THE RÔLE OF RENAL METABOLISM IN HYPERTENSION AND UREMIA*†

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Although the identity of the chemical mediator of renal hypertension has not as yet been established, the development of a method for the production of persistent arterial hypertension (2) has stimulated studies which may lead to its identification and isolation. Meanwhile, the availability of the hypertensive animal has opened an avenue of study of the nature of the mediator by indirect means, chiefly by the investigation of its physiological properties. In the past few years we have utilized the Goldblatt method to study some of the properties of this mediator. In the present communication we report further studies along this line. No attempt will be made to analyze the literature critically, but we consider it important to recapitulate some conclusions from our previous studies.

While renal excretory insufficiency and hypertension are frequently associated, the mechanisms responsible for them are independent (3). Renal hypertension is apparently not the result of a diminished production of a depressor substance by the kidney since no persistent change in arterial pressure follows total nephrectomy in the normotensive animal (4). The absence of any persistent further rise in blood pressure in hypertensive dogs after total nephrectomy (4) makes unlikely the possibility that a depressor substance is manufactured by the normal kidney in the presence of hypertension.

Within a period of one year, the chemical mediator of renal hypertension does not lead to permanent changes which tend to perpetuate the hypertension, since removal of ischemic kidney tissue within this time leads to a return of the blood pressure to normotensive levels (4). It is probably not a sympathetico-mimetic substance since its action is unaffected by the dioxane derivative 933 F which reverses the action of epinephrine (5). The mediator has no demonstrable vasoconstrictor effect upon the arterioles in the pulmonary circuit since the arterial pressure in the lesser circuit is not elevated in marked systemic arterial hypertension (6). Moreover, since normotension persists after total nephrectomy, whether the animal be normotensive or hy-

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pertensive before the nephrectomy (4), it is unlikely that the mediator is a factor in the maintenance of normal blood pressure.

Renal hypertension appears to be a function of the ratio of ischemic to normal kidney tissue, the normal kidney tissue being implicated in the elimination or neutralization of the mediator. Thus, removal of the non-ischemic kidney in dogs with unilateral renal ischemia leads to an intensification of the hypertension, or to its appearance for the first time (7). Further, in dogs with hypertension due to unilateral renal ischemia, removal of the ischemic kidney results in a return of the blood pressure to normotensive

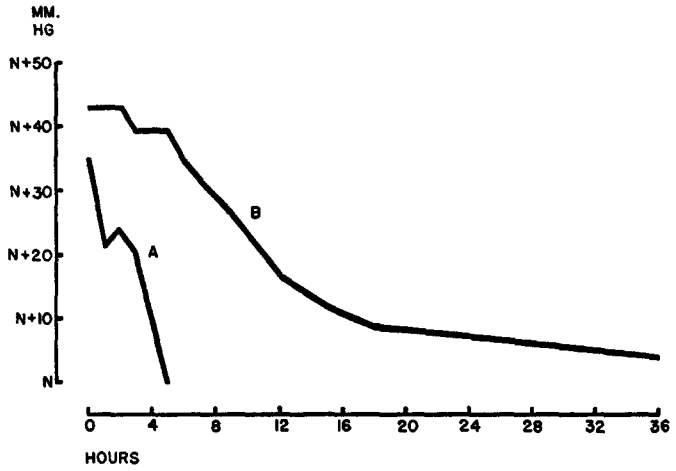

FIG. 1. The rate of dissipation of hypertension following removal of the ischemic kidney in seven dogs with the remaining kidney normal (curve A) and in six dogs with no remaining kidney (curve B). Abscissa gives time in hours. Zero time is the time during the operation when the blood supply to the kidney to be removed is occluded. Ordinates show the average diastolic pressure readings in mm. Hg in each series. N is the diastolic pressure level which existed before renal hypertension developed. These curves summarize results of a previous communication (4).

levels within 6 hours if a normal kidney remains in the body; but if no normal kidney is present, the blood pressure falls more slowly and reaches the normotensive level in about 25 hours (4, 8) (Fig. 1).

