

RENAL INSUFFICIENCY FOLLOWING TRYPSIN INJECTION INTO THE RENAL ARTERIES*

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For many years, it has been accepted that derangement of kidney function is intimately related to hypertension. Fishberg (1), de Wesselow (2) and Volhard (3) have pointed out that, with the exception of amyloid degeneration of the kidneys, severe kidney derangement is consistently accompanied by hypertension. The frequent absence of hypertension in amyloid involvement of the kidney has been supposed to be due to the cachexia accompanying this disease.

However, the direct proof of the relationship of deranged kidney function to hypertension is still lacking in the patient. Carrière *et al.* (4), Kylin (5), Brems (6), Loewenstein (7), Bohn (8), Hülse and Strauss (9) and Major (10) have reported the presence of abnormalities in the chemical composition of the blood in patients suffering with hypertension. These results were not substantiated by Page (11), Elliott and Nuzum (12), Weinstein and Weiss (13), Leiter (14), de Wesselow and Griffiths (15), Aitken and Wilson (16), Jackson *et al.* (17) and Andes *et al.* (18), who have reported that the blood of patients suffering with hypertension is apparently normal except when marked kidney excretory insufficiency is present. Nor could these workers establish the presence of abnormal pressor substances. The inability to demonstrate conclusively any qualitative or quantitative change in the blood of hypertensive patients who have kidney function essentially normal does not disprove the possibility that hypertension is related to derangement in the kidney, but it does tend to deter the facile assumption that this relationship has been demonstrated clinically.

Experimental studies upon laboratory animals also fail to give any clear indication of a relationship between kidney function and hypertension. Pässler and Heineke (19), Chanutin and Ferris (20), and Wood and Ethridge (21) have reported hypertension following the surgical removal of such large amounts of normal kidney tissue as to cause renal excretory insufficiency. However, Anderson (22) found excretory insufficiency alone, without hypertension, after a similar procedure. Cash (23) on the other hand observed the occurrence of hypertension following partial nephrectomy and renal artery ligation leading to kidney necrosis and renal excretory insufficiency. Arnott and Kellar (24) observed hypertension

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with concomitant renal insufficiency following the repeated administration of sodium oxalate, although their results could not be confirmed by Scarff and McGeorge (25). Hartman *et al.* (26) observed hypertension to result from repeated irradiation of the kidney, sufficient to lead to severe renal excretory insufficiency. Apfelbach and Jensen (27) could detect no hypertension in their animals following the injection of charcoal into both renal arteries with consequent severe renal excretory insufficiency. Finally, Goldblatt *et al.* (28) have reported that hypertension occurred following the production of either unilateral or bilateral renal ischemia. This last work has been confirmed by numerous workers, but the mechanism responsible for this hypertension is still unknown. Apparently this hypertension can occur following renal ischemia without gross evidence of renal excretory insufficiency, although there is little doubt that the type of hypertension produced in this manner can be masked by the presence of normal kidney tissue (29). The frequent temporary retention of blood nitrogen products immediately following bilateral renal artery clamping indicates that the renal excretory efficiency does suffer, at least temporarily.

This brief review makes it apparent that there is no agreement concerning the relationship between renal excretory insufficiency and hypertension or that between renal parenchymal damage and hypertension. In an effort to determine the interrelation of these three variables, renal excretory insufficiency, renal parenchymal damage and hypertension, a study was made of the effect of injection of trypsin into the arterial supply of the kidney of normal dogs. Trypsin was tried because, according to Rich and Duff (30), it produced hemorrhagic necrosis and rapid arteriolar hyalinization when injected subcutaneously, and preliminary experiments showed that trypsin injected into the renal artery produced renal damage. In addition, a study was made of the effects of renal ischemia produced by the Goldblatt clamp on kidneys previously damaged by trypsin injection and another of the effects of renal ischemia of one kidney in the presence of damage to the second produced by trypsin. It was hoped in this way that it would be possible to evaluate more clearly the interrelation of renal hypertension to renal parenchymal damage and renal excretory insufficiency.

Methods

(a) *The Injection of Trypsin Solution into the Renal Artery.*—A purified beef extract was the source of the trypsin. A concentrated solution of this was procured.¹ On the day of use, a 1 per cent suspension was prepared in normal saline,

¹ Procured from the Wilson Laboratories through the kindness of Dr. D. Klein.

shaken strongly for 15 minutes, filtered through paper once and then Berkefeld filtered. Just before injection, the solution was warmed to body temperature.

