

# THE RENAL FACTOR IN ARTERIAL HYPERTENSION WITH COARCTATION OF THE AORTA<sup>1</sup>

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Consideration of the hydrodynamics in coarctation of the aorta indicates that the arterial hypertension which is a feature of that disease is not to be explained upon the grounds of mechanical obstruction to blood flow *per se*. Such consideration has led to experiments which show that this variety of hypertension is owing to interference with renal blood supply.

*Pathological physiology of coarctation of the aorta.* In this condition, arterial pressure is practically always high in the arms, while it is usually low or normal (occasionally even high) in the legs (1). The hypertension in the upper part of the body is often attributed to the mechanical obstruction of the stenotic aortic isthmus to blood flow, but as Lewis (2) pointed out, the total cross section area of the collateral bed is at least equal to that of the normal aorta. However, the collateral vessels are long and tortuous and may easily account for the reduced pressure in the lower body as compared with the upper. Although the resistance of the collateral bed explains the difference between arm and leg pressure, it is not an explanation of the absolute pressure levels; were mechanical obstruction the only factor, one would always expect to find low pressure in the legs and less increase of pressure in the arms than actually occurs.

If the increased arterial pressure in the arms were a result of redistribution of blood such as occurred in the experiments of Barcroft and Samaan (3), then the cardiac output and flow of blood through the upper part of the body should be increased; this, however, has not been found (2, 4, 5, 6, 7). Failure to demonstrate abnormally high rates of flow can mean only that peripheral resistance is increased in all the small vessels of the upper part of the body; the increased resistance in this region requires just as much explanation as does the generalized in-

creased resistance in any other variety of hypertension.

The presence of an increased resistance in the upper part of the body in coarctation of the aorta may perhaps be made clearer by a mathematical demonstration, using the well-known formula

$$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$$

With pressure in mm. Hg and flow in liters per minute, resistance may be expressed in arbitrary units with less confusion than when dynes are introduced (8).

When the regional fractionation of the cardiac output of a normal man weighing 70 kgm. and with a blood pressure of 125/80 mm. Hg is calculated from the data of Levy and Blalock (9) for the dog, and with mean pressure equal to diastolic pressure plus 43 per cent of pulse pressure (10), the representative results noted in Table I are obtained.

TABLE I  
*Calculated (approximate) regional blood flow and resistance for normal man*

Region	Blood flow	Resistance in arbitrary units
	<i>liters per minute</i>	$\left( \frac{100 \text{ mm. Hg}}{\text{liters per minute}} \right)$
Upper trunk, arms, head, neck, and heart . . . . .	2.00	50 (A)
Kidneys . . . . .	1.00	100 (B)
Liver and portal bed . . . . .	1.50	67 (C)
Lower trunk and legs . . . . .	0.65	154 (D)
Entire body (excluding lungs)	5.15	19 (E)*

\* The resistance for the entire body (E) may also be calculated from A, B, C, and D by the formula  $\frac{1}{E} = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$ , for calculating the total resistance offered by several resistances in parallel.

If now we consider a patient with coarctation of the aorta whose cardiac output is normal (6, 7), whose regional blood flow is normal or very nearly so (2, 4, 5, 11), and whose blood pressure is 195/100 mm. Hg in the arms and 80/60 mm.

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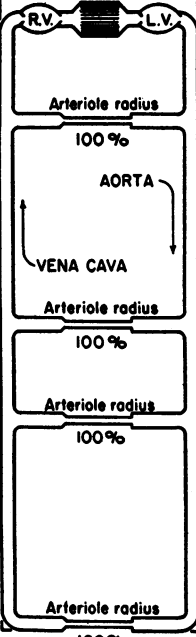
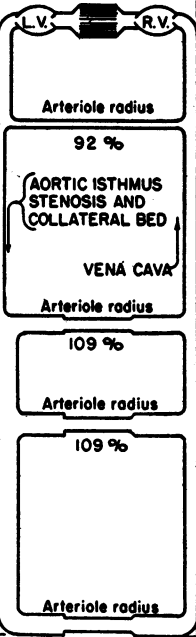
NORMAL	Resistance Arbitrary Units	Pressure Gradient (mm. Hg)	Blood Flow (Liters/minute)	REGION	Blood Flow (Liters/minute)	Pressure Gradient (mm. Hg)	Resistance Arbitrary Units	COARCTATION OF THE AORTA
	50	100	2.0	Lungs	2.0	140	70	
Arteriole radius 100%				Upper trunk, arms, heart, head and neck.				
AORTA	100	100	1.0	Great Vessels	3.15	70	22	(AORTIC ISTHMUS STENOSIS AND COLLATERAL BED)
VENA CAVA				Kidneys				VENA CAVA
Arteriole radius 100%	67	100	1.5	Liver and Portal	1.5	70	47	Arteriole radius 109%
Arteriole radius 100%				Lower trunk and legs				Arteriole radius 109%
Arteriole radius 100%	154	100	0.65		0.65	70	108	Arteriole radius 109%

FIG. 1. REGIONAL RESISTANCE, BLOOD FLOW, ARTERIAL PRESSURE AND RELATIVE ARTERIOLAR RADIUS IN A NORMAL SUBJECT (BLOOD PRESSURE 125/80 MM. HG) AND IN A SUBJECT WITH COARCTATION OF THE AORTA (BLOOD PRESSURE, ARMS 195/100, LEGS 80/60' MM. HG)

Note. The combined caliber of aortic isthmus stenosis and collateral bed approximates that of the normal aorta. Its width is narrow in the diagram to indicate the resistance due to length and tortuosity.

