

THE HYPERTENSION-REDUCING FUNCTION OF THE KIDNEY

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THE recent synthesis of angiotonin (hypertensin) II by members of this Division¹ has opened important vistas in the search for participation of humoral agents in the genesis of hypertension.

Angiotonin when injected into an experimental animal or a human being causes a rise in blood pressure. Does it follow that its pressor activity is responsible for human hypertensive cardiovascular disease or even for chronic experimental renal hypertension? Enough data to answer this question are not yet available.

In our enthusiastic recognition of the pressor substances, we should not forget that although the participation of the renin-angiotonin system in experimental renal hypertension seems beyond doubt, many phenomena can be better explained if it is assumed that the kidney in addition to its excretory function has two opposing blood-pressure-regulating functions. One of these is the liberation of renin. Renin acts on renin-substrate to form angiotonin. The second is the formation of a material that reduces elevated blood pressure.

I shall present a working hypothesis developed by Dr. Irvine H. Page and myself for the pathogenesis of hypertensive cardiovascular disease, which takes into account the experimental evidence obtained in animals deprived of their kidneys. The hypertension that then occurs is called "renoprival" hypertension. This review is not complete. I shall mention the facts that support our views and leave it to others to contradict them. I shall quote mainly from our own published work. Due credit to earlier investigators has been given in those earlier publications; here the concern is not with priority of accomplishments but with the possible relationship of the facts.

Section I

Dogs from which both kidneys have been removed develop hypertensive cardiovascular disease.² Figure 1 shows that the regimen on which the dogs are kept after bilateral nephrectomy has some influence upon the rate at which hypertension develops. Overhydration with electrolyte solution increases the rate during the first few days,³ but avoidance of severe overhydration as judged by constancy of body weight does not prevent the development of renoprival hypertension. A high-protein diet⁴ seems to encourage the development of hypertension, especially in rats⁵; frequent peritoneal lavage does not prevent or

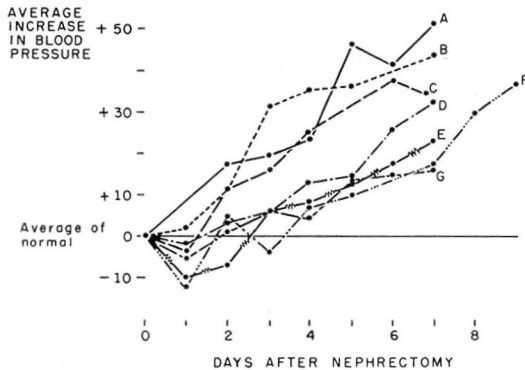


Fig. 1. Renoprival hypertension. Average increase above the normal arterial pressures in 7 groups of nephrectomized dogs.

Group	No. of dogs	Nephrectomy, no. of stages	Over-hydration	Dialysis	Diet: 4-6 gm. protein/kg./day	16 ml. saline/kg./day
A	7	One	++	—	—	—
B	6	Two	++	—	—	—
C	3	One	++	++	—	—
D	3	One	—	+	—	—
E	2	One	—	+	+	—
F	5	One	—	+	+	+
G	5	One	—	+	—	—
					(vomiting or unfed)	
Total	31					

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modify it.⁴ Variations in the amount of serum sodium in the nephrectomized dog can influence the height of blood pressure.⁶ This relationship is seen in Figure 2, where the experimental variations in serum sodium were followed by changes in blood pressure; this is not a phenomenon limited to renoprival hypertension since other forms of hypertension also are susceptible to changes in serum sodium.

Extrarenal factors have been blamed for renoprival hypertension. The adrenals well may be excluded as a decisive factor since Turner and Grollman⁷ produced renoprival hypertension and vascular disease in dogs from which both kidneys and adrenals had been removed.