The injection was done under ether anesthesia. The renal artery of the dog was exposed by retroperitoneal approach, dissected free from the pedicle, encircled by a thread and temporarily constricted by manual traction. The freshly prepared and warmed trypsin suspension was placed in a 10 cc. syringe to which a curved hypodermic needle was attached. The artery was entered and 8 to 10 cc. of the suspension slowly injected over a period of 2 to 3 minutes. The artery was kept constricted for 2 minutes more after the end of the injection. This slow injection and temporary renal artery occlusion was found to be essential in order to produce the renal damage. Preliminary experiments showed that faster injections and shorter artery occlusions were ineffective, apparently because the rapid blood flow diluted and washed away the trypsin. Further, it was found that the daily injection of 20 cc. of this trypsin suspension into the brachial vein of normal dogs over a period of several months did not damage the kidneys or cause the blood pressure to rise.

(b) *The Production of Renal Ischemia.*—Under ether anesthesia the renal artery was dissected free *via* retroperitoneal approach, a Goldblatt clamp applied, the clamp closed completely and then released one complete turn.

(c) *The Determination of the Blood Pressure.*—All blood pressures were determined by means of a calibrated Hamilton recording manometer (31) connected to a needle inserted directly into the femoral artery. The dogs with one exception (K-2) were trained for this procedure, and a basal control level was obtained in repeated daily readings before any operative procedures were done. No anesthesia was found necessary for the blood pressure determinations. The dog would show little or no reaction to the needle puncture. Details of the procedure are given in a previous communication (32).

(d) *The Blood Non-Protein Nitrogen Determination and Urinary Concentration Test.*—Blood non-protein nitrogens were determined in the usual manner using the Koch method (33).

Urinary concentration was determined after the dog had been deprived of water for 24 hours. At the end of this period the dog was watched until it urinated. This first urine was discarded and the second urine when collected was used for the specific gravity determinations. Water was withheld until this second urine was collected. The first urine was discarded because many dogs were found to retain urine in their bladders for over 24 hours, thus making this urine unsuitable for concentration measurements.

RESULTS

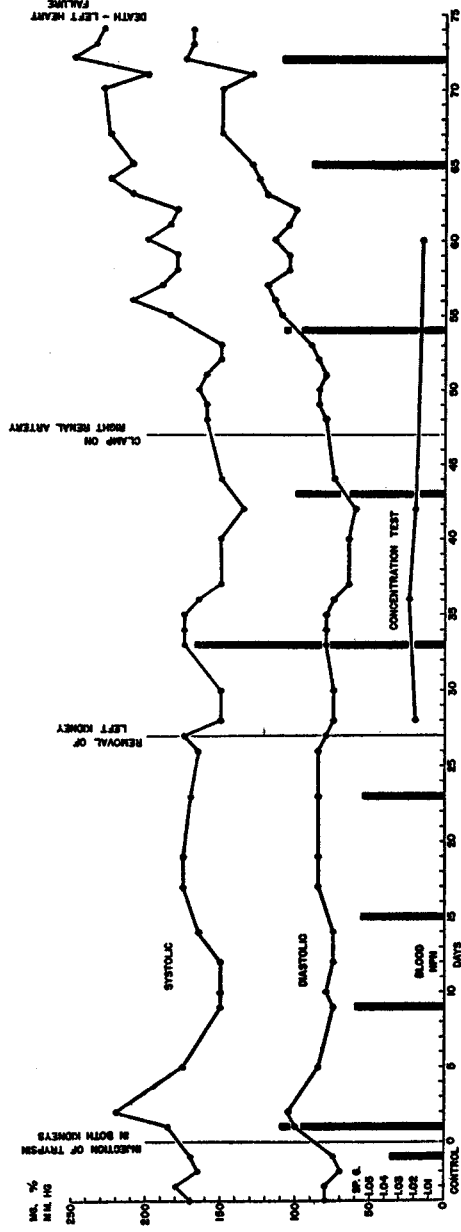
1. *The Injection of Trypsin into Both Renal Arteries of the Normal Dog.*—Thirteen dogs were used in this study, of which six died or were sacrificed within 48 hours, the remainder living for a period of from 1 to 12 weeks. In one, T-57, the injection was made in the remaining kidney, the other having been removed at the time of the

operation. Table I is a summary of the results in these animals and Text-figs. 1 to 3 show the essential findings graphically.

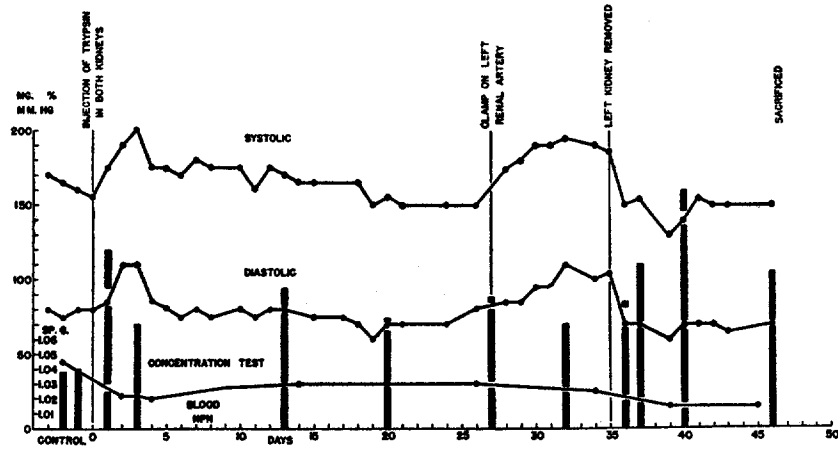
(a) *Effect of Trypsin Damage on the Gross and Histological Appearance of the Kidneys.*—