Hg in the legs, we may make the following calculations. Since the mean pressure in the lower aorta is approximately 70 mm. Hg and that above the stenosis of the isthmus is 140 mm. Hg, the resistance of the stenosis and collateral bed is represented by the pressure gradient (140—70 = 70 mm. Hg) divided by the blood flow which they carry (abdominal viscera, lower trunk, and legs, or, 3.15 liters per minute), or 22 arbitrary units. As the tissues just mentioned are perfused with a normal volume flow per minute (2, 11) at a reduced pressure head, the resistance in this region must be decreased by 30 per cent. If the resistance had not decreased and the pressure had fallen from 125/80 to 80/60 mm. Hg, then the flow would have been 30 per cent less than the observed level. But in the upper trunk, arms, head, neck, and heart, 2.0 liters per minute still circulate under a pressure head of 140 mm. Hg, so that here the resistance must have increased

from 50 to 70 arbitrary units or by 40 per cent. Figure 1 shows these changes, the fundamental significance of which is not altered by the probable inaccuracies in the calculated absolute values of the regional flows.

Since the resistance varies inversely with the fourth power of (arteriolar) radius, a decrease in radius of 10 per cent increases the resistance 50 per cent, and a decrease in radius of 15 per cent doubles the resistance. In coarctation of the aorta the resistance of the upper part of the body usually varies between 150 and 200 per cent of that in the lower part, so the radius of an arteriole from the arm would be only 15 per cent smaller than that of one from the leg. Bearing in mind the difficulties inherent in measuring fixed arterioles, one could have predicted that no significant difference in caliber of such vessels from arm and leg would be observed, a theoretical conclusion compatible with actual measurement (12). In

this particular series, the calculated expected difference was only 10 per cent.

It seemed that the cause of the increased resistance and pressure in the upper body in coarctation of the aorta might be the same as that of the generalized changes in the Goldblatt dog (13), for in each case renal tissue is distal to a partially occluded artery. It has been shown that the kidney is apparently unique in the pathogenesis of hypertension when an organ's artery is partially occluded (13). Bell's suggestion that the hypertension in coarctation of the aorta is fundamentally similar to that in the dog with a partially occluded renal artery was rejected by Goldblatt (14);<sup>2</sup> the problem has now been studied experimentally.

Hypertension as evidenced by left ventricular cardiac hypertrophy was produced in 11 rats by partial occlusion of the aorta between the right (proximal) and left (distal) renal arteries. With similar occlusion hypertension did not occur in 25 other rats when the left kidney was removed simultaneously. In other words, *partial occlusion of the aorta at the same site in two groups of rats produced hypertension only in that group with renal tissue distal to the occlusion*, even though the blood flow was hindered by the same mechanical obstruction owing to stenosis and a collateral bed in both groups. Hypertension was also produced in 12 rats by partial occlusion of the aorta just above both kidneys, a site more nearly analogous to that of the obstruction in coarctation of the aorta.

#### METHODS

The results in this paper were obtained from over 175 experiments on albino rats, each sacrificed 20 days after operation. The general conditions and methods used in this laboratory have been reported previously; the diet contained 10 per cent casein and 19 per cent total protein (15).

*Operative technique.* The operative technique is a modification of Collins' method (16). No attempt at asepsis is made. The rat is anesthetized with ether and a long midline abdominal incision made. If the left renal artery is to be tied, it is dissected free, usually be-

tween the kidney and the suprarenal vein; occasionally it is best freed between the latter and the aorta. A wire 0.4 mm. in diameter is placed parallel to the exposed artery, and a silk thread passed beneath both wire and artery. The thread is then tied, the ligature of course including wire and artery. The wire may then be gently withdrawn, the ligature remaining; the abdominal incision is closed in the usual manner. If the aorta is to be tied, it may be freed at the desired site (between the renal arteries or just above them) and tied together with a wire 0.9 mm. in diameter. Occasionally the thoracic duct is ruptured, but heals spontaneously. The sizes of the wires given above are satisfactory for rats of about 100 to 200 grams, but practice is necessary to learn the appropriate force with which to tie the ligature. In a successful experiment, the kidney blanches on tying, then undergoes reactive hyperemia immediately on removal of the wire.

