RENAL HYPERTENSION PRODUCED BY AN AMINO ACID*

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PLATE 13

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Holtz (1, 2) and Bing (3, 4) showed that the anaerobic incubation of extracts of the renal cortex with amino acids converted these substances into their corresponding amines. The presence of the amines was demonstrated by their effect on the blood pressure of the cat or by their chemical isolation (1, 2). Holtz demonstrated that the amines were produced from amino acids by the action of decarboxylating enzymes contained in the renal cortex. The reaction occurred only under anaerobic conditions. When the incubation was carried out in the presence of oxygen the amino acids were converted, probably by deaminization, into substances differing pharmacologically and chemically from amines. Holtz *et al.* (5) and Bing and Zucker (4) found that the amino acid decarboxylases were specific for certain amino acids and varied with the animal species.

Bing (3) demonstrated that the isolated ischemic kidney of the cat, perfused *in vitro* with blood containing *l*-dopa (*l*-dihydroxyphenylalanine) transformed this amino acid into hydroxytyramine by decarboxylation. Since this amine, in contrast to dopa, is a pressor substance, it was possible to demonstrate its presence by the injection of the perfusion fluid into a cat. The amount of amine produced by the kidney varied inversely as the rate of blood flow. Only negligible amounts of pressor substance were found in the perfusate when the renal blood flow was normal.

It is generally believed that in experimental hypertension the kidney elaborates a substance causing arteriolar constriction. The conditions under which the pressor substance is formed are believed to be renal ischemia (6) or a reduction in the renal pulse pressure (7). The fact that the ischemic kidney converts dopa, which has no effect on the blood pressure, into a pressor substance, presumably hydroxytyramine, suggested that renal decarboxylation might play some part in the etiology of hypertension. The purpose of the present investigation was to ascertain whether or not hypertension could be produced in animals by the intrarenal conversion of dopa into a pressor substance.

Methods

In all experiments cats anesthetized with nembutal (39 mg. per kilo body weight, intraperitoneally) were used. The kidneys and their pedicles were exposed retro-

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peritoneally. In some experiments the collateral circulation through the capsule and ureter was left intact; in others it was destroyed by freeing the kidney from the peritoneum and fat, tying and cutting the ureter, and dissecting the pedicle. No attempt was made to leave the renal nerves intact. Complete renal ischemia was achieved by the application of serrefines to both renal pedicles for a period of from 2 to 4 hours. Dopa was injected into the left kidney, the right kidney serving as a control. Partial ischemia was created by placing a Goldblatt clamp (8) on the left renal artery. The right pedicle was clamped throughout the experiments and dopa was injected into the left kidney. From 10 to 50 mg. of *l*-dopa (*l*-dihydroxyphenylalanine)[1] dissolved in 3 to 5 cc. of Ringer's solution were used; in the majority of experiments 10 mg. in 3 cc. were injected. The solutions were freshly prepared.

Two alternative methods of injecting the dopa solution were employed. In some instances the fluid was injected by syringe through the renal capsule into the kidney tissue, in others into the renal blood supply through the aorta. In the latter method, the renal vein and the aorta above and below the origin of the renal artery were clamped with serrefines. The dopa solution was injected into the left renal artery through a 26 gauge needle inserted into the lumen of the aorta below the renal artery. After the injection, a third clamp was placed on the aorta proximal to the site of the injection and the needle was withdrawn. The serrefine on the aorta above the renal artery was removed to wash the dopa solution into the kidney and 20 seconds later the renal artery was clamped. Immediately afterwards the remaining clamps on the aorta were removed. The aorta was compressed for 5 minutes with a gauze tampon to prevent hemorrhage from the point of injection. The circulation through that vessel was then reestablished. A slightly different procedure which will be described below was employed in the experiments on the partially ischemic kidney.

The release of the pressor substance formed from dopa was detected by its effect on the blood pressure, measured from the carotid artery by a mercury manometer.

EXPERIMENTAL

Experiments on the Completely Ischemic Kidney

Thirteen experiments were performed to investigate whether the completely ischemic kidney is able to convert dopa into a pressor substance.