Acute Changes.—All six animals examined within 48 hours after trypsin injection had kidneys which showed, on gross examination, marked edema and large areas of hemorrhage and necrosis of varying extent. In those dogs dying naturally within this period, the entire kidney substance appeared to be necrotic. On microscopic examination (Fig. 1) the picture was predominantly one of severe necrosis with widespread hemorrhage and polymorphonuclear leucocyte infiltration of the interstitial tissue, glomerular capsules and lumina of the tubules. Tubular autolysis and glomerular compression were also present. The tubules appeared to be damaged the most and necrosis appeared chiefly here. The arteries and arterioles, on the other hand, appeared to be uninvolved. The damage histologically was patchy, and sharp boundaries were discernible between the damaged and the apparently normal kidney substance.

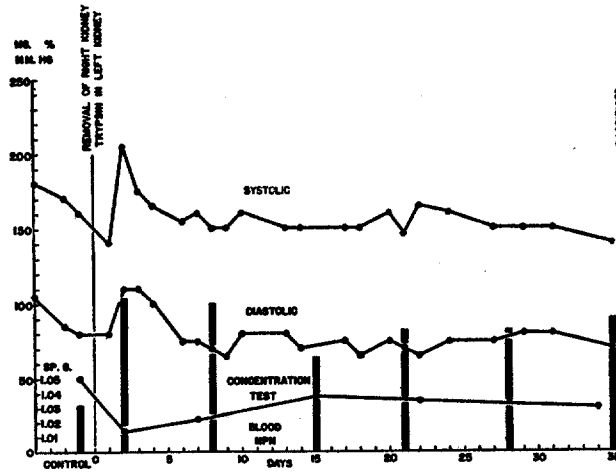
Chronic Changes.—The kidneys of the seven dogs dying or sacrificed 1 to 12 weeks after the trypsin injection showed a different picture from the above. On gross examination, all the kidneys appeared to be greatly contracted, with large depressed yellow scars occupying as much as half of the kidney. Between the scars, the kidney appeared normal in architecture and color. On microscopic examination, there were focal areas of extensive fibrosis with complete obliteration of glomeruli and occasional dilatation of the tubules. It is important to point out that there were no indications of a persisting inflammatory or other parenchymal change either in these scarred areas or elsewhere in the kidneys. No indications were found in any of the kidneys of crescent formation or chronic vascular changes. The contrast between the findings in the scarred area and the normal areas between scars is striking macroscopically, as a comparison of Figs. 2 and 3, both taken from the same kidney, will show. In the latter area the glomeruli and tubules appear normal. In short, the picture is one of a normal kidney with large areas of scar formation, indicating that the injection of trypsin had produced a focal acute involvement which had resolved into focal scarring.



TEXT-FIG. 1. Effect of trypsin damage to the kidneys on the blood pressure, blood non-protein nitrogen and concentration ability of the kidney in K-1. Also the effect of removing one of the trypsin-damaged kidneys, and of the later production of ischemia in the remaining trypsin-damaged kidney.



TEXT-FIG. 2. Effect of trypsin damage to the kidneys on the blood pressure, blood non-protein nitrogen and concentration ability of the kidney in K-9. Also the effect of renal ischemia of one of these trypsin-damaged kidneys and later removal of this ischemic and trypsin-damaged kidney.



TEXT-FIG. 3. Effect of trypsin damage to the remaining kidney (the other having been removed) on the blood pressure, blood non-protein nitrogen and concentration ability of the kidney in T-57.

(b) *Effect of Trypsin Damage of the Kidneys on the Urinary Findings.*

—For the first day or two, there was usually an anuria. The first urine voided always contained red blood cells, white blood cells, granular and hyaline casts and large amounts of albumin. As can be seen in Table I, the red blood cells in the urine tended to disappear within 2 weeks, but the casts and albumin could still be found for weeks. The most persistent abnormality was the albuminuria. In some dogs the albuminuria, slight in degree, lasted for the duration of the experiment.

(c) *Effect of Trypsin Damage of the Kidneys on Excretory Efficiency.*

—A severe renal excretory insufficiency was produced in all dogs, as can be seen in Table I and Text-figs. 1 to 3. In every case, blood nitrogen retention occurred and lasted throughout the course of the experiment, but it was usually greatest during the first week. In one dog, K-1, removing one of the kidneys injected with trypsin 4 weeks after the injection, elevated the blood nitrogen for the following 3 weeks.

