ESTIMATION OF RENAL VENOUS RESISTANCE AND ITS SIGNIFICANCE TO AUTOREGULATION IN THE DOG KIDNEY

BY

CHARLES HENRY WELLS II

AN ABSTRACT

Submitted to the College of Science and Arts
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ABSTRACT

It has been suggested that the degree of functional distention of the kidney may be related to the severity of experimentally produced hypertension (Swann et al., 1959). The mechanisms controlling this distention have not been described.

Although pressure to distention and flow to distention relationships have not been adequately studied, much work has been done on renal pressure to flow relationships. As the perfusing pressure increases, renal blood flow increases. The rise in flow rate is rapid at first and then progressively slower. This indicates a rise in renal resistance to blood flow at high perfusion pressures. The mechanism responsible for this resistance rise has not been described with certainty, although numerous theories have been proposed.

In an attempt to locate the site of this resistance change, a method was developed which allows separation of renal resistance into two components, that coming before, and that after the peritubular capillary bed. Pressure, distention relationships for the organ were simultaneously determined.

Isolated dog kidneys were perfused with the animals' own blood under varying arterial and venous pressures. The flow rate was measured directly, and the distention determined by recording the organs weight changes. The mean peritubular capillary pressure was estimated by an indirect method.

When the renal artery is clamped and the venous pressure is set at some desired level, this pressure is transmitted equally throughout the kidney. The distention which results from each of a number of "distending pressures" can be recorded and thus the distending pressure to distention relationship established for the organ. This distending pressure is the interstitial pressure, and is developed at the site of interstitial fluid formation. This is the peritubular capillary bed. Studies have shown that the peritubular capillary pressure and interstitial pressures are essentially the same during perfusion (Gottschalk et al., 1956). The peritubular capillary pressure can now be computed from the observed distention of the kidney under any set of perfusion conditions.

Blood flow, arterial and venous pressures were measured directly. Using data obtained by these methods, the post-peritubular capillary resistance was calculated and it was found that this was linearly proportional to the distending pressure. A study of the relative contributions of the pre- and post-peritubular capillary resistances to the total renal resistance revealed that the resistance rise in autoregulation was located in the post-peritubular capillary segment of the vascular system. All theories thus far offered as explanations of autoregulation have assumed the resistance rise to be in the pre-peritubular capillary segment of the organ. The findings of this study seem incompatable with such theories and suggest that the resistance rise of autoregulation is due to venous constriction, perhaps by interstitial pressure.

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REVIEW OF LITERATURE

Although it has long been recognized that there was some relationship between renal contraction as seen in chronic pyelonephritis, and elevated levels of systemic arterial pressure (Tyson, 1883), only recently has it been realized that the kidney is distended in its functional state. This property was examined by Swann et al. (1958a) in a study in which they froze mouse kidneys in situ, then removed and sectioned them. The cortices of these organs, exclusive of glomeruli and vessels were found to be 45% interstitial fluid.

Another method of measuring distending fluid was described by Swann et al. (1955a). Simultaneous clamping of the renal blood vessels was followed by removal and drainage of the organ. The quantity of drainage fluid, and its hematocrit, allowed estimation of the volume of the drained vascular bed and of the draining, cell-free fluid when the systemic hematocrit was known. For dogs it was found that functionally distended kidneys will drain 13 to 30% of their distended volume (Swann et al., 1956a). The hematocrit of the drained fluid was about half that of blood. From these data the relative proportion of blood and "diluting fluid" in the draining fluid was calculated. Studies of the electrolyte and protein contents of draining fluid, renal lymph, urine and blood, led Swann and co-workers (1956a, b, 1958b) to suggest that this distending

fluid was a mixture of capillary filtrate and tubular resorbate, and that it occupies the interstitial space in the distended organ.

Overbaugh et al. (1957) repeated this for several other mammals and found that all those tested had a sizeable degree of renal distention.