Dopa was either injected into the substance of the left kidney or into the blood supply of that organ through the aorta. 2 to 4 hours after the blood supply had been interrupted, measurement of the blood pressure was started. The clamp was removed from the pedicle of the uninjected kidney, restoring its circulation. 10 to 15 minutes later the circulation to the injected organ was similarly reestablished.

In every instance the removal of the clamp from the pedicle of the kidney containing the dopa solution was followed by a rise in blood pressure (Fig. 1). The peak of the pressure rise was reached within 2 minutes after the restoration of the circulation. The elevation varied from 15 to 115 mm. Hg (Table I). The wide variation was probably due to the loss of small amounts of dopa solu-

[1] Hoffmann-La Roche, Inc.

TABLE I

Experiments on the Completely Ischemic Kidney

Date	Control kidney			Injected kidney			
	Collateral circulation	Duration of ischemia	Rise in blood pressure	Dopa injected	Injected into	Duration of ischemia	Rise in blood pressure
			mm. Hg	*mg.*			*mm. Hg*
12/ 6/40		5 hrs., 6 min.	35	50	Aorta and tissue	4 hrs., 30 min.	40
12/ 7/40		2 hrs., 50 min.	5*	50	Aorta and tissue	2 hrs., 45 min.	85
1/25/41	Present	3 hrs., 8 min.	10 mm. fall then 100 mm. rise†	10	Aorta	2 hrs., 55 min.	10 mm. fall then 100 mm. rise
1/27/41	Absent	4 hrs.	45	10	Aorta	4 hrs.	18
2/ 4/41	Absent	4 hrs., 17 min.	110				
2/ 6/41	Present	2 hrs., 42 min.	30 mm. fall	10	Tissue	2 hrs., 45 min.	15 mm. fall then 30 mm. rise
2/ 6/41	Present	2 hrs., 30 min.	15*	10	Tissue	50 min.	45
2/ 7/41	Present	3 hrs., 20 min.	0	10	Tissue	3 hrs., 8 min.	20 mm. fall then 80 mm. rise
2/10/41	Absent	3 hrs.	5*	10	Tissue	2 hrs., 49 min.	115
2/11/41	Absent	3 hrs., 30 min.	10*	10	Tissue	3 hrs., 13 min.	95
2/11/41	Absent	3 hrs., 6 min.	0	10	Tissue	2 hrs., 53 min.	0‡
2/22/41	Absent	3 hrs., 4 min.	0	10	Tissue	1 hr., 43 min.	20 mm. fall then 75 mm. rise

* Rises occurred within 8 seconds, probably due to increase in blood volume.

† Dopa probably reached the kidney through its collateral circulation.

‡ Circulation could not be reestablished since a clot had formed in the renal artery.

tion during the injections or to differences in the ability of the kidneys to decarboxylate dopa.

In eight experiments the reestablishment of the circulation to the uninjected

kidney after 2 to 3 hours of complete ischemia produced no rise in the blood pressure even after the destruction of the collateral circulation. In three instances in which the renal circulation had been interrupted for 4 to 5 hours, however, pressor effects of 35 to 110 mm. Hg were observed. The rises differed from those observed after the removal of the serrefine from the injected kidney, since they were slower and did not reach their peaks for 7 to 8 minutes. These experiments suggested that the uninjected kidney of the cat, anesthetized with nembutal, was unable to form a pressor substance in less than 3 hours of complete ischemia.

Properties of the Pressor Substance

It seemed probable that the rises in blood pressure following the release of the pedicle of the ischemic kidney previously injected with dopa were caused by hydroxytyramine, since Holtz was able to isolate this amine after the anaerobic incubation of kidney extracts with dopa. To investigate this assumption, a series of experiments was performed to determine the properties of the pressor substance originating from dopa.

In two experiments the collateral circulation to both kidneys was destroyed and the right renal pedicle was clamped with a serrefine. 25 mg. of dopa dissolved in 4 cc. of Ringer's solution were injected into the left kidney through the aorta. The left pedicle was then clamped with a serrefine and 25 mg. of dopa in 3 cc. of Ringer's solution were injected into the renal parenchyma. 2½ hours after the injection the right renal pedicle was ligated close to the origin of the renal artery and cut between the ligature and the serrefine. The renal artery was cannulated, the serrefine removed, and the kidney perfused with 30 cc. of Ringer's solution through a syringe. The perfusate was collected in a beaker, whipped, and the clots removed by centrifugation. One half of the perfusate was heated to 100°C. for 3 minutes. The injected kidney was treated in an identical manner. The heated and unheated perfusates were then injected into the animal.