*Organ weights.* In rats sacrificed 20 days after operation, the heart and kidneys were weighed on torsion balances and compared with the predicted weights of those organs in normal rats of the same weight and sex. The predictions were based on the following formulae derived by Dr. T. Addis from data collected in this laboratory on over 1500 rats:

$$\begin{aligned} \text{Male heart:} & \quad \text{HW} = 12.6\text{BW}^{0.75} + 8. \\ \text{Female heart:} & \quad \text{HW} = 12.56\text{BW}^{0.75} + 1.5. \\ \text{Male kidney (single):} & \quad \text{KW} = 15.0\text{BW}^{0.717} + 10.3. \\ \text{Female kidney (single):} & \quad \text{KW} = 20.18\text{BW}^{0.648} + 6.1. \end{aligned}$$

In these formulae, more accurate than the similar formulae based upon surface area ( $\text{kBW}^{0.67}$ ), organ weights are in milligrams, body weights in grams. Statistical studies show that the normal variability of heart weight is so small that its coefficient of variation at a given range of body weight of 10 grams is only 3.7 per cent. This means that an observed deviation (from the weight predicted by the equations) of  $\pm 10$  per cent occurs only once in 143 normal rats; a deviation of  $\pm 15$  per cent occurs once in every 15,770 rats; any individual deviation of  $\pm 12$  per cent or more is "almost certainly" significant. Kidney weight is normally more variable, its coefficient of variation being 9.8 per cent. Therefore, an observed deviation in kidney weight of  $\pm 10$  per cent occurs as often as once in every 3 rats,  $\pm 15$  per cent once in 8,  $\pm 25$  per cent once in every 143; in order to be statistically significant, a single observed kidney weight must deviate  $\pm 28$  per cent from the prediction. Averages of groups of hearts or kidneys are much less variable. The rats in the present experiment were under exactly the same conditions as were those from which the data were obtained for the formulae (same diet, constant temperature, etc.), and the formulae are believed to apply only under constant conditions.

The degree of cardiac hypertrophy was used as an index of the effect of the procedures on the arterial pressure. In the absence of anemia or metabolic disease, and when an increased *L/R* ratio is present, the increase in heart weight seems to be a better criterion of the average daily level of arterial pressure than readings obtained

<sup>2</sup>Goldblatt and Kahn (J. A. M. A., 1938, 110, 49, footnote 1 (h), and personal communication) find in the dog that partial occlusion of the aorta below both renal arteries is not followed by hypertension; similar occlusion immediately above both renal arteries produces hypertension.

under anesthesia by methods which are, in our hands, not satisfactory. Anemia was excluded by the fact that hematocrit values in a group of hypertensive rats averaged 93 per cent of those of controls. The hearts from 23 nonhypertensive and 14 unselected hypertensive rats were fixed, and the right and left ventricles separated and weighed. The *L/R* ratio, corrected as previously described (15), was 21 per cent greater in the hypertensive group, a difference five times its probable error and therefore statistically significant.

In order to translate the observed cardiac hypertrophy into blood pressure levels, it may be noted that Chanutin and Barksdale (17) have shown that in the rat a hypertrophy of 25 per cent occurs with a chronic hypertension of 160 to 170 mm. Hg, 50 per cent with 180 mm. Hg or over. Since the present experiments were of shorter duration, the existing pressure levels were probably higher at any given degree of cardiac hypertrophy.

#### RESULTS

Detailed protocols are given in the Tables; a summary is presented in Figure 2. The experiments are best discussed in six divisions.







EXPERIMENT	ORGAN WEIGHTS,					
	% DEVIATION FROM NORMAL					
	RIGHT	LEFT	HEART	KIDNEY	NUMBER	
			RIGHT	LEFT	OF RATS	
A			+2%	+38%	-100%	14
			±0%	+39%	-75%	3
B			-2%	+34%	-100%	25
			±0%	+28%	-76%	1
C			+28%	+39%	-65%	9
D			+26%	+37%	-49%	7
E			+29%	-100%	+16%	4
F			+20%	-1%	-4%	12

FIG. 2. SUMMARY OF RESULTS OBTAINED IN RATS SACRIFICED 20 DAYS AFTER THE OPERATIVE PROCEDURE INDICATED BY THE DIAGRAMS

*A. Partial occlusion of the left renal artery, with left nephrectomy.* This combined procedure was of course a control. These 14 rats were not expected to have hypertension and in fact did not. The average heart weight was +2 per cent of

that predicted, while the right kidney presented the usual degree of compensatory hypertrophy (+38 per cent). In addition, three more rats (operated upon as in Experiment C) are included because in them the ligature was too tight; as a result the left kidney became necrotic (auto-nephrectomy).

*B. Partial occlusion of the aorta between the renal arteries, with left (distal) nephrectomy.* If the hypertension of coarctation of the aorta is to be explicable upon the basis of mechanical obstruction, these rats should have hypertension. On the contrary, the average heart weight of 25 rats was 2 per cent less than predicted, and not a single rat had cardiac hypertrophy. A possible objection is that the ligatures may have been too loose; the answers are (a) that these rats were operated upon alternately with those of Experiment D, in which hypertension occurred in one-third of the rats, and (b) in 6 rats of this series the aorta became *completely* obstructed (pulsations entirely absent) by intimal proliferation (Figure 3 shows the collateral circulation in such a rat). To these 25 rats may be added 1 from Experiment D in which the left kidney was completely necrotic.

