friedman, B.: Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension. Proc. Soc. Exper. Biol. & Med., **35**, 122, 1936.

[23] Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension. Surg., Gynec. & Obstet., **62**, 314, 1936.

[24] Levy, S. E., Mason, M. F., Harrison, T. R., and Blalock, A.: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs. ANNALS OF SURGERY, **1**, 238, 1937.

[25] Goldblatt, H.: Personal communication, 1937.

[26] Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension. Clinical Science, **2**, 209, 1936.

[27] Dock, William, and Rytand, D. A.: Absence of Vasoconstrictor Substances in Blood of Rats with Renal Hypertension. Proc. Soc. Exp. Biol. & Med., **32**, 374, 1934.

[28] Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension. Jour. Clin. Invest., **14**, 27, 1935.