Rises in blood pressure were observed following the injection of both the heated and unheated perfusates of the kidney containing dopa. The perfusate of the uninjected kidney, however, had no effect (Table II). These experiments demonstrated, therefore, that the pressor substance formed from dopa was heat-stable.

Two experiments were performed to investigate whether the pressor substance could pass through a collodion membrane.

The right renal pedicle was clamped with a serrefine. 10 mg. of dopa dissolved in 3 cc. of Ringer's solution were injected into the left kidney through the aorta; its pedicle was then clamped. After 2½ hours of complete ischemia, both kidneys were excised without restoring their blood supply and perfused as described above. 2½ cc. of each perfusate were set aside. The remainder was diluted to 50 cc. with distilled water, placed in cellophane bags, and filtered in an ultrafiltration apparatus (9). The

protein-free filtrates were then distilled to dryness *in vacuo* at 60°C., the residue dissolved in 5 cc. of distilled water and injected into a test cat.

Pressor effects were obtained following the injection of both the filtered and unfiltered fractions of the perfusate of the kidney containing dopa, indicating that the pressor substance is ultrafilterable (Table II).

Since it has been shown that cocaine enhances the effect of hydroxytyramine (1, 10) and abolishes that of tyramine (11), experiments were performed to investigate the effect of this drug on the action of the pressor substance originating from dopa.

TABLE II

Experiments on the Properties of the Pressor Substance

Date	Injected kidney			Uninjected kidney		
	Perfusate was	Amount injected	Rise in blood pressure	Perfusate was	Amount injected	Rise in blood pressure
		cc.	*mm. Hg*		*cc.*	*mm. Hg*
12/ 9/40	Heated	1	13	Heated	1	5
	Unheated	2	25	Unheated	2	0
5/22/41	Heated	3.2	80	Heated	3.2	10
	Unheated	3.0	120	Unheated	3.0	10
1/29/41	Ultrafiltered	2	95	Ultrafiltered	2	0
	Ultrafiltered	2	20			
	Unfiltered	2	10			
3/ 8/41	Ultrafiltered	2.5	25	Ultrafiltered	3	0
	Unfiltered	2.5	20	Unfiltered	2	0

In five experiments both renal pedicles were clamped with serrefines. 10 mg. of dopa dissolved in 3 cc. of Ringer's solution were injected into the substance of each kidney in order to obtain equal distribution of the amino acid in both organs. 2 to 3 hours after the injection, artificial respiration was started and the clamp on the pedicle of the right kidney was removed. When the blood pressure had returned to its control level, cocaine hydrochloride (6 mg. per kilo of body weight dissolved in 2 cc. of Ringer's solution) was slowly injected into the femoral vein. The circulation of the left kidney was then restored.

After the release of the clamp placed on the pedicle of the right kidney the blood pressure rose an average of 30 mm. Hg, the effect lasting 1 to 2 minutes except in two experiments in which the blood pressure did not return to its control value (Table III). Following the injection of cocaine, the removal of the serrefine on the left renal pedicle produced rises averaging 50 mm. Hg, lasting from 6 to 16 minutes. From these results it was evident that cocaine enhanced the effect of the pressor substance.

The assumption might be ventured that the pressor substance originating

from dopa was identical with hydroxytyramine since (*a*) Holtz crystallized this amine after the anaerobic incubation of renal cortical extracts with dopa, (*b*) the kidney formed a pressor substance during 3 hours of ischemia only when dopa was present, (*c*) the pressor substance formed from this amino acid was heat-stable and ultrafilterable, and (*d*) its effect was potentiated by cocaine.