These observations raised the question of whether the elimination of the chemical mediator is accomplished by the excretory function or by the metabolic process of the normal kidney. The present study was undertaken to distinguish between these two closely associated functions in order to determine which mechanism is involved in neutralizing the hypertensive effect of the ischemic kidney. During the course of the study, observations were also made upon the effect of the metabolic activity of the kidney on the development of the uremic syndrome.

Methods

The rôle of renal excretory activity in hypertension was investigated in dogs with unilateral renal ischemia by permitting the urine excreted by the normal kidney to return to the blood stream *via* a uretero-venous fistula. Utilization of this procedure permits the metabolic and excretory activities of the kidney to continue presumably unchanged while the excreted products are returned to the blood stream. Should the mediator be excreted into the urine, it would automatically be returned to the blood and its pressor activity should not be lessened.

The rôle of the metabolic activity of the normal kidney in hypertension was investigated in such dogs with unilateral renal ischemia and contralateral uretero-venous fistula by determining the time for dissipation of the hypertension after removal of the ischemic kidney. If the kidney process neutralizing hypertension is metabolic, it would be expected that the rate of dissipation of the hypertension following removal of the ischemic kidney would be as rapid as when a normal kidney without such a fistula remained. If the renal process neutralizing hypertension is of an excretory nature, then the rate of dissipation of the hypertension would be as slow as that which occurs in the totally nephrectomized animal. The experiment was controlled by a similar procedure in normotensive dogs with unilateral uretero-venous fistulae.

All blood pressure determinations were made with the Hamilton needle manometer technique (9) upon trained unanesthetized dogs according to the method previously described by us (10). The period of training was considered completed when the diastolic blood pressure on at least three successive readings was found to be constant within ± 5 mm. Hg.

All operations on these animals were done aseptically under nembutal or ether anesthesia. Ether was used whenever the total renal excretory processes were eliminated, in order to insure adequate excretion of the anesthetic. Unilateral renal ischemia was produced in some of these trained animals by means of Goldblatt clamps (2) or linen ligatures used in a manner similar to the method of Drury (11). Some days after the development of hypertension, the ureter of the non-ischemic kidney was cannulated to the central end of a lumbar vein or directly into the inferior vena cava. A small glass cannula was employed for this purpose and its patency was checked at necropsy, by determining whether the injection of India ink into the pelvis of the kidney led to the presence of the pigment in the inferior vena cava. At necropsy a mild to moderate hydronephrosis of the kidney with the uretero-venous fistula was consistently found. Whenever the anastomosis was broken, a leak occurred and a urinary fistula developed along the line of incision; the data on these experiments were discarded.

The course of the blood pressure was followed for a variable number of days before the next stage was pursued. After this period of observation, the ischemic kidney was removed, leaving the non-ischemic kidney with its uretero-venous fistula *in situ*. Hourly

blood pressure determinations were made to discover the point at which the normotensive level was reached. As in our previous studies (4), the end point of the hypertensive level was selected as the time at which the diastolic pressure first reached within 5 mm. Hg of its normal control level; zero time was considered to be the time of occlusion of the blood supply of the kidney to be removed. Estimates were made of the rate and intensity of the development of uremia as indicated by the development of apathy, gastrointestinal irritation (vomiting and diarrhea), and increased nervous irritability (twitching and tremors) and terminal narcosis. The blood non-protein nitrogen was also determined from time to time.

Similar procedures were carried out on the control animals, the details being identical, with the exception that unilateral renal ischemia was not produced.