*C. Partial occlusion of the left renal artery.* This series was designed to demonstrate that a modification of the Goldblatt technique would produce hypertension in the rat. That it does in fact do so is shown by the cardiac hypertrophy in 9 animals, as much as +54 per cent and averaging +28 per cent. In these animals the left kidney atrophied (-65 per cent) with little or no necrosis.

*D. Partial occlusion of the aorta between the renal arteries.* In this experiment 7 rats had hypertension as evidenced by cardiac hypertrophy averaging +26 per cent (as high as +37 per cent), and in these the left (distal) kidney atrophied (-49 per cent) just as in Experiment C.

This is a series of rats operated upon alternately with those of Experiment B and at *exactly the same site*; hypertension occurred *only when there was renal tissue distal to the obstruction*, and only when this tissue was atrophic but not necrotic.

*E. Partial occlusion of the aorta between the renal arteries, with right (proximal) nephrectomy.* So far in these studies hypertension has been uni-



FIG. 3. ROENTGENOGRAM AFTER INTRACARDIAC INJECTION OF OPAQUE MATERIAL SHOWING THE COLLATERAL CIRCULATION IN A NONHYPERTENSIVE RAT (LEFT NEPHRECTOMY, COMPLETE OCCLUSION OF AORTA DISTAL TO RIGHT KIDNEY)

formly associated with unilateral renal atrophy. In this series there were 4 rats with cardiac hypertrophy up to + 55 per cent (average + 29 per cent), and in these there was actually hypertrophy (+ 16 per cent) of the remaining kidney distal to the partial occlusion. In 3 of these the aorta was completely occluded.

*F. Partial occlusion of the aorta above both kidneys.* In this series the situation is unlike the previous ones or the Goldblatt dog but is similar to that existing spontaneously in coarctation of the aorta. Here, as in coarctation, the aorta is partially occluded above both kidneys and there is (as in Experiments B, D, and E) a collateral circulation supplying tissues distal to the obstruction. In 12 rats in this series the cardiac hypertrophy averaged + 20 per cent (as high as + 38 per cent) and the kidneys were entirely normal (within 4 per cent of the prediction). The aortic obstruction was complete in 1 rat and very nearly so in another.

In Experiment C there were 6 rats and in D 16 rats in which neither cardiac hypertrophy nor left renal atrophy occurred; presumably, the ligatures in these instances were too loose to alter hydrodynamics appreciably. Likewise, there were 23 rats in Experiment E and 7 in F without cardiac hypertrophy; the same explanation probably holds. Such animals are therefore omitted from consideration since there is no evidence, direct or indirect, of aortic or renal artery stenosis. Since they serve as controls, their pertinent data are included in Tables IV to VII, but averaged separately. In another 51 rats in which the ligature was too tight, necrosis of tissues beyond it occurred in a few days; when this occurred with the tie on the left renal artery the kidney became necrotic, with the aorta tied the animal died.

The concentration of urea in the blood is normal in coarctation. In the rats of Experiment F it varied from 30.6 to 38.9 mgm. per cent, well within normal limits. In those experiments in which unilateral nephrectomy was done, the blood

TABLE II

Experiment A. Partial occlusion of the left renal artery with left nephrectomy

Sex	Body weight	Weight of heart			Weight of kidneys					
		Predicted	Observed	Deviation of observed from predicted	Predicted	Right kidney		Left kidney		
						Observed	Deviation of observed from predicted	Observed	Deviation of observed from predicted	
	grams	mgm.	mgm.	per cent	mgm.	mgm.	per cent	mgm.	per cent	
F	230	743	823	+11	691	990	+43			
F	176	608	662	+ 9	581	816	+40			
F	212	699	744	+ 6	655	977	+49			
F	166	582	604	+ 4	560	730	+30			
F	186	634	645	+ 2	602	834	+38			
F	174	603	616	+ 2	577	780	+35			
F	186	634	644	+ 1	602	757	+26			
F	194	654	662	+ 1	619	840	+36			
F	176	608	610	± 0	581	870	+50			
F	174	603	600	± 0	577	912	+58			
F	194	654	650	- 1	619	848	+37			
F	212	699	696	- 1	655	873	+33			
F	182	624	612	- 2	594	730	+23			
F	152	544	512	- 6	530	706	+33			
		Average, 14 rats			+ 2			+38		
(Necrotic)										
F	160	565	588	+ 4	547	778	+42	150	-73	
F	190	644	664	+ 3	611	850	+39	134	-78	
F	208	689	633	- 8	647	880	+36	164	-75	
		Average, 3 rats			± 0			+39	-75	

TABLE III

Experiment B. Partial occlusion of the aorta between the renal arteries, with left (distal) nephrectomy