Experiments on the Partially Ischemic Kidney

A series of 40 experiments was performed to investigate whether the partially ischemic kidney could transform dopa into the pressor substance. In 29 experiments the dopa solution was injected into the left kidney through the aorta; in 11 cases, into the renal parenchyma. The contralateral kidney was clamped

TABLE III

The Effect of Cocaine on the Pressor Substance

Date	Renal pedicle unclamped before the injection of cocaine		Renal pedicle unclamped after the injection of cocaine	
	Duration of ischemia	Rise in blood pressure	Duration of ischemia	Rise in blood pressure
		mm. Hg		*mm. Hg*
1/10/41	2 hrs., 28 min.	55	2 hrs., 42 min.	65
1/10/41	2 hrs., 22 min.	20	2 hrs., 17 min.	75
1/20/41	2 hrs., 12 min.	25	2 hrs., 8 min.	20 mm. fall then 90 mm. rise
1/21/41	3 hrs., 11 min.	10	2 hrs., 58 min.	40
4/ 1/41	3 hrs., 30 min.	30	3 hrs., 30 min.	40

in every instance to avoid the destruction of hydroxytyramine which occurs in kidneys with normal blood flow (3).

In 29 experiments the right renal pedicle or the right renal artery alone was clamped with a serrefine. The left kidney and its pedicle were exposed and the abdominal aorta was dissected for approximately 1 cm. on either side of the origin of the renal artery. A Goldblatt clamp was placed on the renal artery, but was not tightened until after the injection of the dopa solution. Serrefines were placed on the renal vein and on the aorta above and below the origin of the renal artery. 10 mg. of dopa dissolved in 3 cc. of Ringer's solution were injected through the aorta as described above. The serrefines on the aorta were removed and the aorta was compressed with a gauze tampon until bleeding from the point of injection had ceased. The Goldblatt clamp was then adjusted to obtain partial renal blood flow. Finally the serrefine on the renal vein was removed. Compression of the aortic wound made complete renal ischemia lasting from 2 to 13 minutes unavoidable.

In some instances one animal was used for a series of injections. Control experiments in which Ringer's solution instead of dopa was injected were performed in a similar fashion.

In 15 instances the injection of dopa into the renal artery was followed by a rise in blood pressure averaging 100 mm. Hg (Table IV). In 11 of these experiments the curves obtained were steep and the peaks were reached 40 seconds after the partial restoration of the renal blood flow. In one instance in which 4 minutes elapsed between the injection of the dopa solution and the restoration

TABLE IV

*Experiments on the Partially Ischemic Kidney**

Date	Rise in blood pressure	Duration of complete ischemia	Remarks
	mm. Hg	*min.*	
12/21/40	100	11	Initial rise of 40 mm. Hg. Further rise of 60 mm. when Goldblatt clamp was opened
12/26/40	120	2	Blood pressure rose slowly 20 mm. Further opening of the Goldblatt clamp was followed by a rapid rise of 100 mm. Hg
1/15/41	130	4	
1/16/41	110	6	
2/14/41	150	13	Initial rise of 60 mm. Hg. Further rise of 90 mm. when Goldblatt clamp was opened
2/15/41	120	6	
2/24/41	70	12	
2/25/41	120	4	
2/26/41	90	1.5	Blood pressure rose slowly 25 mm. Further opening of the Goldblatt clamp was followed by a rapid rise of 90 mm. Hg
2/28/41	80	8	Blood pressure rose slowly
3/ 1/41	100	9	
3/ 3/41	100	10	
3/ 3/41	100	3	Initial rise of 40 mm. Further rise of 60 mm. when Goldblatt clamp was opened
3/ 4/41	75	2	Blood pressure rose slowly 30 mm. Closing clamp caused fall to control levels. Fig. 4 shows subsequent changes in blood pressure
3/11/41	70	9	

* In these experiments, 10 mg. dopa in 3 cc. Ringer's solution were injected through the aorta. For negative results, see text.

of the renal circulation the rise amounted to 120 mm. Hg. In four experiments more gradual rises were observed (Figs. 2 to 4).

The pressor substance was not formed from dopa in the partially ischemic kidneys of four cats. In three of these animals the kidneys were possibly deficient in dopa decarboxylase; in the fourth the renal artery was not found to be patent at the end of the experiment. In other instances in which an injection of dopa was not followed by a pressor response, a previous or subsequent

injection gave a positive result. It is probable that the dopa solution had not reached the kidney in these experiments.

In four experiments in which Ringer's instead of dopa solution was injected, no rises in blood pressure were observed. This indicated that the reduction of renal blood flow alone could not produce acute renal hypertension, a result which is in agreement with that obtained by Schroeder (12).