RESULTS

1. The Immediate Effect of Contralateral Nephrectomy on Blood Pressure in Dogs with Unilateral Uretero-Venous Fistulae.—Experiments were carried out successfully on seven dogs with hypertension caused by unilateral renal ischemia. A uretero-venous fistula of the contralateral normal kidney was established 12, 15, 5, 35, 49, 10, and 27 days respectively after the induction of the unilateral renal ischemia. The ischemic kidney was removed in these animals 7, 1, 5, 2, 0, 2, and 1 days respectively after establishing the uretero-venous fistula. In the first of these animals uremia was well developed at the time of the nephrectomy, the blood non-protein nitrogen being 264 mg. per cent at this time. The lag in the disappearance of the hypertension following nephrectomy in these animals is shown in summary fashion in Fig. 3 and a typical experiment is presented in Fig. 2. It was found that the hypertension was dissipated in 1, $6\frac{1}{2}$, 2, 7, 4, $6\frac{1}{2}$, and $5\frac{1}{2}$ hours respectively following removal of the ischemic kidney, or on the average within $4\frac{1}{2}$ hours.

In control experiments four normotensive dogs with unilateral uretero-venous fistulae were used, in which contralateral nephrectomy was performed 1, 2, 5, and 29 days respectively after establishing the fistula. Following nephrectomy a transient rise of diastolic pressure, 15 mm. Hg, occurred in one, returning to the control value in 4 hours. In the other three dogs no such immediate change in blood pressure occurred.

It is apparent that in dogs with a uretero-venous fistula *in situ* the time for dissipation of the hypertension following the removal of the ischemic kidney was of the same order as in these cases in which a normal kidney, excreting into the urinary bladder, remained (4) (compare Figs. 1 and 3). Actually, the maximum time for the dissipation was somewhat less than in the previous experiments referred to. This may be due to an improvement in our technique of nephrectomy whereby damage to the perirenal nerve plexuses was minimized with a consequent reduction in intensity of the

post-nephrectomy "neurogenic" blood pressure rise. This is suggested by the fact that in only one of the four control animals did a "neurogenic" rise occur and then it was small in amount.

We have therefore demonstrated that the rapid elimination of the pressor activity of the mediator continues even after the excretory function of the

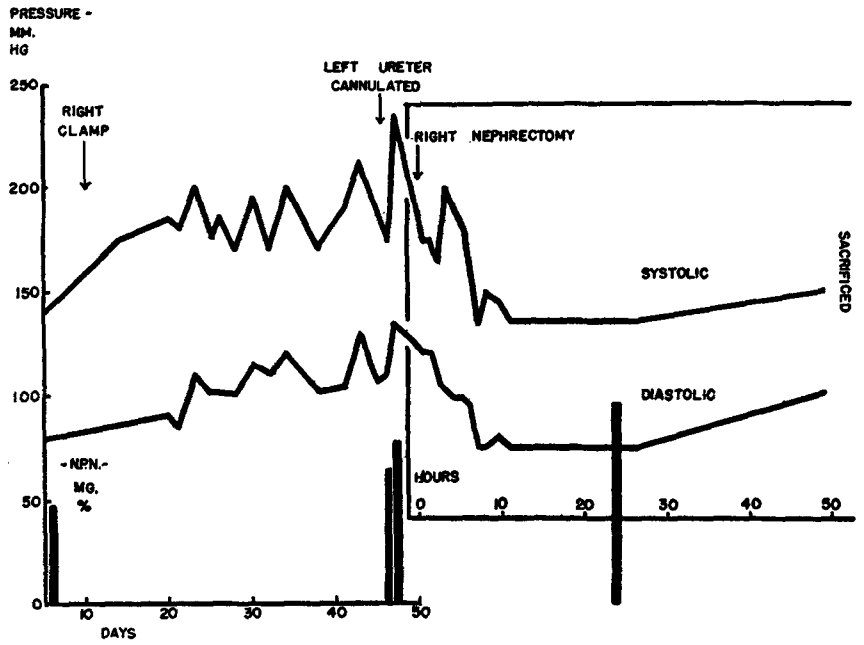

FIG. 2. The rate of dissipation of hypertension in a dog with unilateral uretero-venous fistula, following removal of the contralateral ischemic kidney. The chart also shows the control blood pressure and blood non-protein nitrogen, and the effect on these two variables of unilateral renal ischemia and subsequent contralateral uretero-venous fistula. The effect of the removal of the ischemic kidney is enclosed in the frame; the time scale in this frame is in hours instead of days as in the earlier part of the figure. Zero time in the frame is the time during the operation when the blood supply to the right kidney was completely occluded.

kidney is effectively removed by the uretero-venous fistula. This indicates clearly that the hypertension-neutralizing action of the normal kidney is due to its metabolic activity.