HYPERTENSION-REDUCING FUNCTION OF KIDNEY

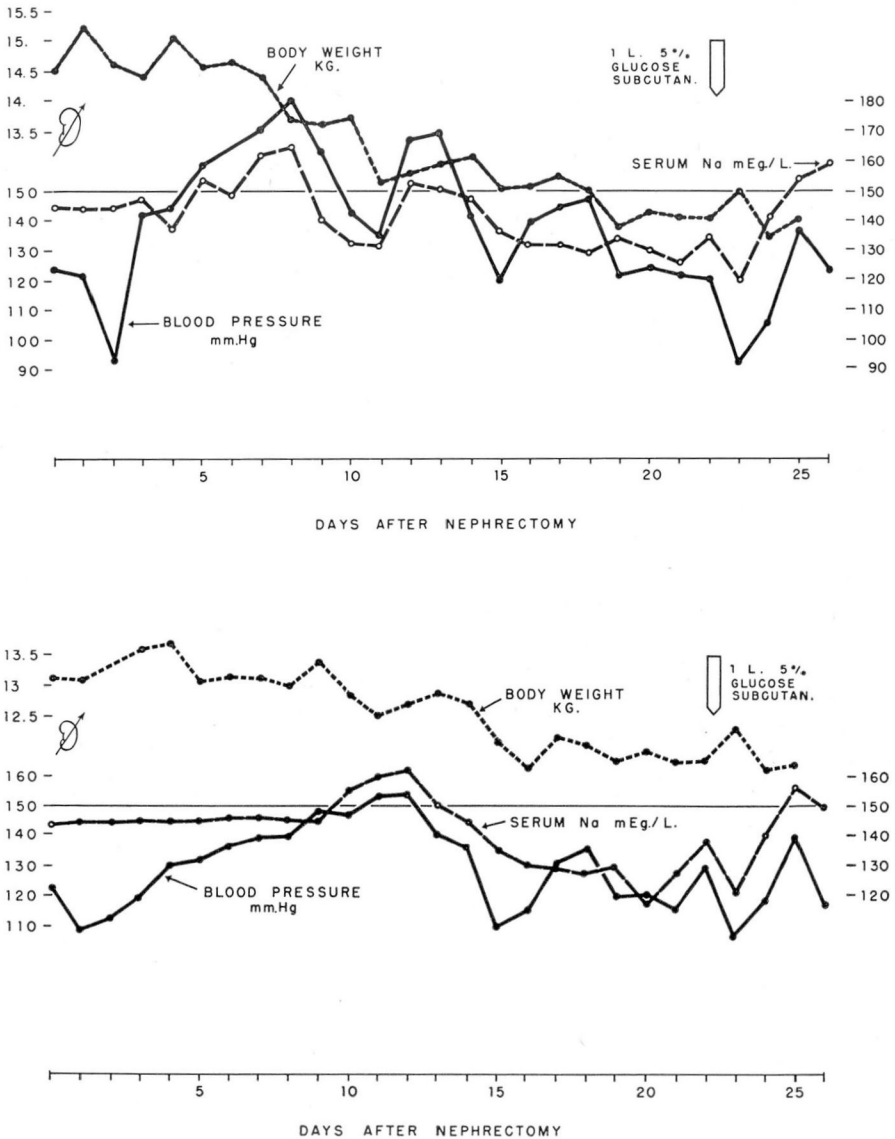


Fig. 2. Courses of two dogs in which serum sodium was deliberately varied. Both graphs show an association between the changes in serum sodium and arterial pressure independent of body weight. Sodium content of dialyzing fluid was varied in the experiment above from the fifth day on, and in that below from the eighth day. Initial rinsing fluid sodium was 148 mEq./l. and the subsequent concentrations 168 and 128 mEq./l. Hypodermoclysis with 5% glucose on the 22nd postnephrectomy day, in both experiments, caused gains in weight and decreases in serum sodium concentration and arterial pressure. *Reproduced through the courtesy of the American Journal of Physiology.*⁶

Some experimental animals do not develop renoprival hypertension after nephrectomy. This may be due to several factors: (1) an "untreated" non-dialyzed nephrectomized dog is not a happy animal and is not a qualified "control." It is likely to be sick with vomiting, uremia, dehydration, or shock. (2) The observation time may be too short. (3) Occasionally, the dog does not follow the pattern.⁴ There is no obvious reason. Figure 3 shows the graphs of two dogs: one developed renoprival hypertension, the other did not.

As we have seen, renoprival hypertension occurs rapidly in nephrectomized dogs that are overhydrated by intraperitoneal injection of electrolyte solution. However, hypertension does not occur in similarly overhydrated dogs with

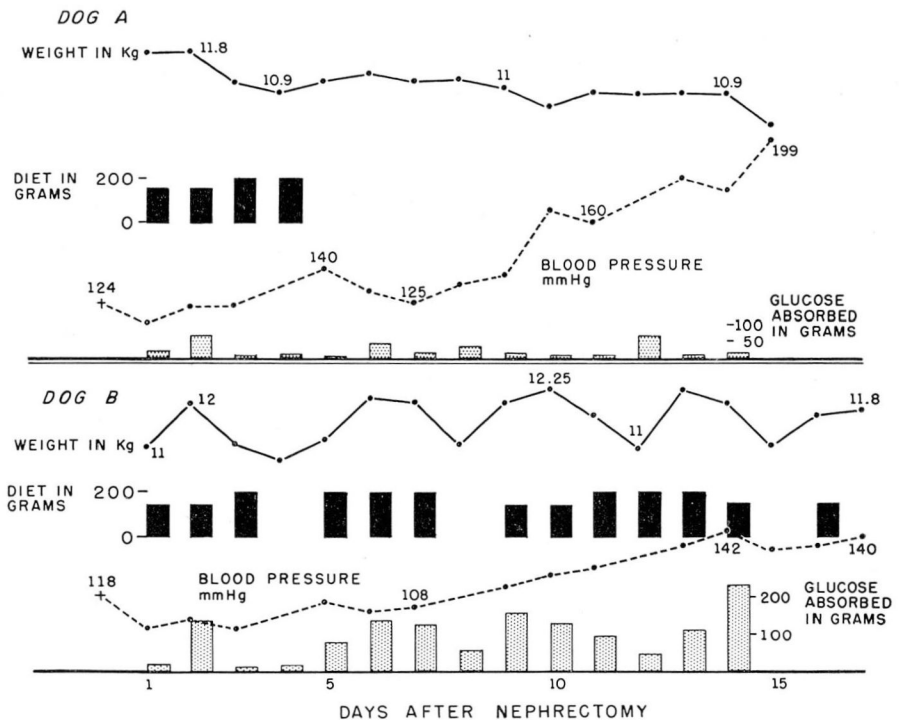


Fig. 3. Courses of arterial pressure in two nephrectomized dogs maintained for 15 or 17 days with peritoneal lavage. *Dog A* (upper half of the figure) developed hypertension notwithstanding loss in weight, discontinuance of forced feedings on the 4th day, and failure to absorb appreciable amounts of glucose from the peritoneal lavage fluid. *Dog B* (lower half of the figure) had only a small increase in arterial pressure, notwithstanding maintenance of weight, adequate dietary intake and absorption of sufficient glucose from the peritoneal lavage fluid. The average serum sodium and potassium and the blood urea levels were closely comparable in both dogs. *Dog A*—Serum Na, 148 mEq./l. (147-150); serum K, 4 mEq./l. (3.5-4.7); blood urea on the 12th day, 144 mg.%. *Dog B*—Serum Na, 148 mEq./l. (147-150); serum K, 4 mEq./l. (3-4.6); blood urea on the 12th day, 144 mg.%. Reproduced through the courtesy of the American Journal of Physiology.⁴

kidneys, but whose ureters are transplanted into the venae cavae. This is beautifully shown in an experiment first reported by Grollman, Muirhead, and Vanatta,² and later by us,⁶ which contrasts the effects of nephrectomy with those of ureteral transplantation (Fig. 4). These experiments show that even if the excretory function of the kidney is frustrated by having the urine led back into the blood stream, the mere presence in the body of functional renal tissue