In eleven experiments the amino acid was injected into the parenchyma of the partially ischemic kidney. This method reduced the period of complete renal ischemia which existed between the injection of dopa and the reestablishment of the renal circulation to less than 30 seconds.

A Goldblatt clamp was placed on the left renal artery and tightened immediately. A serrefine was placed on the left renal vein and 10 mg. of dopa dissolved in 3 cc. of Ringer's solution were injected into the renal tissue. The Goldblatt clamp was slightly opened and the serrefine removed from the vein.

The injection of dopa was followed in four experiments by a slow rise in the blood pressure, amounting to 35 mm. Hg in three cases and to 65 mm. in the fourth. The rises extended over a period of 4, 16, 11, and 35 minutes respectively. When leakage of the injected solution occurred following the withdrawal of the needle, as it did in six instances, the injection of dopa had no effect on the blood pressure. The degree of ischemia was of importance for the formation of the pressor substance. This was indicated in one experiment in which the blood pressure rose only 25 mm. Hg after the injection of dopa. Following slight tightening of the clamp, however, an additional elevation of 40 mm. Hg occurred, lasting 35 minutes. Complete closing of the clamp resulted in a fall in blood pressure to its control level. In a second experiment a rise from 110 to 145 mm. Hg, lasting for 37 minutes, occurred during partial renal ischemia. In this case, as in the preceding one, occlusion of the renal pedicle caused a return of the blood pressure to its control level. These experiments indicated that dopa had been transformed into the pressor substance during partial renal ischemia.

Experiments on Kidneys with Normal Blood Flow

Nine experiments were performed to ascertain whether the kidney with normal blood flow was able to form the pressor substance from dopa.

In four experiments 10 mg. of dopa dissolved in 3 cc. of Ringer's solution were injected into the renal tissue, without interruption or reduction of the renal circulation. In five instances the solution was injected through the aorta in the following manner: After placing a hemostat on the aorta below the renal artery, the dopa solution was injected. A second hemostat was placed above the point of injection, slightly below the renal artery, for the remainder of the experiment, thus entirely abolishing the period of complete ischemia. Handling and dissection of the kidney and its pedicle were avoided as far as possible.

In three instances no change in blood pressure was noticeable after the injection of the dopa solution into the renal blood supply. In two experiments, however, the blood pressure rose 25 mm. Hg, the rise extending over a period of 6 minutes. Since in these cases the kidneys had been slightly moved, the formation of the pressor substance, if any occurred, may have been the result of renal ischemia following traumatic vasoconstriction. The injection of dopa into the kidney substance had no effect on the blood pressure in three out of four cases. In the fourth instance, a rise of 15 mm. Hg occurred within 2 minutes after the injection. The animal on which this experiment was performed, however, showed spontaneous fluctuations in blood pressure. It was evident from these experiments that no pressor substance is formed from dopa when the renal circulation is completely unimpaired. The injection of the amino acid following slight trauma of the kidney, however, appears to result in the production of the pressor substance.

DISCUSSION

Experiments in which dopa (*l*-dihydroxyphenylalanine) is injected into completely ischemic kidneys of cats demonstrate that this amino acid is converted into a strong pressor substance. After 2 to 4 hours of ischemia, the rises in blood pressure observed following the reestablishment of the circulation to the injected kidney vary from 15 to 115 mm. Hg. The removal of the clamp on the pedicle of the uninjected kidney after 2 to 3 hours of ischemia does not cause a rise in the blood pressure either in the presence or absence of the collateral renal circulation. When the blood supply is restored following 4 to 5 hours interruption, however, pressor effects amounting to 110 mm. Hg are observed. The formation of a pressor substance in the uninjected, completely ischemic kidney has been reported by several workers. Rises in blood pressure have been observed in dogs after ½ to 24 hours of renal ischemia (13–16), in the cat after 4 to 6 hours (17). The effect of shorter periods of ischemia has not been previously reported in the cat. Since the interruption of the blood supply to the uninjected kidney for 2 to 3 hours does not lead to the formation of a pressor substance, the effects observed following the injection of dopa into the completely ischemic kidney of the cat must be caused by the transformation of this amino acid into a pressor substance.