Sex	Body weight	Weight of heart			Weight of kidneys				
		Pre-dicted	Ob-served	Devia-tion of observed from pre-dicted	Pre-dicted	Right kidney		Left kidney	
						Ob-served	Devia-tion of observed from pre-dicted	Ob-served	Devia-tion of observed from pre-dicted
grams	mgm.	mgm.	per cent	mgm.	mgm.	per cent	mgm.	per cent	
M	166	590	628	+ 6	596	744	+25		
M	170	600	630	+ 5	606	954	+57		
F	143*	521	545	+ 5	509	732	+44		
F	146	529	552	+ 4	516	672	+30		
M	164	585	608	+ 4	591	834	+41		
M	180	626	646	+ 3	631	842	+33		
M	153	556	572	+ 3	563	786	+40		
M	184	637	645	+ 1	641	908	+41		
M	164*	585	582	± 0	591	872	+48		
M	138	515	517	± 0	523	694	+33		
M	184	637	636	± 0	641	980	+53		
M	184	637	634	± 0	641	870	+36		
M	164	585	580	- 1	591	848	+43		
M	140	521	514	- 1	528	660	+25		
M	170*	600	587	- 2	606	846	+40		
M	188	648	632	- 2	651	894	+37		
F	108	422	412	- 2	425	537	+26		
M	290*	894	860	- 4	885	1020	+15		
F	138	507	486	- 4	498	592	+19		
M	210*	704	672	- 5	704	952	+35		
F	152	544	510	- 8	530	764	+44		
F	122	462	422	- 9	459	580	+26		
M	154	558	506	- 9	565	680	+20		
F	122	462	414	-10	459	522	+14		
M	122*	470	415	-12	480	604	+26		
Average, 25 rats				- 2					+34
					(Necrotic)				
M	174	610	612	± 0	616	786	+28	150	-76

\* Represents complete occlusion of aorta.

urea concentrations of the hypertensive rats were 40.3 to 50.0 mgm. per cent, the usual values for nonhypertensive rats 20 days after unilateral nephrectomy.

Proteinuria is not ordinarily present in coarctation of the aorta. Nor was it found in these hypertensive rats (average 1.3 mgm. per day (females), as compared to the controls of 1.1 mgm. per day).

DISCUSSION

Partial occlusion of either the aorta or one renal artery in rats is followed by cardiac hypertrophy only when there is living renal tissue beyond the occlusion: the left ventricle undergoes hypertrophy relative to the right, and other causes of cardiac hypertrophy are absent; under

these conditions we feel justified in stating that such rats are hypertensive. Proteinuria does not occur and renal function is normal as judged by blood urea concentration, just as in coarctation of the aorta. The nutritional state of the animals is not impaired. On the other hand, when renal tissue is absent distal to the occlusion, hypertension does not occur even though blood must flow in the presence of the same degree of mechanical obstruction.

Just as the pressure head beyond the stenosis of the aortic isthmus is lower than that proximal to the stenosis, so Blalock and Levy (18) have shown that the pressure beyond a partial occlusion of the renal artery is lower (by 50 per cent) than the general arterial pressure. It is not known whether the important hypertensive factor in interference with the renal blood supply is local hypotension, reduced pulse pressure, or reduced blood flow.

The kidney beyond a partially occluded renal artery has often been spoken of as "ischemic." On the other hand, its function is said to be normal. If Van Slyke *et al.* (19) are correct in correlating renal function with blood flow, one or

TABLE IV

Experiment C. Partial occlusion of the left renal artery

Sex	Body weight	Weight of heart			Weight of kidneys				
		Pre-dicted	Ob-served	Devia-tion of observed from pre-dicted	Pre-dicted	Left kidney		Right kidney	
						Ob-served	Devia-tion of observed from pre-dicted	Ob-served	Devia-tion of observed from pre-dicted
grams	mgm.	mgm.	per cent	mgm.	mgm.	per cent	mgm.	per cent	
F	180	619	955	+54	590	135	-77	791	+34
F	154	549	756	+38	534	180	-67	952	+78
F	194	654	902	+38	619	426	-31	740	+20
F	122	462	591	+28	459	126	-73	650	+42
F	172	598	767	+27	573	174	-70	856	+50
F	174	603	730	+21	577	182	-69	770	+33
F	184	629	740	+18	598	184	-69	835	+40
F	254	801	940	+17	736	338	-54	1000	+36
F	196	659	742	+13	623	162	-74	720	+16
Average, 9 rats				+28			-65	+39	
F	228	739	795	+ 8	687	667	- 3	710	+ 3
F	214	704	760	+ 8	659	650	- 1	754	+14
F	190	644	680	+ 6	611	468	-23	675	+10
F	162	571	588	+ 3	551	514	- 7	668	+21
F	154	549	560	+ 2	534	560	+ 5	594	+11
F	170	593	584	- 2	569	570	± 0	596	+ 5
Average, 6 rats				+ 4			- 6	+11	