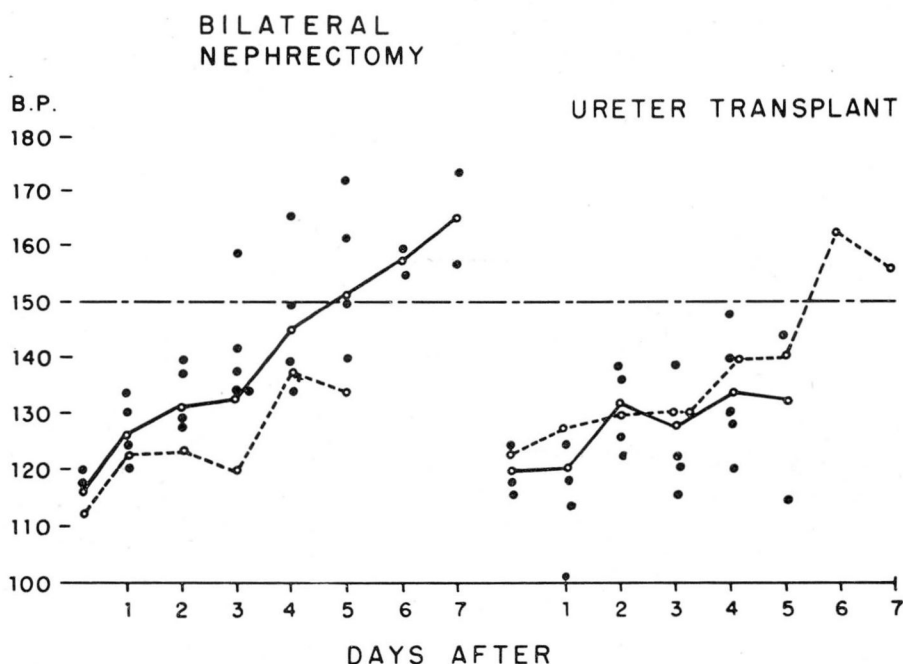


Fig. 4. Comparison of dogs after bilateral nephrectomy and dogs after ureteral transplantation into the vena cava.

Group	Prep.	No. of Dogs	Time of Obs., days	Wt. Increase, %	Serum Na, mEq./l.	Av. Highest B.P., mm. Hg	No. of Dogs With		
							Hypertension	Arteriolar necrosis	'Grotesque' edema of gastric mucosa
1	One-stage bilateral nephrectomy	7	4-7	29 (18-44)	150 (138*-160)	160 (140-172)	6†	4	6
2	Ureteral transplantation into vena cava	7	4-7	29 (12-49)	150 (135*-157)	139 (125-165)	1†	2‡	0

All dogs greatly overhydrated by filling the peritoneal cavity with electrolyte solution.

*Lowest value found corrected same day with NaCl. †The one exception that developed no hypertension suffered from a necrotic intussusception. ‡The one exception that developed hypertension had pyelonephritis and hydronephrosis; it also had arteriolar necrosis. The table is reproduced through the courtesy of the American Journal of Physiology.⁶

protects against the development of hypertension. This then is a demonstration of a protective nonexcretory function of the kidney, a function that prevents an abnormal rise in blood pressure.

In conclusion: *Although a variety of factors influences the occurrence or the rate of development of renoprival hypertension, the essential factor in its pathogenesis is "the absence of renal tissue."*

Section II

Those who disagree with the concept of renoprival cardiovascular hypertension sometimes argue that renoprival hypertension actually is not high enough to be true *hypertension*. It is admitted that in trained*, unanesthetized, renoprival hypertensive dogs, the mean arterial pressures taken by direct puncture of the femoral artery often are not higher than 160 mm. Hg. They are significant only in contrast to those in pre-nephrectomy controls, but elevations to more than 200 mm. Hg do occur. It seems to me that more important than the actual elevation of the blood pressure are the vascular changes that take place.⁸ Figures 5 through 10 show necrotizing and fibrinoid changes in the media of arterioles and proliferative changes under the intima of small vessels in dogs, and necrotic changes in the aorta of a rat. All these animals had renoprival cardiovascular disease. Some investigators have proposed and others have denied that many of the pathologic changes here depicted are identical or similar to vascular changes seen in human cardiovascular disease.

In conclusion: *Our experiments support the view first vigorously expressed by Grollman² that there is a kind of hypertensive cardiovascular disease that depends on the absence of renal tissue for its existence, and I believe that the same pathogenesis occurs in human hypertensive cardiovascular disease.*

Section III

Is it possible that renoprival hypertension is caused by renin or its reaction product, angiotonin? In Belgium and in Spain it was formerly believed that renin of extrarenal origin might be a factor in hypertensive disease. With the help of Dr. George E. Wakerlin in Chicago and Dr. Erwin Haas in the laboratory of Dr. Harry Goldblatt in Cleveland, we have tested this hypothesis.⁹ Dogs were protected with antirenin either by injection of antirenin serum or by active immunization with renin. Determinations of antirenin activity in the blood serum demonstrated a concentration of at least 10 units per milliliter in each dog. These animals showed virtual absence of a rise in blood pressure after the injection of renin. For these reasons it is assumed that they were well protected against renin.

*A trained dog here means a dog that does not actively resist lying on the table and has become used to puncture of the femoral artery.