The observation that this substance is heat-stable and dialyzable differentiates it from the protein-like pressor substance, resembling renin, which is said to originate in the completely ischemic kidney of the cat (17). On the basis of the work of Holtz the assumption might be ventured that the pressor substance formed from dopa is the amine hydroxytyramine as it originates only in ischemic kidneys containing dopa and its effect is enhanced by cocaine.

Rises in blood pressure are similarly observed after the injection of dopa into kidneys made partially ischemic by the application of a Goldblatt clamp. It is conceivable that the pressor substance is formed during the period of com-

plete renal ischemia existing between the injection of the dopa solution and the reestablishment of the renal circulation rather than during the period of partial ischemia. Rises in blood pressure are observed, however, in experiments in which partial ischemia was caused by traumatic vasoconstriction provoked by handling of the organ. It is evident, therefore, that the partially ischemic kidney can convert the amino acid into the pressor substance, presumably hydroxytyramine. This conclusion is supported by the work of Bing (3) on the perfused organ. The importance of renal ischemia for the production of the pressor substance is demonstrated in experiments in which the injection of dopa into kidneys with normal blood flow failed to produce any change in the blood pressure.

The connection between Goldblatt hypertension (8) and the hypertension produced by the injection of dopa is as yet only hypothetical. It is possible, however, that the transformation of dopa into a pressor substance by decarboxylation represents the pattern of events taking place in the hypertensive kidney. According to this concept, hypertension would be caused by an interference with the normal enzymatic breakdown of amino acids and amines in the kidney. This organ contains specific amino acid decarboxylases (4) and an unspecific deaminase (18). Any decrease of the oxygen consumption of the kidney would inhibit deaminization, since oxygen is a necessary factor in this reaction (19). Decarboxylation, however, being an anaerobic process, would occur, leading to the formation of substances similar to hydroxytyramine in chemical constitution and pharmacological action. Rodbard and Katz (20) found that the normal kidney destroys the pressor substances present in experimental hypertension by metabolic processes not connected with its excretory function. It is possible that this destruction occurs by deaminization. The observation of Mason, Robinson, and Blalock (21) that the ammonia production of Goldblatt kidneys is reduced furnishes further evidence in favor of diminished deaminization. On the basis of the experiments reported in this paper, the action of tyrosinase in reducing the blood pressure of hypertensive animals and man (22) is of particular interest, since this enzyme destroys phenolic compounds resembling hydroxytyramine in their chemical constitution and pharmacological action.

SUMMARY

Acute renal hypertension is produced by the injection of the amino acid dopa (*l*-dihydroxyphenylalanine) into the partially or completely ischemic kidney of the cat.

Evidence is presented suggesting that the rise in blood pressure following the injection of dopa is caused by its conversion into hydroxytyramine, a pressor amine.

Kidneys with normal blood flow fail to transform dopa into a pressor substance.

The possible importance of this reaction in the etiology of Goldblatt hypertension is discussed.