The concentration test revealed a great depression in the ability of the kidneys to concentrate the urine (*cf.* Table I and Text-figs. 1 to 3). The greatest depression occurred in the first 2 weeks, the specific gravity of the concentrated urine falling, in two dogs, to as low as 1.014 compared with the normal value of 1.040 and 1.050. However, after the first week, the specific gravity of the concentrated urine tended to rise, but in no instance did it return to the control level.

(d) *Effect of Trypsin Damage of the Kidneys upon Blood Pressure.*—

Daily blood pressures revealed a postoperative hypertension lasting a few days (Table I and Text-figs. 1 to 3). The maximum pressure occurred usually on the 3rd day, the rise being on the average 35 mm. Hg for the systolic pressure and 30 mm. for the diastolic. By the end of the first week the blood pressure was found to be back to normal, or even slightly below normal, despite the continuation of the renal excretory insufficiency; this state of affairs lasted as long as 3 months.²

² The longer persistence of the high blood pressure in K-2 probably represents the effect of lack of training of this dog, since similar apparent blood pressure elevations have been found by us to be present in over 60 dogs before they were trained. The training of K-2 was not begun until after the trypsin was injected.

Effect of Trypsin Injection into Renal Art

Dog.....	K-1						K-2*						K-9								
	Blood pressure		NPN	Concentration test	Urinary findings			Blood pressure		NPN	Concentration test	Urinary findings			Blood pressure		NPN	Concentration test	Urinary findings		
	mm. Hg	mg. per cent			Albumin	RBC	Casts	mm. Hg	mg. per cent			Albumin	RBC	Casts	mm. Hg	mg. per cent			Albumin	RBC	Casts
Control values	170/80	34					32	1.040	0	0	0	160/80	39	1.055	0	0	0				
Type of experiment	Trypsin in both kidneys						Trypsin in both kidneys						Trypsin in both kidneys								
Days 1-7, 1		101		0	0	0	84		0	0	0	175/85	120		0	0	0				
2	185/105	110		3+	3+	3+	90		0	0	0	190/110		1.020	3+	3+	3+				
3	220/105	80					69		3+	3+	3+	200/110	70	1.022	3+	3+	3+				
4		69										175/85	64	1.020	3+	3+	3+				
5												175/80	54		3+	3+	3+				
6	175/85	67					92					170/75	54								
7							90					180/80	50								
Days 7-14†	150/75	60	1.018				218/105	88				170/80	94	1.030	3+	2+	3+				
14-21	170/80	56					210/105	70	1.014			160/70	92	1.030	2+	0	+				
21-28	170/80	55					170/85	136		+	0	2+	150/70	88	1.030	0	0	0			
28-35	Left kidney removed						175/90	98				Left renal artery occlusion									
	170/80	164	1.020									185/85	68	1.025	0	0	+				
35-42	Right renal artery occlusion						160/80	98	1.022			Left kidney removed									
42-49	150/70	57	1.020	+	0	0	170/85	46		+	0	0	145/70	160	1.015	+	0	0			
49-56	160/90	108	1.015				170/80	110	1.028	+	0	0	150/70	105	1.015						
56-63	190/110	96	1.018	0	0	0	165/80	66	1.030	+	0	0									
63-70	220/125	90					165/80	50		+	0	0									
70-77	Right renal artery occlusion						205/115	88	1.020	+	0	0									
77-84	230/155	110					205/105	150		0	0	0									
Cause of death	Left ventricular failure						Uremia						Sacrificed								
Necropsy findings	Both kidneys extensively scarred but portions of kidney between scars normal both in the gross and microscopically						Both kidneys extensively scarred with portions of kidney between scar areas normal both in the gross and microscopically. Kidneys were extremely shrunken						Left kidney very shrunken with large focal scars but normal tissue between these scar areas. Right kidney small, contracted with multiple small depressed scars								

* No control blood pressures taken on K-2.

† After first week, average blood pressure is given and non-protein values are maximum values in ea