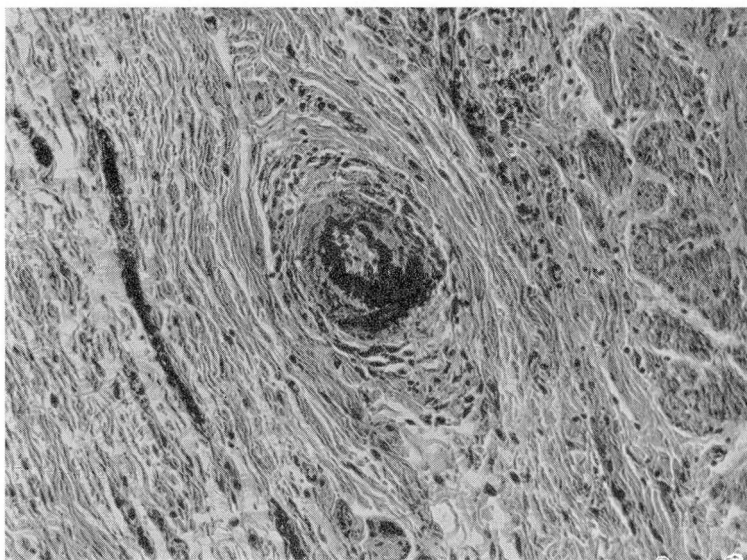


Fig. 5. Fibrinoid necrosis of intestinal arteriole of dog. Masson stain, X 150.

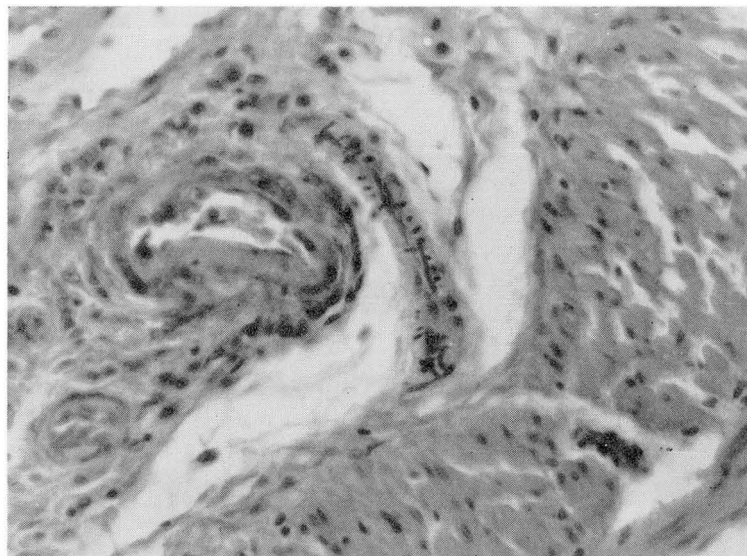


Fig. 6. Fibrinoid degeneration of arteriole of intestine of rat. X 300.

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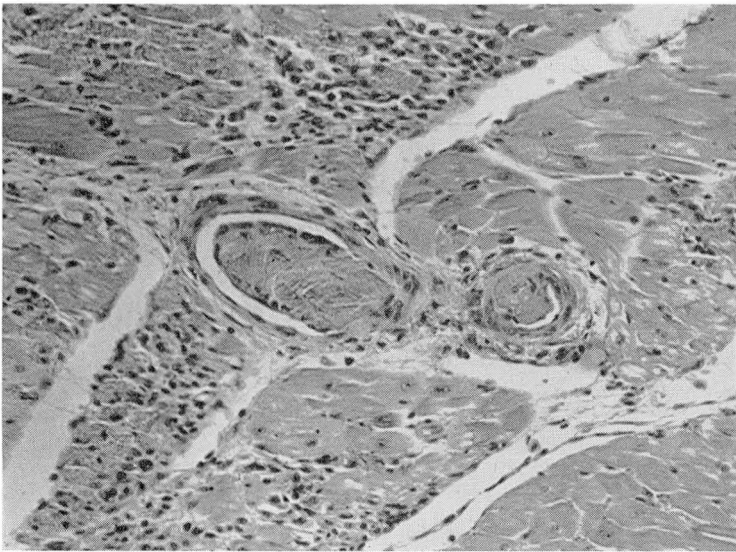


Fig. 7. Vessel of dog showing focal fibrinoid change and partial occlusion of lumen. X 150.

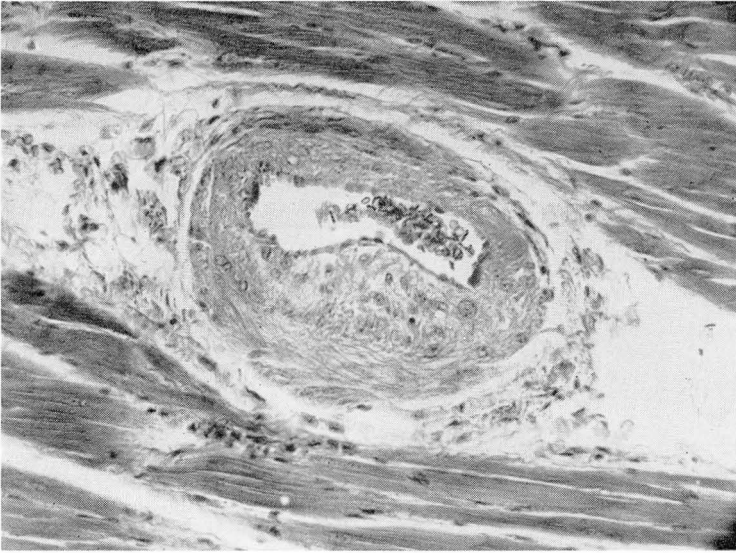


Fig. 8. Myocardial arteriole of dog, demonstrating proliferative change. X 300.