TABLE V

Experiment D. Partial occlusion of the aorta between the renal arteries

Sex	Weight of heart				Weight of kidneys				
	Body weight	Pre-dicted	Ob-served	Devia-tion of observed from pre-dicted	Pre-dicted	Left kidney		Right kidney	
						Ob-served	Devia-tion of observed from pre-dicted	Ob-served	Devia-tion of observed from pre-dicted
	grams	mgm.	mgm.	per cent	mgm.	mgm.	per cent	mgm.	per cent
M	150	548	748	+37	555	296	-47	774	+40
M	132	499	655	+31	507	128	-65	834	+65
M	122	470	606	+29	480	252	-48	608	+27
M	122	470	606	+29	480	396	-17	576	+20
M	132	499	640	+28	507	240	-53	698	+38
M	320*	962	1130	+17	948	514	-46	1240	+31
F	204	679	762	+12	639	196	-69	886	+39
Average, 7 rats				+26			-49		+37
M	206	694	754	+ 9	694	652	- 6	696	± 0
M	194	663	725	+ 9	666	665	± 0	692	+ 4
M	202	684	738	+ 8	685	666	- 3	744	+ 8
M	180	626	673	+ 7	631	598	- 5	622	- 1
M	172	605	638	+ 7	611	682	+12	700	+15
M	170	600	634	+ 6	606	580	- 4	572	- 6
M	160	574	590	+ 3	580	500	-14	544	- 6
M	192	658	680	+ 3	661	634	- 4	680	+ 3
M	128	487	500	+ 2	496	437	-12	484	- 2
M	176	616	630	+ 2	621	602	- 3	615	- 1
M	180	626	641	+ 2	631	624	- 1	672	+ 7
M	160	574	570	± 0	580	548	- 6	574	- 1
M	314	949	950	± 0	935	890	- 5	970	+ 4
M	292	899	880	- 2	889	772	-13	768	-14
M	320	962	940	- 2	948	864	- 9	890	- 6
M	305	928	876	- 6	916	872	- 5	825	-10
Average, 16 rats				+ 3			- 4		± 0

\* Represents complete occlusion of aorta.

the other of the above statements is incorrect. Actually, neither renal blood flow nor renal function by rigid tests has ever been studied adequately under these conditions; Mason, Evers, and Blalock (20) have failed to demonstrate ischemia, using A-V oxygen differences. In dogs with ureteral obstruction, renal blood flow is uniformly reduced but hypertension does not always occur (21), while in still another variety of hypertension (after subtotal nephrectomy) rats have normal renal blood flows (22). It seems probable that in the Goldblatt dog, renal flow is near the lower limit of normal as long as hypertension is present.

Perhaps only the kidney, of all the tissues, has the power to raise general blood pressure when its blood supply suffers interference. Hartmann, Ørskov, and Rein (23) showed that, in spite of

pressor reflexes and adrenalin, renal blood flow remains constant although flow through the leg undergoes simultaneous wide fluctuations; they suggest that the kidneys may regulate the circulation in the same sense as does the carotid sinus. It is not clear whether this supposed regulatory action is explicable wholly on some metabolic process specific to renal tissue, or whether the peculiarities of the arrangement (24) of the renal blood vessel are also involved. The present experiments on rats do not show whether partial occlusion of the aorta proximal to the celiac axis can cause hypertension of greater degree than distal occlusion, nor has it been proved that hypertension does not follow narrowing of the splanchnic arteries.

Hypertension may be produced by partial occlusion of the blood supply of a completely dener-

TABLE VI

Experiment E. Partial occlusion of the aorta between the renal arteries, with right (proximal) nephrectomy

Sex	Body weight	Weight of heart			Weight of left kidney		
		Pre-dicted	Ob-served	Devia-tion of observed from pre-dicted	Pre-dicted	Ob-served	Devia-tion of observed from pre-dicted
F	117*	448	695	+55	447	552	+23
M	178	621	764	+23	626	738	+18
M	114*	447	534	+20	458	494	+ 8
F	119*	454	537	+18	452	526	+16
Average, 4 rats				+29			+16
F	140	512	561	+10	502	615	+22
M	166	590	642	+ 9	596	759	+27
F	112	434	463	+ 8	435	546	+25
M	116	453	482	+ 6	463	614	+33
M	200	679	714	+ 5	680	813	+20
F	126	474	500	+ 5	469	556	+18
F	144	523	546	+ 4	511	612	+20
M	136	510	530	+ 4	518	702	+36
M	168	595	618	+ 4	601	702	+17
M	177	618	640	+ 3	623	882	+42
M	198	673	688	+ 2	675	908	+35
M	150	548	554	+ 1	555	770	+39
M	143	529	532	+ 1	536	690	+29
M	168	595	596	± 0	601	746	+24
M	202	684	682	± 0	685	850	+24
M	190	653	644	- 1	656	824	+26
M	158	569	558	- 2	575	763	+33
M	93	385	378	- 2	397	433	+ 9
M	190	653	634	- 3	656	815	+24
M	196	668	643	- 4	670	763	+14
M	102	412	395	- 4	423	494	+17
M	134	504	478	- 5	513	674	+31
M	136	510	482	- 5	518	694	+34
Average, 23 rats				+ 2			+26

\* Represents complete occlusion of aorta.