TABLE I
ery on Renal Structure, Function and Blood Pressure

T-41						T-47						T-55						T-57																			
Blood pressure mm. Hg	NPN mg. per cent	Concentration test sp. gr.	Urinary findings			Blood pressure mm. Hg	NPN mg. per cent	Concentration test sp. gr.	Urinary findings			Blood pressure mm. Hg	NPN mg. per cent	Concentration test sp. gr.	Urinary findings			Blood pressure mm. Hg	NPN mg. per cent	Concentration test sp. gr.	Urinary findings																
			Albumin	RBC	Casts				Albumin	RBC	Casts				Albumin	RBC	Casts				Albumin	RBC	Casts														
170/80	26		0	0	0	155/80	38																														
Trypsin in both kidneys						Trypsin in both kidneys						Trypsin in both kidneys						Trypsin into left kidney Removal of right kidney																			
160/85	54		3+	2+	3+	150/85	50				3+	2+	3+	110/60	75		0	0	0	140/80	74		0	0	0	140/80	74		0	0	0						
180/90						160/85	53							160/85		1.014	2+	3+	3+	205/110	104	1.014	3+	3+	3+	160/85											
225/125						185/110								175/95	60		2+	2+	2+	175/110						175/110											
160/80	76					155/80	77							160/95			2+	2+	2+	165/100			3+	3+	3+	165/100											
160/80	70					145/75	76							170/95	82					155/75	84					155/75	84										
						140/75	54							160/85	88	1.018	2+	2+	2+	160/70		1.022	2+	0	2+	160/70		1.022	+	0	3+						
						140/75	60							Left renal artery occlusion							150/75	100	1.022	+	0	3+	150/75	100	1.022	+	0	3+					
														185/105	150					140/75	68	1.038		0	+	140/75	68	1.038		0	+						
														180/100	240	1.015	+	0	0	155/70	82	1.035	+	0	+	155/70	82	1.035	+	0	+						
																				145/75	90	1.030	+	0	0	145/75	90	1.030	+	0	0						
Hemorrhagic peritonitis						Rupture of incision with peritonitis						Uremia						Sacrificed																			
Both kidneys showed extensive edema with large hemorrhagic areas closely resembling huge infarcts with normal appearing spaces between infarcts						Both kidneys showed extensive focal damage with old hemorrhagic areas still present with great increase in connective tissue in these areas of former necrosis. Remainder of kidney normal						Left kidney showed a large hemorrhagic cyst almost as large as the kidney. Large scars throughout kidney with normal tissue between. Right kidney was the seat of an acute infection						Right kidney normal in every respect. Left kidney showed large depressed focal scars involving cortex and medulla with normal tissue between scars																			

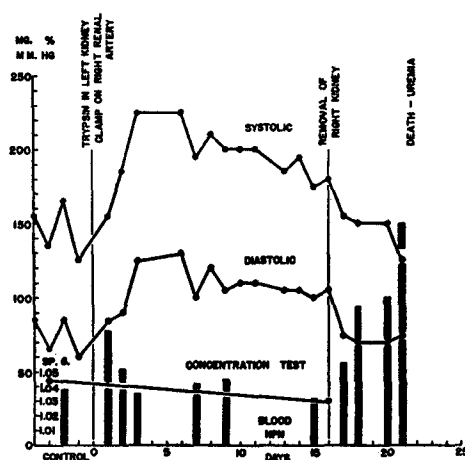
ch week.

(e) *Effect of Trypsin Damage of the Kidneys on General Condition of Dogs.*—Immediately after the trypsin injection, all the animals appeared acutely ill, with symptoms of lassitude, weakness and anorexia. After a few days, however, six of the seven dogs that survived appeared in good condition, ate well and were lively. Gradually, however, the animals that survived lost weight and developed an anemia. None of the animals revealed any evidence of edema. This loss of weight and progressive anemia was not observed in control animals not having trypsin renal insufficiency, and is, therefore, apparently caused by the renal damage.

2. *The Effect of Renal Ischemia in Dogs with Chronic Renal Excretory Insufficiency.*—Unilateral renal ischemia was produced by the application of a Goldblatt clamp in four dogs (K-1, K-2, K-9 and T-55) which had previously been subjected to bilateral renal artery injection of trypsin 2 to 10 weeks previously and which as a consequence had a chronic renal excretory insufficiency. One dog (K-1) had one of its kidneys removed 3 weeks prior to the application of the Goldblatt clamp. Table I and Text-figs. 1 and 2 show clearly that following the application of the clamp, these dogs developed a marked hypertension, the average rise being 45 mm. Hg for the systolic and 35 mm. Hg for the diastolic pressures. The elevation in blood pressure in all instances was higher than the early transitory rise during the first few days of the acute stage of trypsin renal damage. It was observed too that three of these unilaterally clamped dogs showed an exaggeration in the renal excretory insufficiency following the production of renal ischemia. This was so marked in two of them that death in uremia resulted. In one (K-1) (Table I and Text-fig. 1) the acute hypertension which developed was so great that it led to death from acute left heart failure.

The record of K-9 (Table I and Text-fig. 2) is significant. In this dog unilateral renal ischemia caused a rise in blood pressure without altering the renal excretory insufficiency to any extent. However, removal of this trypsin-damaged ischemic kidney caused a fall of blood pressure to the level existing before the clamping where it remained, although both the blood non-protein nitrogen and the concentration test showed an aggravation of the renal excretory insufficiency.

The complete differentiation between hypertension and renal excretory insufficiency in these four dogs indicates unequivocally for the first time that renal excretory insufficiency, *per se*, does not produce hypertension even when the animal can be shown to be potentially capable of developing hypertension. The rapid and marked elevation of blood pressure following the application of the Goldblatt clamp to one of these trypsin-damaged kidneys indicates further that these dogs with chronic renal excretory insufficiency were not too cachectic to develop and maintain a hypertension before the clamp was applied.