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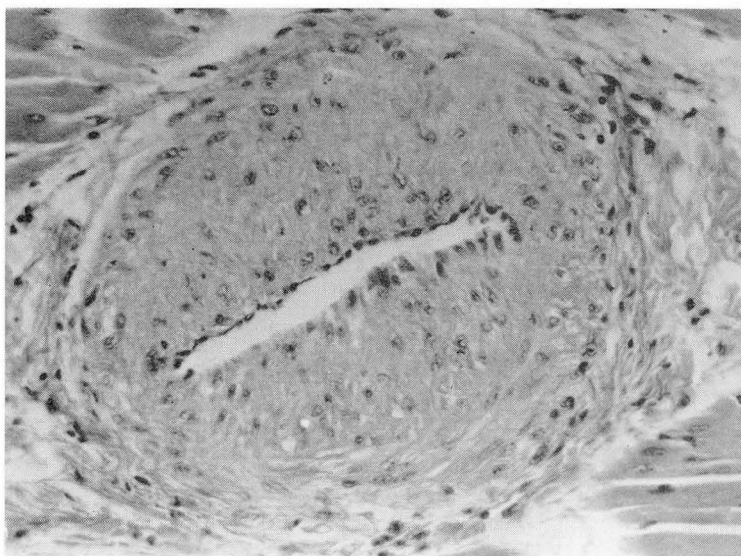


Fig. 9. Proliferative vascular lesion in dog. X 300.

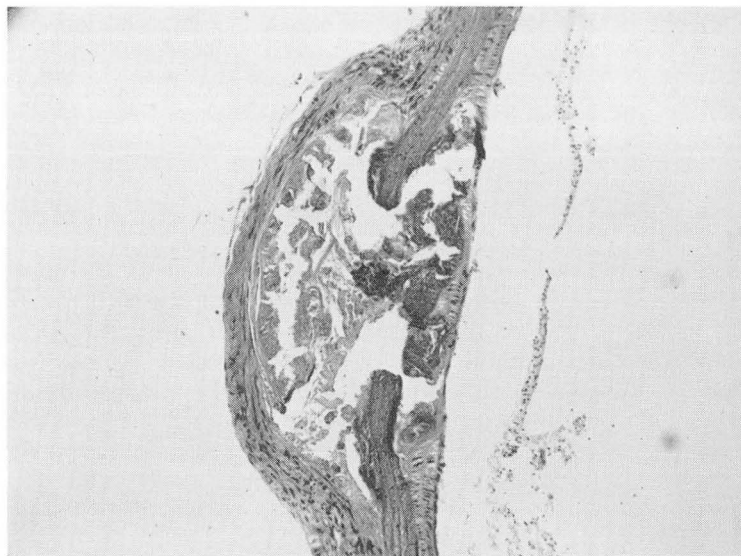


Fig. 10. Extreme necrosis and cystic change in aortic media of rat. X 70.

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The suppression of renin by antirenin did not prevent the development of renoprival hypertension in overhydrated nephrectomized dogs (Fig. 11) or reduce it in normally hydrated renoprival hypertensive dogs (Fig. 12). Nor did it prevent the development of the arteriolar necrosis and multiple focal myocardial hemorrhagic necrosis associated with renoprival hypertensive disease.⁹

In conclusion: *Renoprival hypertension and its associated vascular changes are not attributable either to residual renin or to renin of extrarenal origin.*

Section IV

If chronic experimental renal hypertension* were due to the pressor effect of continuously released angiotonin, the hypertension should not persist after total nephrectomy. Figure 13 shows that if the kidneys are removed from dogs with experimental renal hypertension, the hypertension persists.¹⁰ How can this be explained? (a) It is unlikely that circulating renin and angiotonin would persist so long; (b) it has been suggested that in chronic experimental hypertension the blood pressure is maintained at its high level because the arterioles have become irreversibly hardened or the carotid sinuses have become reset. However, Floyer^{11,12} has shown that these mechanisms, insofar as they exist, are quickly reversible. Floyer removed the clip from the renal artery of the sole remaining kidney in rats with renal hypertension. Promptly after the removal of the clip the blood pressure went down to normal. Thus, if the results obtained in rats can be trusted, it can be concluded that the arteries are not hardened and the sinuses evidently can be easily reset. It will be shown later that the same prompt fall in blood pressure occurs after transplantation of normal kidneys in a hypertensive dog, and that a comparable fall occurs after such a procedure in man.

We have seen that renoprival hypertension takes a few days to develop. However, if the kidneys are removed from dogs having chronic experimental hypertension, the blood pressure does not first fall and then gradually rise again, but rather remains unchanged.^{10,11} An explanation might be that the same mechanism underlies both renoprival and renal hypertension. The working hypothesis is now as follows: *Chronic experimental renal hypertension and hypertensive cardiovascular disease are not caused by the direct pressor action of the renin-angiotonin mechanism, but depend on the same mechanism that causes renoprival cardiovascular disease.*

Section V

It is known that renal hypertension develops in some animals, especially in rats, when a clamp is applied to the renal artery of only one kidney.¹¹ Evidently the normal kidney is not able to counteract effectively the

*Acute or acute malignant hypertension, which well may be caused by direct pressor effect of angiotonin, is not under consideration here.