The above results further strengthen and amplify the thesis that the presence and persistence of hypertension is a function of the ratio:

$$\frac{\text{amount of ischemic kidney tissue}}{\text{amount of normal kidney tissue}}.$$

Our experiments do not preclude the possibility that the mediator of

hypertension is also destroyed by the ischemic kidney. However, since the ischemic kidney appears to be the source of the mediator, any such destruction must be exceeded by its production. Clinically, kidneys with both ischemic and non-ischemic portions may occur and result in no change in blood pressure. As yet, however, we have no satisfactory experimental method for demonstrating both normal and ischemic tissue in the same kidney.

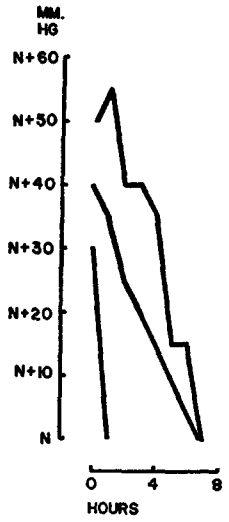

FIG. 3. The rate of dissipation of hypertension in seven dogs with unilateral ureterovenous fistulae following removal of the contralateral ischemic kidney. Conventions as in Fig. 1. The top and bottom curves give the range and the middle curve shows the average of the blood pressure readings.

The middle curve in this figure was obtained by averaging the pressures at each time interval. The average time for the dissipation of hypertension computed in this way is longer than that obtained in the text. The latter is the average time for the return to the normal level in the seven experiments.

In indicating that the chemical mediator of renal hypertension is produced primarily by the ischemic kidney and metabolized to a non-pressor state by the normal kidney, our experiments lead us to suggest that the kidney normally is able to manufacture as well as destroy the mediator. It would be peculiar indeed, if this ability to destroy the mediator developed in the non-ischemic kidney only after the mediator was formed in ischemic kidney tissue. It is more in accord with known biological mechanisms to assume that in normal kidney both processes go on at about the same rate. This suggests the hypothesis that the mediator is a normal product of renal intermediate metabolism and is usually destroyed before it can accumulate

in the blood sufficiently to cause a blood pressure rise. Whenever abnormal conditions such as ischemia arise, the reaction is blocked at the stage in which the intermediate products are pressor in nature and these can then pass into the blood stream. However, the presence of a normal kidney enables this pressor product of renal intermediate metabolism to be converted to non-pressor forms, thereby more or less effectively neutralizing the tendency to hypertension.

2. The Development of Uremic Symptoms and the Blood Non-Protein Nitrogen Changes Following a Uretero-Venous Fistula.—A total of fifteen unilateral uretero-venous fistulae were made. Neither uremic nor "nephrotoxic" symptoms developed and no rise in blood non-protein nitrogen occurred as long as the opposite kidney remained. This was true when the other kidney was normal, or when its renal artery was constricted, even to the point of causing hypertension.[1]

This confirms and extends the recent findings of Geer and Dragstedt (12). It is contrary to the reports of several investigators (13–18) who found that a unilateral uretero-venous fistula led to symptoms like uremia which they attributed to a postulated "nephrotoxin."