Experimental renal hypertension has been produced by a variety of methods. One of these involves incarceration of one kidney in a relatively non-distensible cast and removing the contralateral organ (Soskin and Saphir, 1932, Page, 1939, Corcoran and Page, 1942). It can also be produced by placing a constrictive clamp on the renal artery (Goldblatt et al., 1934). This results in a reduction of arterial pressure at the kidney (Mason et al., 1940). Inasmuch as it has been shown that, in the normal subject, renal distention increases with increased arterial pressure (Swann et al., 1955b), we may logically conclude that distention of the kidney in Goldblatt hypertension is reduced. It has been suggested that the reduction in renal distention may be the critical factor in these forms of experimental hypertension (Swann et al., 1959).

Arguments that the arterial clamping experiment caused an elevation of blood pressure initiated by reduced renal blood flow have been contested (Schroeder and Steele, 1940, Corcoran and Page, 1941, Friedman et al., 1941). Corcoran and Page (1941) were unable to detect persistant diodrast, phenol red,

inulin clearance changes in animals rendered hypertensive by renal arterial constriction. Also, in renal incarceration with silk crepe, hypertension persists without changes in renal plasma flow (Corcoran and Page, 1942).

If on the basis of the above studies of Corcoran and Page, Friedman et al., and Schroeder and Steele, we reject the hypothesis that the level of a circulating pressor substance is dependent upon the degree of renal ischemia, then we must explore the possibility of the level of pressor substance being dependent in some manner on the degree of renal distention. In view of this the renal pressure-flow-distention relationships and mechanisms would seem to be fruitful areas to explore.

Although little is known about the distention-pressure or distention-flow relationships, there is a wealth of knowledge about pressure-flow relations in the kidney. As arterial pressure increases in the intact normal kidney, the flow increases, rapidly at first and then progressively more slowly (Selkurt 1946, Weiss et al., 1959, Hinshaw et al., 1959).

As may be seen from Figure 1 there is no flow with pressures of 14 mm Hg or less. Burton (1951) proposed the concept of critical closing of the renal vessels as a possible explanation of this phenomenon.

The cause of the resistance rise at high flows has been the subject of much controversy. Perhaps the oldest and most generally favored theory is that the rise in resistance is due to constriction of renal arterioles (Thompson et al., 1957, Haddy et al., 1958, Forster and Maes, 1947, Shipley and Study, 1951). This concept is re-enforced by the finding that cyanide produces irreversible vasodilation and abolishes autoregulation while procaine will reversibly abolish it (Lochner and Ochwadt, 1954).

On the basis of rising resistance with elevations in venous pressure, at a constant perfusion rate, Lochner and Ochwadt (1954) postulated the presence of pressure-sensitive structures in the renal vessels. Such sensing devices were thought to initiate a feedback mechanism leading to vasoconstriction in other renal vessels. Haddy et al. (1958) too, felt that autoregulation must be due to an intrarenal reflex. Extrinsic denervation, inactivation of circulating catecholamines, and the use of ganglion blocking agents failed to abolish it (Haddy, et al., 1958). It has been demonstrated, however, that the abolition of autoregulation is accompanied by a rise, not a fall, in renal resistance. When the renal resistance

approaches twice that of the normal, autoregulation disappears, but the organ still responds to Levophed (nor-epinephrine) (Weiss, et al., 1959).

These findings suggest that the vasodilation which results from treatment with cyanide is not the factor which is directly responsible for the loss of autoregulation in these experiments. Conversely, the inability of the kidney to autoregulate when renal resistance is high can hardly be interpreted as vasospasm if Levophed will cause further resistance rises, as reported by Weiss. The inability of the active vasoconstriction theory to explain the lack of autoregulation on the basis of vasomotor paralysis, or as an inability of the vessels to respond further because of maximal contraction of the vessel musculature, raises some doubts as to validity of the theory.