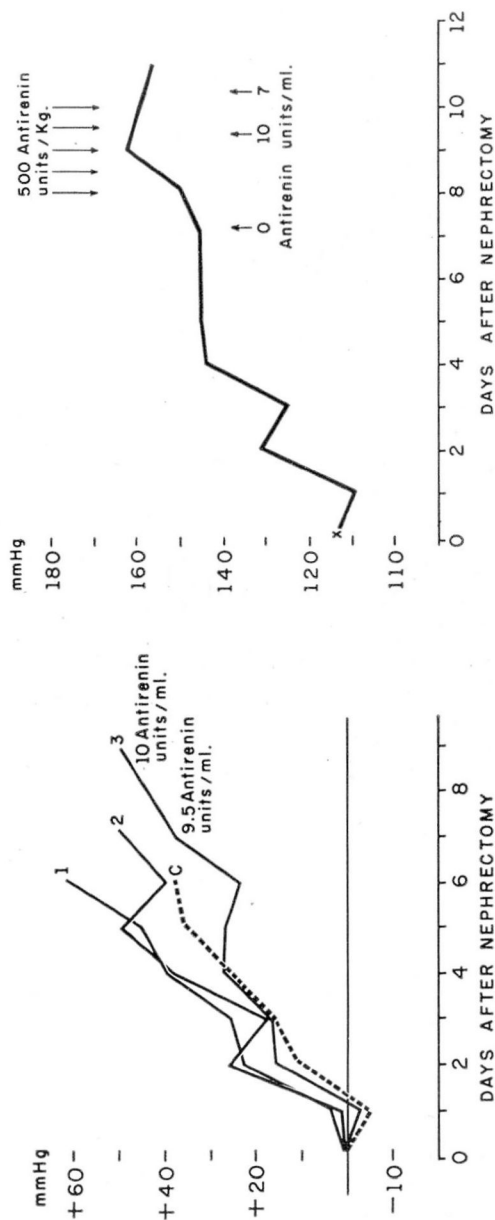


Fig. 11. Rise in blood pressure above the average before operation in 3 nephrectomized overhydrated dogs after prophylaxis with antirenin, as compared to average rise in blood pressure of 3 dogs without antirenin. C—average change in blood pressure in 3 controls; dog 1—antirenin serum injected on the day of and following nephrectomy; dog 2—antirenin serum injected on the day of and following nephrectomy; dog 3—treated with renin injections until antirenin titer 9-10 U/ml., thereafter nephrectomized.

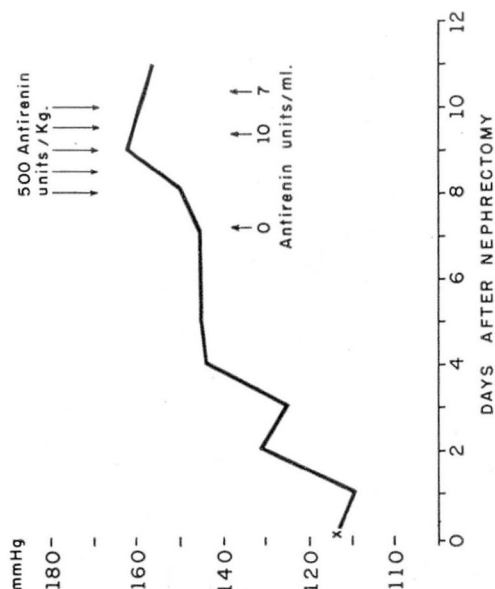


Fig. 12. Effect of antirenin on renovascular hypertension in a dog without overhydration, dog 4. Large arrows indicate the injections of antirenin serum (Wakerlin). The antirenin titer of the blood serum is indicated under the small arrows and was found to rise from 0 to 10 antirenin units/ml. In dog 5 (not shown) the antirenin titer rose from 0 to 15 AU/ml.; the course of the blood pressure was almost the same.

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BLOOD PRESSURES OF RENAL HYPERTENSIVE DOGS

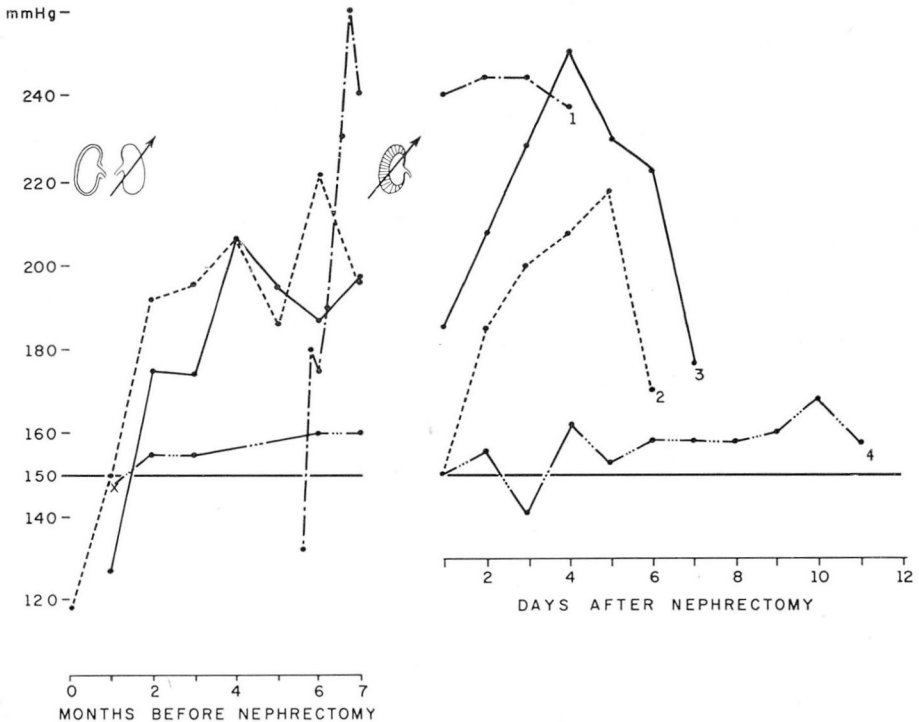


Fig. 13. Arterial blood pressures in dogs with renal hypertension before and after nephrectomy. 1. Malignant hypertension of five weeks' duration; persisted after nephrectomy. 2. Renal hypertension of 7 months' duration; persisted after nephrectomy (after reduction to 150 mm. Hg on 1st day only). 3. Renal hypertension of 4 months' duration; persisted with temporary increase after nephrectomy. 4. Only mild hypertension (160 mm. Hg) after the kidney slipped out of a rubber capsule; after removal of that kidney, blood pressure stayed around the same level. Reproduced through the courtesy of the *American Journal of Physiology*.¹⁰

hypertensive action of the clamped kidney. The originally normal, let us with Floyer¹¹ call it the "untouched" kidney, after some time participates in the maintenance of the high blood pressure. After the removal of the clamp from the clamped kidney,¹¹ but leaving the untouched kidney in place, the blood pressure comes down but not to a normal level. Removal of the previously clamped kidney, leaving the untouched kidney in the body, will result in a mild hypertension. However, removing the untouched kidney, leaving only the clamped kidney from which the clamp has been removed, reduces the blood pressure to a normal level. A possible explanation of this phenomenon is that a