TABLE VII  
Experiment F. Partial occlusion of the aorta above  
both kidneys

Sex	Body weight	Weight of heart			Weight of kidneys				
		Predicted	Observed	Deviation of observed from predicted	Predicted	Left kidney		Right kidney	
						Observed	Deviation of observed from predicted	Observed	Deviation of observed from predicted
	grams	mgm.	mgm.	per cent	mgm.	mgm.	per cent	mgm.	per cent
M	130	493	680	+38	502	502	± 0	480	- 4
M	142	526	676	+28	534	568	+ 6	667	+25
M	112	442	546	+23	452	412	- 9	435	- 4
M	172	606	736	+21	611	568	- 7	544	-11
M	122	470	568	+21	480	475	- 1	510	+ 6
M	114	447	536	+20	458	414	-10	445	- 3
M	158	569	666	+17	575	604	+ 5	648	+13
M	178*	621	726	+17	626	540	-14	556	-11
M	154	558	640	+15	565	535	- 5	532	- 6
M	162	579	666	+15	586	568	- 3	570	- 3
M	128	487	562	+15	496	474	- 4	460	- 7
M	160	574	657	+14	580	562	- 3	546	- 6
Average, 12 rats				+20			- 4		- 1
M	170	600	652	+ 9	606	660	+ 9	660	+ 9
M	178	621	670	+ 8	626	552	-12	624	± 0
M	140	521	548	+ 5	528	517	- 2	527	± 0
M	175	613	638	+ 3	618	588	- 5	604	- 2
M	224	738	718	- 3	737	670	- 9	693	- 6
M	100	406	390	- 4	417	340	-18	350	-16
M	144	532	480	-10	539	466	-14	474	-12
Average, 7 rats				+ 1			- 7		- 4

\* Represents complete occlusion of aorta.

vated kidney transplanted into the neck (18, 25); all the afferent nerves being severed, some chemical substance produced in the kidney must be involved. If the hypertension of coarctation is also brought about, as we believe, by a substance derived from the kidney, then we must explain how it is that this material increases peripheral resistance in the upper part of the body but allows a normal or even decreased resistance in the lower part. This need not be a stumbling block, for the all important factor in determining blood flow to a given tissue is the metabolic requirements of the tissue itself. Prinzmetal and Wilson (4) and Pickering (5) have demonstrated that when conditions in the arm tissues are such as to evoke hyperemia, then hyperemia occurs as adequately in hypertensive individuals as it does in normal subjects. In fact, it may be calculated from their data that peripheral resistance in the reactive-hyperemic arm of either a hypertensive or a normal subject is only 7 to 12 per cent as great as

the resistance in the same subject under control conditions. Since tissue needs for blood may reduce local resistance in generalized hypertension by 90 per cent, it becomes understandable that the resistance in the lower part of the body in coarctation may easily be reduced only as much as the usual 30 to 50 per cent (as compared with the upper part of the body).

The results of Pickering (5) show a similarity between patients with essential or chronic renal hypertension and those with coarctation of the aorta, while Prinzmetal and Wilson (4) found a difference. The latter felt that the hypertension of coarctation was of vasomotor origin, in distinction to the alleged peripheral origin of other varieties of hypertension (including that of acute glomerulonephritis in which Pickering (26) affirms a vasomotor origin). In view of such divergent opinions, and since local conditions (including the metabolites produced locally) act to maintain an adequate local blood flow as long as the cardiac output is normal and the arterial pressure not greatly lowered, it seems unwise to attempt to draw conclusions as to the site of action of the agent causing hypertension in man from data on blood flow in the arm.

Pickering's (5) explanation of the increased peripheral resistance in the upper body in coarctation of the aorta was a supposed failure of growth of that vascular bed, particularly the arteriole-venous anastomoses; such an assumption lacks supporting evidence and is not necessary.

Blumgart *et al.* (11) found no difference in arteriolar pressure between the arms and legs in coarctation of the aorta. This means only that the fall of pressure gradient occurred proximal to the site of measurement; since the method was an indirect one, the observation is of doubtful significance.

#### SUMMARY AND CONCLUSIONS

A consideration of hydrodynamics indicates that the arterial hypertension which is present in the upper part of the body in coarctation of the aorta may not be explained upon the purely mechanical grounds of obstruction to blood flow. In this condition, there is an increased resistance in the smaller vessels (arterioles) which receive blood from the aorta proximal to the stenosis of its isthmus. The cause of this localized increased



resistance is the same as the cause of the generalized increased resistance in a Goldblatt dog (with partially occluded renal artery); that is, interference with blood supply to the kidneys.

This conclusion is supported by the production of hypertension (cardiac hypertrophy) in rats by partial occlusion of the aorta proximal to one or both renal arteries. With partial occlusion of the aorta between the renal arteries, hypertension occurs only when living renal tissue is present distal to the occlusion; after simultaneous distal nephrectomy, hypertension never occurs even though there exists the same degree of mechanical obstruction to blood flow offered by the stenosis and presence of a collateral bed.