In contrast to theories of autoregulation which are based on active vessel constriction, there are theories which attempt to explain it on the basis of physical changes in the system. Winton (1951) discussed the possibility that the rise in resistance could be due to increase in viscosity of the blood following concentration during filtration. He challenged the idea, however, by referring to work by Whittaker and himself (1933) in which they added red cells to blood perfusing the isolated hindlimb of a dog. From this work he concluded that viscosity changes which one could expect could cause only a small fraction of the resistance rise normally seen.

Pappenheimer and Kinter (1956) recognized that blood flowing through a tube tended to concentrate its formed elements in the center and leave the periphery relatively cell free. The degree of concentration of the cells depends upon the velocity of flow. They felt that the relatively cell poor plasma would be progressively skimmed off delivering cell rich blood to the terminal arterioles. This blood was thought to be shunted past the peritubular capillaries to the renal vein. Since the effective viscosity varies directly with the third power of the red cell concentration, relatively small changes in cell concentration in the terminal arterioles will result in rather large increases in apparent resistance. The concomitant fall in hematocrit in medullary vessels will contribute relatively small decreases in total impedence to flow. Weiss, Passow and Rothstein (1959), on the other hand, were able to show autoregulation in kidneys perfused with cell free fluid.

If autoregulation is not due to arteriolar constriction or plasma skimming, the structures responsible for this phenomenon have not been determined. In view of this, the review of older literature by Koester et al. (1955) on intrarenal venous sinusoidal structures is particularly interesting. These structures, which appear to be erectile tissue, protrude into the vascular lumina at the junctions of the arcuate and interlobar veins. Interest in these sinusoidal cushions was renewed by the observation of Swann et al. (1952) that the pressure in the

arcuate veins was much higher than in the interlobars.

These findings led us to undertake the measurement of the resistance to blood flow developed in the venous segment of the renal circulation.

THEORETICAL PRINCIPLES

Understanding the rationale employed in measuring the venous resistance requires consideration of the anatomy of the kidney. Its capsule is a firm fibrous structure and the attainment of functional distention of the organ involves filling and/or stretching of this capsule. The pressure necessary to accomplish this is the interstitial pressure and is derived from the peritubular capillary bed. In view of the discovery that albumins pass freely through these capillaries (Collings and Swann, 1958), one can assume that there is little difference between the colloid osmotic pressure within these vessels and that within the interstitial space. Moreover, Gottschalk (1956) has shown that the mean peritubular capillary hydrostatic pressure very closely approximates that of the interstitial space.

The mean peritubular capillary pressure (P_D) is related to venous pressure (P_V), the resistance of vascular bed (R_T) between the points of measurement of mean peritubular pressure and venous pressure, and blood flow (Q) as follows:

$$P_D = R_T Q + P_V \qquad \text{Equation 1}$$

The resistance of the vascular bed (R_T) is related to the capillary pressure (P_D), flow and venous pressure by the following equation:

$$R_T = \frac{P_D - P_V}{Q} \qquad \text{Equation 2}$$

If the renal artery is clamped and renal vein pressure increased, this pressure is transmitted throughout the kidney as in any liquid-filled system. In this way the distention which results from any given peritubular capillary pressure can be determined. Once the relationships of peritubular capillary pressure and renal distention are determined for a given kidney by this method, one can infer the mean peritubular capillary pressure from the observed distention, when blood is flowing through the kidney.

The sum of the resistances distal to the peritubular capillaries can be determined by dividing the pressure drop from the peritubular capillaries to the renal vein by the renal blood flow. (Equation 2)

This method does not measure the resistance imposed by the sinusoidal cushions alone but rather the sum of all resistances distal to the point of mean peritubular capillary pressure.

Similarly, it is possible to determine the sum of the serial resistances between the renal artery and the point of mean peritubular capillary pressure.

METHODS

Isolated kidneys were obtained by a left flank approach from 6 mongrel dogs of approximately 20 kilograms body weight. These organs were freed from the body wall by doubly ligating and severing small segments of perirenal fat, fascia and peritoneum. This procedure was used to avoid the severe bleeding which would result from stripping the peritoneum from the capsule.