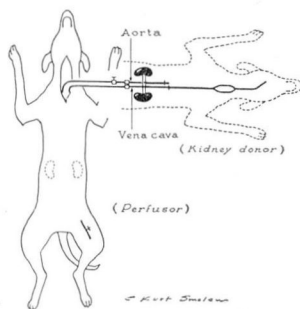
clamped or otherwise damaged kidney produces something (possibly renin) which impairs, blunts, or destroys that function of the other kidney that is normally concerned with reduction of hypertension. The amount of renin to effect this blunting might be very much smaller than the amount necessary to produce an immediate pressor response.

This hypothesis provides an explanation for the well-established blood-pressure-reducing effect of antirenin.¹³ Antirenin would block this very small amount of renin, remove the blunting effect of renin, and re-establish the blood-pressure-reducing function of the kidneys. That antirenin is unable to exert a beneficial effect in renoprival hypertension has already been established, and Shipley¹⁴ has shown that antirenin will not reduce the blood pressure in a renal hypertensive dog after total nephrectomy. Shipley performed only one experiment; if his findings can be confirmed they will indicate that *antirenin for its beneficial effect needs the presence of the good function of the kidney.*

Section VI

If it is true that hypertensive cardiovascular disease is caused by the absence of a specific renal function, then it should be possible to reduce hypertension by transplantation of normal kidneys. Muirhead and associates¹⁵ showed that in dogs having renoprival hypertension, blood pressure became normal after transplantation of normal kidneys. We produced hypertension in dogs by bilateral nephrectomy and overhydration with electrolyte solution. We then transplanted a pair of normal kidneys to the neck of each dog by means of a special technic that avoids even temporary ischemia during the transfer of the kidneys (Fig. 14). Within two hours after a pair of normal kidneys were included in the circulation¹⁶ the arterial pressure was reduced in 9 of 10 hypertensive

Fig. 14. Kidney perfusion according to Brull.^{23,24} Blood flowed from the carotid artery of the perfusor to the lower part of the aorta and kidneys from another dog and returned via the vena cava and finally to the jugular vein of the perfusor. The dog furnishing the extra kidneys was removed when the circulation with the perfusor had become established. A pipette was used to measure flow in the vena cava. *Reproduced through the courtesy of the American Journal of Physiology.*¹⁶



dogs (Fig. 15). The blood-pressure-reducing ability of the kidneys in renoprival hypertension does not depend on excretion of water or changes in electrolyte balance. *These experiments support the theory that renoprival hypertension is due to the absence of a specific nonexcretory renal function.*

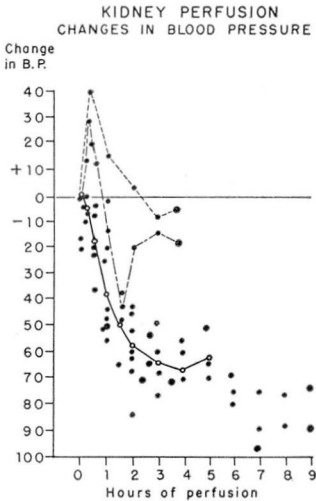


Fig. 15. Changes in blood pressure in mm. Hg of 10 nephrectomized, overhydrated and hypertensive dogs during perfusion of kidneys (*small dots*). The blood pressure came down 42-82 mm. during the first 2 hours of the perfusion in 9 of the 10 dogs. It tended to stabilize thereafter and in two dogs perfused for 9 hours it stayed around -75 and -88 mm. *Solid line* indicates the average fall in blood pressure in 8 dogs. *Heavy dots* indicate blood pressure values at end of kidney perfusion.

In one dog, indicated by a dotted line, after an initial fall of 43 mm. there was a secondary rise.

One exception in the 10 dogs with no fall in pressure occurred, also indicated by a dotted line. It showed a pressor response at the onset of perfusion. *Reproduced through the courtesy of the American Journal of Physiology.*¹⁶

Section VII

I have performed renal transplantations in other renoprival hypertensive dogs and confirmed the above-mentioned results. I have tried to obtain the same results in dogs with experimental renal hypertension produced by wrapping the kidneys with Cellophane.^{17,18} Transplantation of a pair of normal kidneys to the neck of each of 15 dogs with such experimental renal hypertension reduced the arterial pressure significantly in 6 dogs within a period of two hours of perfusion (Fig. 16). The reduction of blood pressure is not a mechanical effect since similar perfusion of a pair of hind legs did not lower the blood pressure, nor did a large arteriovenous anastomosis produce a lowering of the pressure. Although the results of these experiments were less conclusive than those obtained from the perfusion of transplanted kidneys by renoprival hypertensive dogs, they may be indicative of the antipressor action of the transplanted kidney. In the present experiments it may have been counteracted by renin-angiotonin produced by the Cellophane-wrapped kidneys. The blood pressure reduction was more easily obtained after transplantation of large kidneys than of small kidneys. In four additional experiments in which there was at least 8 gm. of transplanted kidney

available for each kilogram of body weight of the perfusor, adequate reduction in blood pressure occurred in all four during the perfusion. These experiments are difficult to perform and any factor, such as blood loss, which is damaging to the perfusor dogs, will tend to produce a fall in blood pressure and may be erroneously interpreted as a positive result. *These experiments suggest that experimental renal hypertension may be reduced by the blood-pressure-reducing function of transplanted kidneys.*