#### BIBLIOGRAPHY

1. King, J. T., The blood pressure in stenosis at the isthmus (coarctation) of the aorta; Case reports. *Ann. Int. Med.*, 1937, **10**, 1802.
2. Lewis, T., Material relating to coarctation of the aorta of the adult type. *Heart*, 1933, **16**, 205.
3. Barcroft, H., and Samaan, A., The explanation of the increase in systemic flow caused by occluding the descending thoracic aorta. *J. Physiol.*, 1935, **85**, 47.
4. Prinzmetal, M., and Wilson, C., The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system. *J. Clin. Invest.*, 1936, **15**, 63.
5. Pickering, G. W., The peripheral resistance in persistent arterial hypertension. *Clin. Sc.*, 1936, **2**, 209.
6. Grollman, A., and Ferrigan, J. P., Jr., Cardiac output; Its related functions in a case of coarctation of the aorta. *Arch. Int. Med.*, 1934, **53**, 35.
7. Strayhorn, W. D., Coarctation of the aorta: A case report with observations on the cardiac output during and after pregnancy. In *Medical Papers Dedicated to Henry Asbury Christian*, Waverly Press, Baltimore, 1936, p. 134.
8. Wezler, K., and Böger, A., Die arterielle Gesamtwiderstand unter verschiedenartigen Sympathicusreizen. *Arch. f. exper. Path. u. Pharmakol.*, 1937, **187**, 65.
9. Levy, S. E., and Blalock, A., Fractionation of the output of the heart and of the oxygen consumption of normal unanesthetized dogs. *Am. J. Physiol.*, 1937, **118**, 368.
10. Böger, A., and Wezler, K., Die Bestimmung des arteriellen Gesamtwiderstandes am Menschen. *Arch. f. exper. Path. u. Pharmakol.*, 1937, **186**, 43.
11. Blumgart, H. L., Lawrence, J. S., and Ernestine, A. C., The dynamics of the circulation in coarctation (stenosis of the isthmus) of the aorta of the adult type. *Arch. Int. Med.*, 1931, **47**, 806.
12. Graybiel, A., Allen, A. W., and White, P. D., A histological study of the arterioles of the muscle and skin from the arm and leg in individuals with coarctation of the aorta. *J. Clin. Invest.*, 1935, **14**, 52.
13. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summer-ville, W. W., Studies in experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exper. Med.*, 1934, **59**, 347.
14. Bell, E. T., and Goldblatt, H., Discussion in *Am. J. Path.*, 1936, **12**, 761.
15. Rytand, D. A., and Dock, W., Experimental concentric and eccentric cardiac hypertrophy in rats. *Arch. Int. Med.*, 1935, **56**, 511.
16. Collins, D. A., Hypertension from constriction of the arteries of denervated kidneys. *Am. J. Physiol.*, 1936, **116**, 616.
17. Chanutin, A., and Barksdale, E. E., Experimental renal insufficiency produced by partial nephrectomy. II. Relationship of left ventricular hypertrophy, the width of the cardiac muscle fiber and hypertension in the rat. *Arch. Int. Med.*, 1933, **52**, 739.
18. Blalock, A., and Levy, S. E., Studies on the etiology of renal hypertension. *Ann. Surg.*, 1937, **106**, 826.
19. Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S., Relationships between urea excretion, renal blood flow, renal oxygen consumption, and diuresis. The mechanism of urea excretion. *Am. J. Physiol.*, 1934, **109**, 336.
20. Mason, M. F., Evers, R., and Blalock, A., Renal oxygen utilization of dogs with experimental hypertension. *Proc. Soc. Exper. Biol. and Med.*, 1937, **36**, 819.
21. Levy, S. E., Mason, M. F., Harrison, T. R., and Blalock, A., The effects of ureteral occlusion on the blood flow and oxygen consumption of the kidneys of unanesthetized dogs. *Surgery*, 1937, **1**, 238.
22. Dock, W., and Rytand, D. A., Renal blood flow after subtotal nephrectomy. *Proc. Soc. Exper. Biol. and Med.*, 1937, **36**, 196.
23. Hartmann, H., Ørskov, S. L., and Rein, H., Die Gefäßreaktionen der Niere im Verlaufe allgemeiner Kreislauf-Regulationsvorgänge. *Arch. f. d. ges. Physiol.*, 1936-37, **238**, 239.
24. Spanner, R., Der Abkürzungskreislauf der menschlichen Niere; Beitrag zur Kenntnis der Leistungs-zerteilung ihres Gefäßsystems. *Klin. Wchnschr.*, 1937, **16**, 1421.
25. Houssay, B. A., and Fasciolo, J. C., in Buenos Aires letter of October 20, 1937. *J. A. M. A.*, 1937, **109**, 2002.
26. Pickering, G. W., Observations on the mechanism of arterial hypertension in acute nephritis. *Clin. Sc.*, 1936, **2**, 363.