When the kidney and its vessels had been dissected free, the ureter was cannulated with polyethylene tubing.

The kidney was returned to its normal position and allowed to perfuse for 20 minutes in order to recover as nearly as possible from the effects of the manipulation. Meanwhile the animal was heparinized and both femoral veins and one femoral artery was cannulated. The femoral vein cannulae were attached to a bubble-trapping reservoir to be used for return of blood to the animal (Appendix 2). The femoral artery cannula was next filled with blood. The distal end of this cannula opened on the inside of the perfusion chamber for eventual attachment of the renal artery.

At the end of the period of *in situ* perfusion both renal vessels were doubly clamped with mosquito forceps and sectioned between the clamps. The vessels of the excised organ were then cannulated with polished stainless steel cannulae which had

previously been filled with blood to avoid air emboli. The renal arterial cannula was now carefully attached to the distal end of the femoral cannula in the perfusion chamber so as to exclude all bubbles and the renal venous cannula was attached by Tygon tubing to a reservoir of adjustable height. (Appendix 3). As soon as the renal vessel cannulae were securely attached to perfusing system, blood flow was established. The average duration of ischemia was 4½ minutes.

The renal outflow drained into a reservoir, the height of which determined the renal venous pressure. This could be set for any value from -20 to +100 mm Hg. Overflow from the reservoir passed through a modified polyethylene graduated cylinder, the outflow of which could be stopped at will. Volume flow was monitored by timing the filling rate of the graduate. Blood was returned to the femoral veins of the dog by a Sigma-motor pump through the bubble-trapping apparatus previously mentioned.

Arterial and venous pressures were measured at the perfusion chamber by Statham strain gauges, models P-23A and P-23VV respectively, located at the same level as the kidney.

The weight of the organ was determined by placing it in a wire basket suspended from a Statham strain gauge, model GI-32-450, mounted in the roof of the perfusing chamber (see Appendix 3).