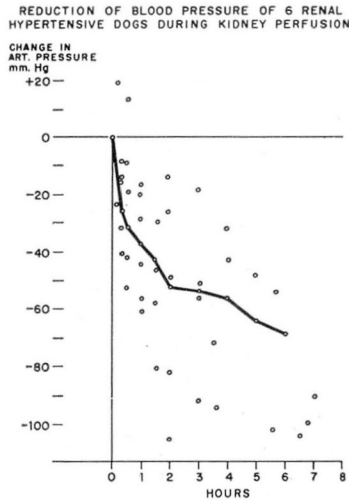


Fig. 16. In 15 dogs with experimental renal hypertension, pairs of kidneys were transplanted to the necks. In 6 of the 15 a significant fall in blood pressure occurred during the first two hours after onset of perfusion. The line indicates the average fall in blood pressure in these 6 dogs.

In 5 of the 15 dogs a fall in blood pressure occurred within 2 hours which was not considered to be significant.

In the 4 remaining dogs, no fall in blood pressure occurred after transplantation of a pair of kidneys to the neck. *Reproduced through the courtesy of the University of Michigan Regional Conference Symposium on Basic Mechanisms of Arterial Hypertension.*¹⁸

Section VIII

Fortunately there is support for this theory from experience with patients treated by Merrill, Murray, Harrison, and Guild.¹⁹ The course in one of their patients is summarized below.

A 24-year-old man had chronic renal failure, probably on the basis of

bilateral pyelonephritis, with severe uremia and hypertension progressing to malignant hypertension with a blood pressure of 220/146 mm. Hg. The optic fundi showed papilledema of two diopters with white patches and hemorrhages. A normal left kidney was removed from his identical-twin brother and was transplanted to the right iliac fossa of the patient. The postoperative course was smooth. The blood-urea concentration dropped to normal and the resting blood pressure to 120/60 mm. Hg. The optic discs returned to normal. The retinal vessels became normal although a few old scars persisted in the optic fundi. Three months after homotransplantation of the kidney, the arterial pressure gradually rose to 152/90 mm. Hg. A left nephrectomy was performed. Five and one-half months after the homotransplantation, his right kidney also was removed because of persistent mild pyuria and mild labile hypertension. After this, the blood pressure really dropped to normal, and 11 months after the homotransplantation of the normal kidney the blood pressure ranged from 125/70 to 146/82 mm. Hg. The patient was active without restriction and had no apparent physical disability.

After transplantation of a normal kidney the blood pressure of this patient with malignant hypertension was lowered. This may be interpreted as evidence of the blood-pressure-reducing function of the transplanted kidney. The pressure started to rise again until the patient's own contracted kidneys were removed. The contracted kidneys apparently impaired or blunted the blood-pressure-reducing function of the normal transplanted kidney. Dr. Warren R. Guild, the Acting Director of the Cardiorenal Laboratory during Doctor Merrill's absence, wrote me that two other twins have successfully received transplanted kidneys. The course of blood pressure in these two patients has been similar to that of the first twin to receive a transplanted kidney.

The number of hypertensive patients to receive a kidney transplanted from an identical-twin brother or sister undoubtedly will increase. The clinical experience thus obtained will obviate the need for more transplantation of dog kidneys such as we have described. *Men and dogs with hypertensive cardiovascular disease so far have shown the same favorable response to renal transplantation. This implies that the mechanism of the disease is the same in both.*

Section IX

The blood-pressure-reducing function of the kidney is not an excretory one. It is not known whether it depends on production of a substance that controls high blood pressure, or on the removal of something pressor from the blood. It is to be hoped that the kidneys produce an incretory, antipressor substance, a hormone that is released into the blood stream, since such a substance may be isolated and used in treatment. Page and co-workers²⁰ prepared renal extracts that had blood-pressure-reducing activity. As these were protein-rich it was difficult to dissociate the nonspecific foreign-protein reactions from the

specific hypotensive effects. Grollman has concentrated his efforts on a different renal antipressor substance²¹ which has smaller molecules, is dialyzable, and is active when given by mouth. He²² believes that it may be the same as a substance found in certain marine oils. It is difficult to evaluate hypertension-reducing substances since they should not lower a normal blood pressure. However, it is possible to produce chronic hypertension in rats and dogs, and these animals are in current use in screening tests.

No investigator should be satisfied until the hypothetical hypertension-reducing substance is purified or synthesized and made available to those who need it.

Summary

Renoprival and chronic renal hypertension may both depend on the same mechanism since hypertension persists after total nephrectomy.

Renoprival hypertension possibly is caused by the absence of a nonexcretory renal function.

Renoprival hypertension can be cured by kidney transplantation. In dogs the reduction of blood pressure occurs within two hours if the transplanted kidneys have not been subjected to ischemia during the transfer.

Chronic renal hypertension may be caused by the blunting or destruction of the blood-pressure-reducing renal function by amounts of angiotonin too small to cause a direct pressor effect.

Chronic experimental hypertension can be cured by the administration of antirenin, which may free the kidneys from the blunting effects of angiotonin. Antirenin is effective only when there is good renal tissue in the body.

Chronic renal hypertension both in experimental animals and in man may be reduced or abolished by: (1) Removal of the source of production of renin. This is effective only when sufficient unimpaired renal tissue is available to exert its blood-pressure-reducing effects. (2) Transplantation of a normal kidney. In man it seems that the diseased kidneys must be removed to maintain the beneficial, blood-pressure-reducing effect.

It seems likely that the blood-pressure-reducing function of the kidney depends on a substance increted into the blood stream. Serious effort should be made to isolate such a substance.

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