TEXT-FIG. 4. Effect of simultaneous trypsin damage to one kidney and production of ischemia in the other on the blood pressure, blood non-protein nitrogen and concentration ability of the kidney in T-59. Also the effect of later removal of the ischemic kidney.

It indicates further that the absence of hypertension was due to the absence of the mechanism that produced hypertension and not to the inability of the animal to respond to the renal excretory insufficiency with a hypertension.

3. *Effect of Combined Unilateral Renal Ischemia with Trypsin Damage to the Other Kidney.*—In a series of four dogs, unilateral renal ischemia by renal artery clamp was produced simultaneously with trypsin damage to the other kidney. The results are shown in Table II and Text-fig. 4. All four dogs developed a hypertension; in

Effect of Unilateral Renal Ischemia and Simultaneous

Dog.....	T-59						T-62			
	Blood pressure	NPN	Concentration test	Urinary findings			Blood pressure	NPN	Concentration test	Albu
				Albumin	RBC	Casts				
	<i>mm. Hg</i>	<i>mg. per cent</i>	<i>sp. gr.</i>				<i>mm. Hg</i>	<i>mg. per cent</i>	<i>sp. gr.</i>	
Control values	130/70	37	1.046	0	0	0	150/80	34	1.050	0
			Operation						Operation	
Days 1	155/85	78					155/95	116	1.027	3-
2	185/90	52								
3	225/125						180/110	76		
4	180/95	34		3+	3+	3+	155/100	82		
5	225/130						160/110	110		
6							160/100	74		
7	190/100	42								
8	200/110									
9	200/105	45								
10	200/110									
11	200/110									
12										
13	185/105									
14	195/105									
15	175/100	32								
16	180/105		1.030	+	0	0				
			(Ischemic kidney removed)							
17	150/75	65								
18	150/70	94								
19										
20	150/70	100								
21	125/65	150								
Cause of death			Uremia						Distemper	
Necropsy findings	Left kidney extensively scarred and contracted with normal areas of tissue between scars. Right kidney normal with clamp on renal artery						Left kidney almost complete hemorrhage throughout, size of right kidney. Right with clamp on renal artery			

TABLE II

Trypsin Damage to Other Kidney on Renal Function and Blood Pressure

Urinary findings*			T-60						T-64						
			Blood pressure	NPN	Concentration test	Urinary findings			Blood pressure	NPN	Concentration test	Urinary findings			
WBC	RBC	Casts	mm. Hg	mg. per cent	sp. gr.	Albumin	RBC	Casts	mm. Hg	mg. per cent	sp. gr.	Albumin	RBC	Casts	
0	0	0	175/85	44	1.055	0	0	0	150/80	34	1.050	0	0	0	
2+	3+	3+	205/125	64	Operation			165/95	44	Operation					
			220/125	118	1.015	3+	3+	3+	175/100	45		2+	0	3+	
			220/125	106					185/105						
									175/95	43					
									175/105		1.045	2+	0	3+	
									175/95						
									200/125	40					
									165/100						
			Hemorrhage						Distemper						
y necrotic with and twice the kidney normal			Left kidney swollen to twice the size of right with large areas of hemorrhage and necrosis. Right kidney was normal with clamp on renal artery						Left kidney edematous with large areas of granulation tissue and old hemorrhage. Right kidney normal in appearance with clamp on renal artery						

two (T-62 and T-64) with distemper, this was not marked. In the other two, it was more intense. All the dogs showed evidence of renal structural damage in the trypsin-injected kidney at autopsy, and three showed signs of renal excretory insufficiency during life.

One of these dogs (T-59) was followed for 16 days and it was found that as the hypertension developed the blood non-protein nitrogen returned to its normal value. On the 16th day the ischemic kidney was removed, leaving behind only the trypsin-damaged kidney. This resulted in a fall in blood pressure to the control level, and at the same time, a rise in blood non-protein nitrogen indicating a progressive renal excretory insufficiency which led to the death of the animal in uremia. This experience again indicates the sharp differentiation between renal excretory insufficiency and hypertension and the absence of any direct relationship between the two. It shows that the ischemic kidney was responsible for the hypertension, although this might have been facilitated by the presence of renal excretory insufficiency in the other kidney. It also shows that the ischemic kidney retained sufficient excretory function to minimize the effect of the damage done by the trypsin in the other kidney.

DISCUSSION

Our experiments indicate that hypertension is not due to chronic renal excretory insufficiency even when this is of marked degree. The lack of hypertension in chronic renal excretory insufficiency cannot be attributed to the inability of these animals to develop hypertension as suggested by Pässler and Heineke (19) and Chanutin and Ferris (20) who pointed out that cachexia in itself can mask the action of the hypertensive mechanism. The fact that four of our dogs with chronic renal excretory insufficiency developed a definite hypertension following the application of a Goldblatt clamp to the renal artery of one of the trypsin-damaged kidneys, indicates that the dogs were not too weak to develop hypertension, had the mechanism for its production been present.