Recordings of pressure and weight were made by a

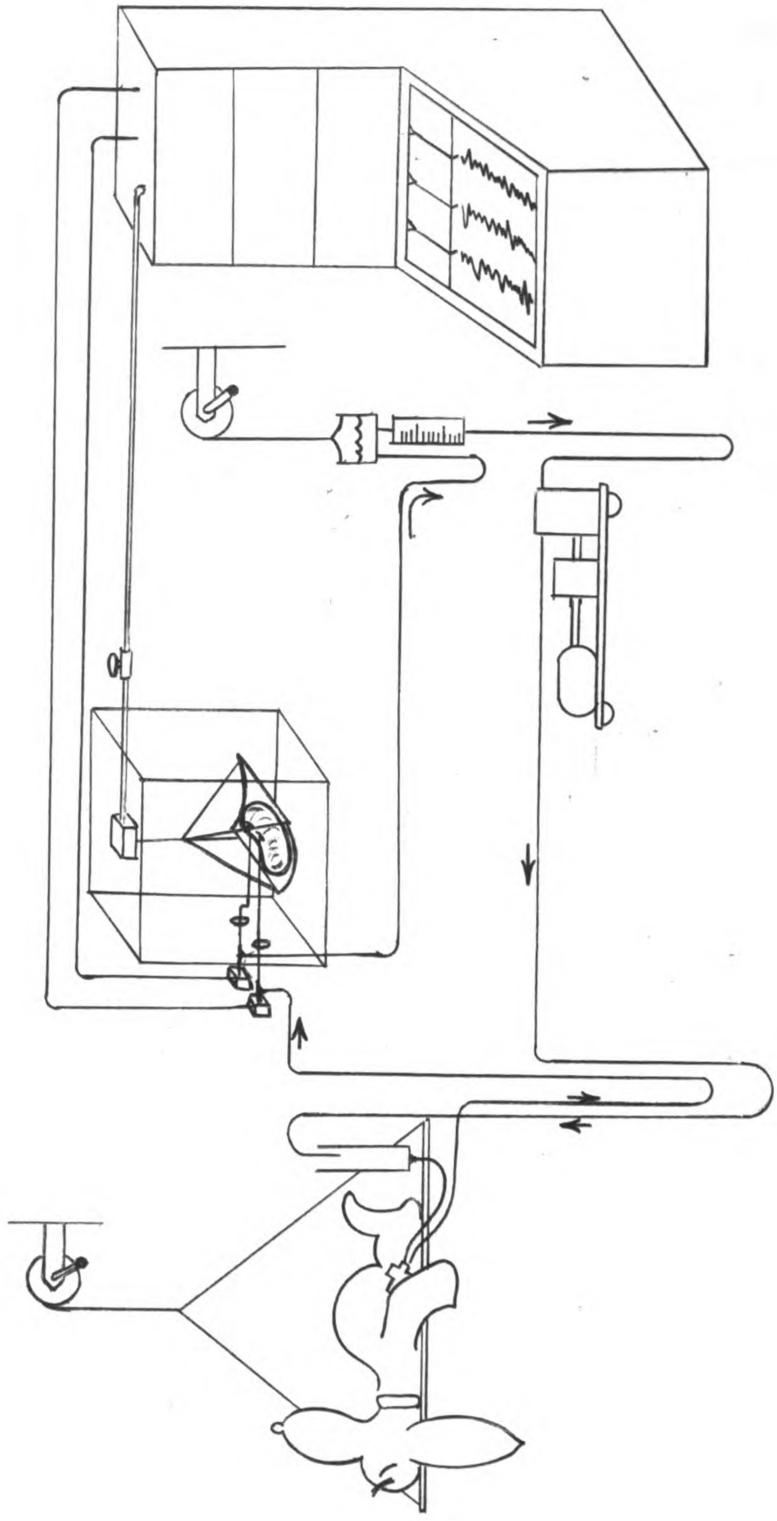
Sanborn polygraph with the output of the pressure transducers amplified by Sanborn carrier amplifiers while the output of the weight transducer was amplified by a Brush Universal Strain Analyzer.

In order to regulate arterial pressure at the kidney, the dog was placed on a platform of readily adjustable height. By varying the height of the animal with respect to the kidney, a hydrostatic pressure was developed which modified the arterial pressure at the kidney. After perfusing ten to fifteen minutes in the warm, humid chamber, the arterial cannula was clamped and the organ was allowed to drain as completely as possible while the venous pressure was set at zero. This was taken to be the drained weight of the kidney and distention was defined as the increase in weight above this drained value.

The arterial pressure was then adjusted to a low level ($\sim$ 35 mm Hg) and flow re-established with the venous pressure set at some point between zero and 6 mm Hg. When distention was thus equilibrated, blood flow was measured.

Arterial pressure was then raised in approximately 10 mm Hg increments, with arterial pressure, distention, and flow measured at each step until the arterial pressure was in the range of 200 mm Hg. The arterial pressure was next dropped by similar increments until it was again at low levels with measurements of flow and distention taken at each increment.

The renal arterial cannula was now clamped and the organ



allowed to drain with venous pressure at zero mm Hg as before. Venous pressure was then raised in increments of 5 mm Hg and time was allowed for distention equilibration at each pressure. After a venous pressure of 60 mm Hg was reached the organ was drained in a similar manner. This procedure was used to determine the relationship of peritubular capillary pressure to distention.

In several of the kidneys studied arterial pressure was held constant and venous pressure was raised in small increments starting at zero mm Hg and ending at 50 mm Hg while flow was maintained instead of maintaining a constant venous pressure and varying the arterial pressure.

RESULTS

Employing the procedure previously described in the discussion of methods, data were obtained on renal blood flow, renal weight, arterial and venous pressures. From these the resistance values were calculated.

A description of the symbols used in this study follows.

Pressures:

P_A: arterial pressure, in mm Hg, at the kidney.

P_R: venous pressure in mm Hg taken at the kidney.

P_D: mean peritubular capillary pressure in mm Hg.