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EXPLANATION OF PLATE 13

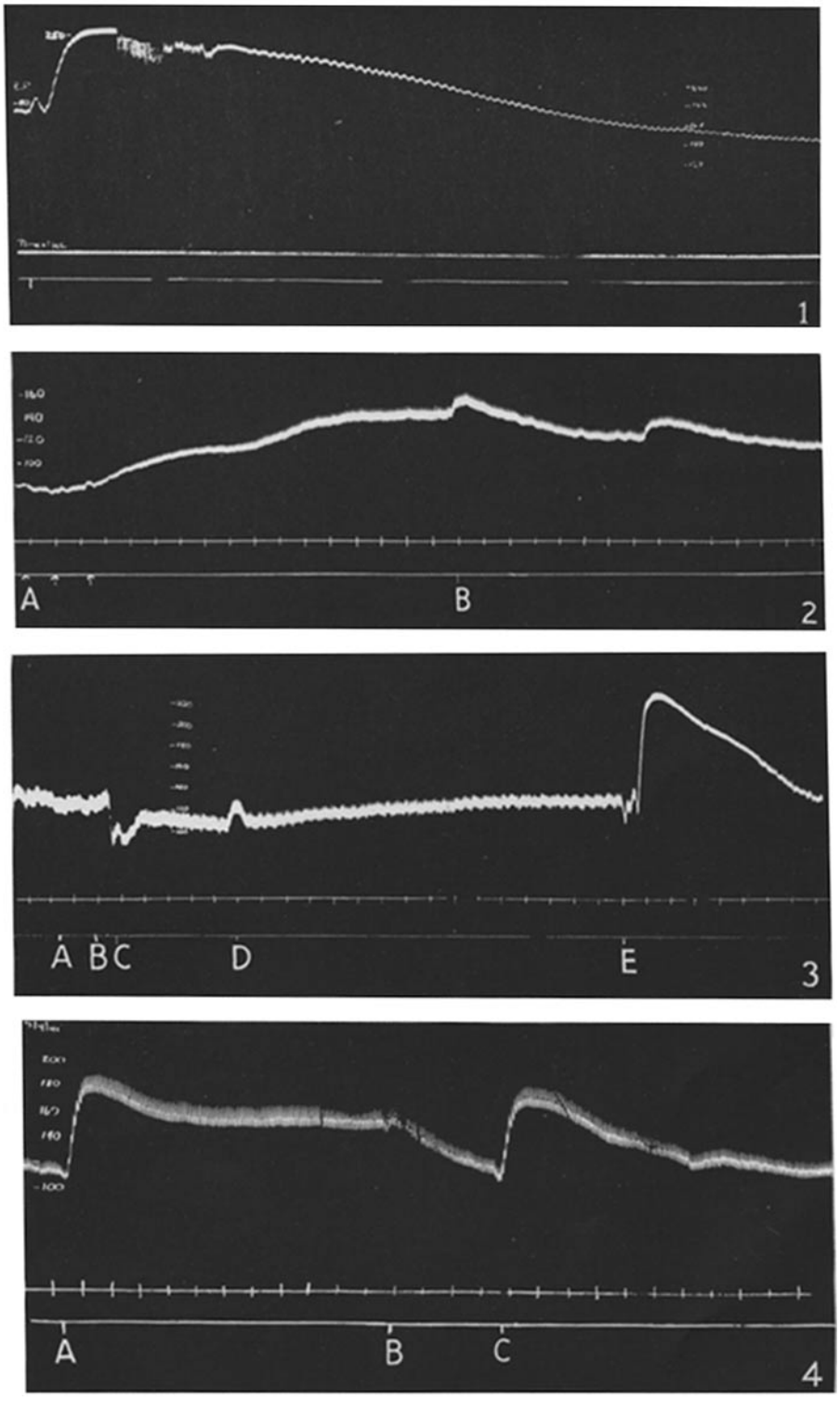
FIG. 1. The effect of removing the serrefine from the left renal pedicle after 2 hours and 45 minutes of complete ischemia. Kidney contained 50 mg. of dopa. The blood pressure rose from 170 to 255 mm. Hg in 40 seconds. Time = 1 second.

FIGS. 2 to 4 demonstrate the effect on the blood pressure of the injection of 10 mg. of dopa into the partially ischemic kidney.

FIG. 2. At *A*, the Goldblatt clamp was opened slightly. The blood pressure rose from 75 to 155 mm. Hg in 16 minutes. At *B*, clamping of the left renal pedicle. The blood pressure fell to 110 mm. Hg. Time = 1 minute.

FIG. 3. At *A*, 10 mg. of dopa were injected into the aorta. At *B*, the Goldblatt clamp was slightly opened. At *C*, the serrefines on the left renal vein and the aorta were removed. The blood pressure rose from 90 to 110 mm. Hg. At *D*, the Goldblatt clamp was further opened. The blood pressure rose from 110 to 130 mm. Hg. At *E*, the Goldblatt clamp was opened completely, causing the blood pressure to rise to 230 mm. Hg. Time = 1 minute.

FIG. 4. At *A*, the Goldblatt clamp was opened slightly. The blood pressure rose from 115 to 190 mm. Hg. At *B*, the Goldblatt clamp was completely closed and the blood pressure fell to 120 mm. Hg. At *C*, the Goldblatt clamp was opened moderately and the blood pressure rose to 180 mm. Hg. Time = 1 minute.



(Bing and Zucker: Renal hypertension from an amino acid)