In evaluating the blood pressure changes in renal excretory insufficiency it is important that the method and manner of determining the

blood pressure be accurate and relatively constant. The employment of various indirect methods, the use of anesthesia during a blood pressure determination and reliance on single determinations of blood pressure even in a large number of animals, as have been done in many previous experiments, introduce the possibility of widely divergent results. It is not impossible that the real cause of the confusion regarding the interrelation of renal excretory insufficiency and hypertension is on this basis. Our use of the Hamilton apparatus allowing direct measurements of the systolic and diastolic pressures in unanesthetized, trained dogs and the determination of the pressure daily for long periods of time, appear to us to reduce the possible error in blood pressure measurements to a negligible factor.

In most previous studies in which renal excretory insufficiency was produced, the possibility was not excluded that renal ischemia, which is known to cause hypertension, coexisted. Thus, several workers (23, 24, 26) reported vascular and glomerular damage in the kidneys having renal excretory insufficiency. Jarrett *et al.* (34) found that vascular damage was present after partial nephrectomy severe enough to produce renal excretory insufficiency, and Wood and Ethridge (21) found such vascular damage 6 months after partial nephrectomy, at the time that an elevated blood pressure occurred. In most of the procedures hitherto employed it has not been possible to limit the damage only to the elimination of excretory units in the kidneys, without the possibility of interfering simultaneously with the blood supply to the remaining kidney substance. Our previous work (29) has shown that the development of hypertension by ischemia is dependent upon the ratio of ischemic to normal kidney substance present rather than on the amount of ischemic kidney alone. It therefore follows that less ischemic kidney is needed to produce hypertension as the number of normal kidney excretory units is decreased. Slight degrees of renal ischemia without effect when the kidneys are normal prior to its induction, may on this account readily lead to hypertension when the number of normal excretory units of the kidney are reduced.

Our results are clear, we believe, in showing that renal excretory

insufficiency develops when the total number of effective excretory units in the kidneys are reduced beyond a minimal critical value. There is no need to have a continued insult or repeated insults to lead to this stage; a single insult applied only once is sufficient, if it causes extensive enough damage. Apparently a minimum number of effective excretory units is essential to avoid renal excretory insufficiency. This concept explains the lack of correlation between the presence of active parenchymal damage and renal excretory insufficiency. Immediately following the injection of trypsin into both kidneys, there occurs acute damage to the kidney parenchyma, acute renal excretory insufficiency and hypertension. At this stage, it would have been impossible to relate the hypertension to either the damaged parenchyma or the altered excretory function of the kidney. However, with the complete invasion of the localized necrotic areas of the kidney by scar tissue, leaving normal kidney tissue between the scar areas, it was seen that no subacute or chronically active process involving the kidney parenchyma was present. Coincident with this change in renal histological appearance, the blood pressure fell to normal and remained so although the renal excretory insufficiency continued. Thus it was discerned that renal excretory insufficiency persisted in the absence of any active continuing damage to the kidney.

The absence of hypertension in chronic renal excretory insufficiency indicates that the latter is not the mechanism responsible for renal hypertension, although it doubtless contributes to the ease of its production. Renal hypertension occurred in these experiments only when there was renal ischemia or active damage to the renal parenchyma. While the relation of hypertension to renal ischemia—clearly shown by the experiments with renal clamping and later removal of the ischemic kidney—accords with previous work on the subject, the relation of hypertension to active damage of renal parenchyma has not hitherto been demonstrated as far as we know. How the hypertension is produced during the period of renal damage immediately following trypsin injection is not established. Three possibilities exist: (a) the damage to the kidney may lead to a sustained pressor

reflex originating in the afferent nerves of the kidney; (b) the damage to the kidney by trypsin may liberate a substance which acts as a humoral mediator for the hypertension; (c) the swelling of the parenchyma of the kidney, resulting from the damage and operating within the restraint of the kidney capsule, may cause a compression of its blood supply with a consequent ischemia. Thus acute swelling of the kidney in the acute stage of trypsin damage would cause renal hypertension by ischemia of its substance in the same way as that produced by a renal arterial clamp.

SUMMARY

1. The injection of trypsin into both renal arteries of the dog was found to cause an acute necrosis of large sections of the kidney, an immediate excretory insufficiency, and a transient hypertension.

2. Dogs surviving the acute phase of the trypsin injection, developed a chronic renal excretory insufficiency with no hypertension, despite the severity and duration of the renal excretory insufficiency.