P_{RK}: the pressure drop between the arterial and the venous pressure measuring points, in mm Hg.

P_{RT}: the pressure drop between the point of mean peritubular capillary pressure and the point of measurement of venous pressure, in mm Hg.

Resistances:

R_K: total renal resistance, in peripheral resistance units, to blood flow.

R_T: resistance in peripheral resistance units from the site of mean peritubular capillary pressure to the site of venous pressure measurement.

R_P: resistance, in peripheral resistance units, between the point of mean peritubular capillary pressure and the point of arterial pressure measurement.

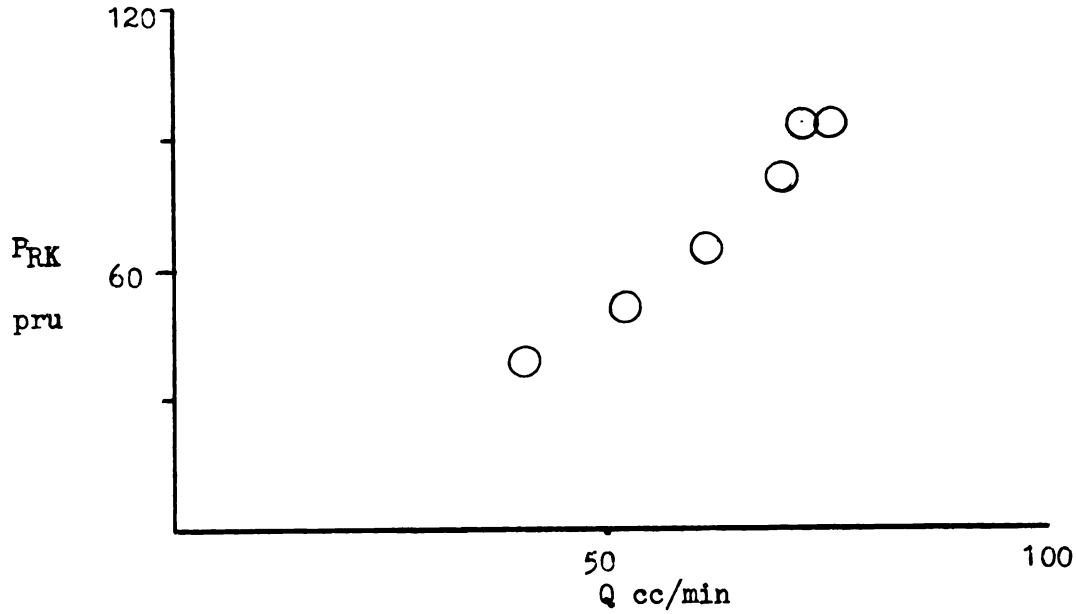
Others:

Q: flow of blood through the kidney in ml/min.

The first group of figures (1-6) illustrates the relationship of the renal blood pressure drop ($P_A - P_V$) to blood flow. The renal venous pressure was maintained at a constant value throughout each of the trials. The original experimental values accompany each plot, except the values for resistance which were calculated. All original data are in Appendix 4.