When the contralateral kidney was removed leaving only the kidney with the uretero-venous fistula *in situ*, a progressive rise in blood non-protein nitrogen was observed in all eleven of the animals. The rate of this non-protein nitrogen rise was 30 to 60 mg. per cent per day. All these animals developed uremic symptoms and died of uremia in much the same fashion as totally nephrectomized dogs. A similar effect was noted in two other dogs when a uretero-venous fistula of the remaining kidney was established 6 and 14 days respectively after uninephrectomy.

Our observations that dogs with uretero-venous fistulae in the remaining kidney developed uremia at a rate and intensity roughly equal to that which follows bilateral nephrectomy indicate that the metabolic activities of the kidney play little or no rôle in neutralizing the products responsible for the uremic syndrome. Thus if specific substances give rise to the uremic syndrome, they must be different from those involved in the production of renal hypertension. The former would be removed by the excretory activity of the kidney and would accumulate whenever this renal function is impaired, whereas the latter are removed by the metabolic activity of the normal kidney.

It is noteworthy that while the hypertension was dissipated after removal of the ischemic kidney within a few hours when the remaining kidney had

[1] The blood pressure changes occurring at the same time are discussed in another communication (19).

a uretero-venous fistula, the renal excretory insufficiency was simultaneously heightened (Fig. 2). This is further evidence for the dissociation existing between the mechanisms involved in the production of renal hypertension and of uremia (3).

SUMMARY

1. The chemical mediator of renal hypertension is rapidly destroyed by the metabolic activity of the normal kidney. The excretory function of the kidney plays little, if any, rôle in eliminating the mediator of hypertension.

2. If specific substances are responsible for the uremic syndrome, they are neither produced nor eliminated to any significant extent by the metabolic activity of the kidneys. The elimination of these postulated uremia-producing substances would have to be primarily dependent upon the excretory activities of the kidney.

3. No evidence was obtained to support the view that a unilateral uretero-venous fistula leads to "nephrotoxic" symptoms.

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BIBLIOGRAPHY

1. Rodbard, S., *Am. J. Physiol.*, 1940, **129,** 448.
2. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W., *J. Exp. Med.*, 1934, **59,** 347.
3. Friedman, M., and Katz, L. N., *J. Exp. Med.*, 1938, **68,** 485.
4. Rodbard, S., and Katz, L. N., *Am. J. Med. Sc.*, 1939, **198,** 602.
5. Katz, L. N., and Friedberg, L., *Am. J. Physiol.*, 1939, **127,** 29.
6. Katz, L. N., and Steinitz, F., *Am. J. Physiol.*, 1940, **128,** 433.
7. Katz, L. N., Mendlowitz, M., and Friedman, M., *Proc. Soc. Exp. Biol. and Med.*, 1938, **37,** 722.
8. Page, I. H., Newer aspects of experimental hypertension, in Blood, heart and circulation, The American Association for the Advancement of Science, 1940, No. 13, 239.
9. Hamilton, W. F., Brewer, J., and Brotman, I., *Am. J. Physiol.*, 1934, **107,** 427.
10. Katz, L. N., Friedman, M., Rodbard, S., and Weinstein, W., *Am. Heart J.*, 1939, **17,** 334.
11. Drury, D. R., *J. Exp. Med.*, 1938, **68,** 693.
12. Geer, W. A., and Dragstedt, L. F., *Ann. Surg.*, 1938, **108,** 263.
13. Brücke, E. T., *Wien. klin. Woch.*, 1926, **38,** 1058.
14. Galehr, O., and Ito, T., *Z. ges. exp. Med.*, 1927, **55,** 115.
15. Hartwich, A., and Hessel, G., *Z. ges. exp. Med.*, 1928, **59,** 633.
16. Enderlen, E., Zukschwerdt, and Feucht, *Münch. med. Woch.*, 1928, **75,** 30.
17. Lozzi, V., *Policlinico sez. chir*, Rome, 1932, **39,** 229.
18. Serra, G., *Boll. soc. ital. biol. sper.*, 1932, **3,** 229.
19. Megibow, R. S., Katz, L. N., and Rodbard, S., to be published.