3. The application of a Goldblatt clamp to the renal artery of one of the two kidneys, previously injected with trypsin, led to a rise in blood pressure which returned at once to normal when the ischemic kidney was removed, even though the pre-existing renal excretory insufficiency was augmented. This experience demonstrated unequivocally that chronic renal excretory insufficiency and hypertension are not directly related.

4. The application of a Goldblatt clamp to the renal artery of one kidney and the simultaneous injection of trypsin into the other led to a hypertension. The later removal of the ischemic kidney led to a severe renal excretory insufficiency, at the same time the pre-existing hypertension disappeared. This indicated again that renal excretory insufficiency and renal ischemia produced different phenomena and that the former had no direct relation to hypertension.

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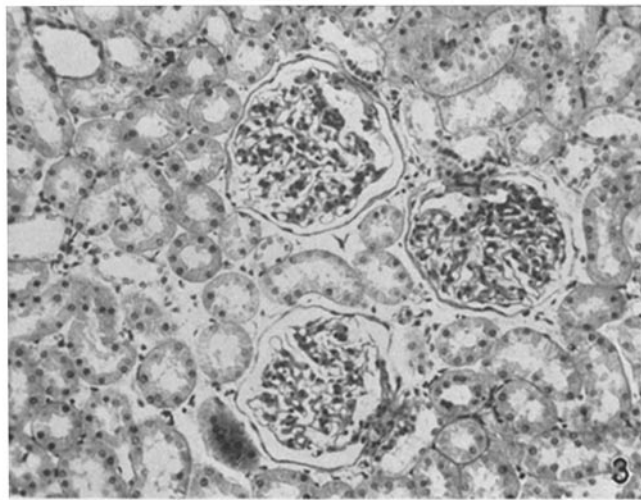
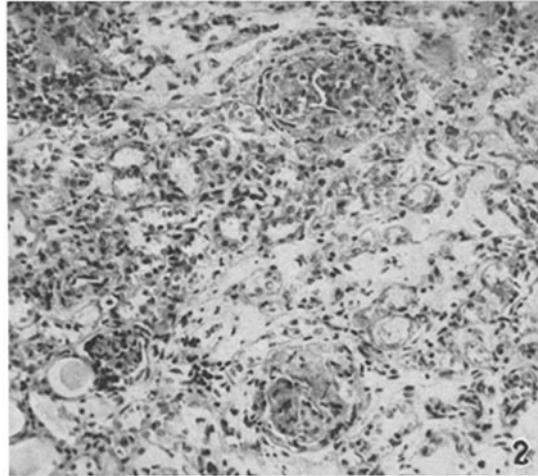
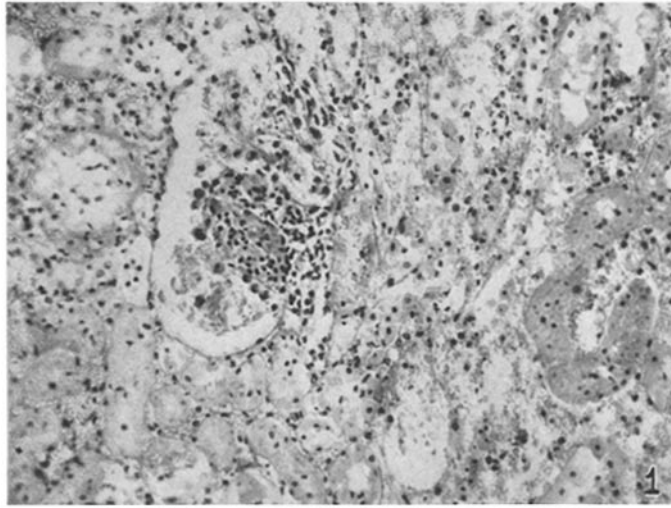
EXPLANATION OF PLATE 16

The sections were stained with hematoxylin and eosin.

FIG. 1. Acute effect of trypsin injection into the kidney. Section taken in B-1, 24 hours after the injection of trypsin. Widespread hemorrhage can be seen in the glomerular capsules, in the interstitial tissue and in the lumina of the tubules. Autolysis and desquamation of the tubuli and interstitial infiltration of polymorphonuclear leucocytes are clearly demonstrable. A glomerulus is shown, in which there is compression with infiltration of polymorphonuclear leucocytes and free red blood cells. $\times 140$.

FIG. 2. Chronic change following trypsin injection into the kidney. Section taken in K-1, 4 weeks after the injection of trypsin. This section is from an area scarred in the gross. The complete obliteration of two glomeruli by scar replacement is shown. The increase in connective tissue, the infrequency of tubuli and the presence of round cell infiltration are clearly demonstrable. $\times 140$.

FIG. 3. Chronic change following trypsin injection into the kidney. Section taken in K-1, 4 weeks after trypsin injection. This section is from a portion of the kidney appearing normal in the gross. The normal appearance of glomeruli and tubules is evident. The dark staining tubule is a photographic defect. $\times 160$.



(Friedman and Katz: Trypsin injection into renal arteries)