Figure 1

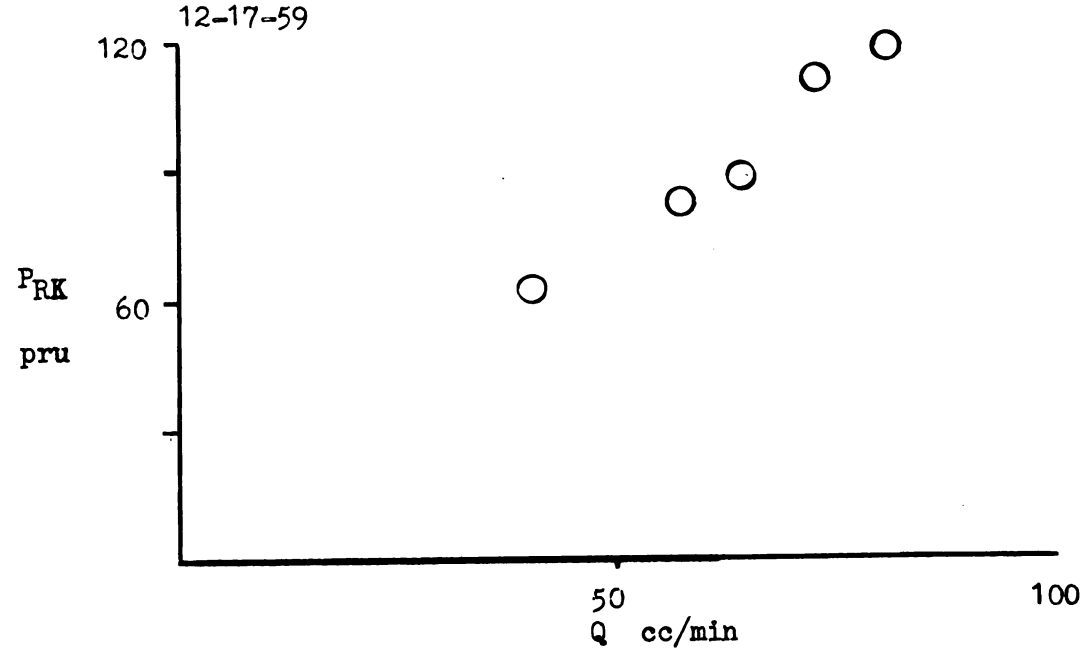
12-18-59



P_{RK}	40	56	66	81	94	94
Q	40	52	60	69	72	75

Figure 2

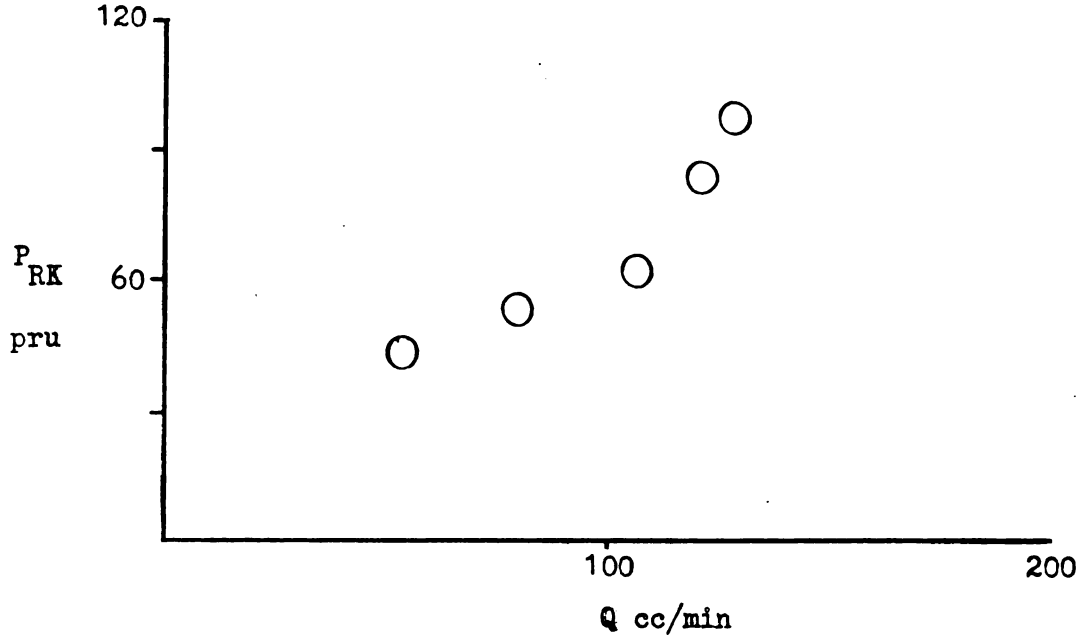
12-17-59



P_{RK}	85	88	113	118	66
Q	57	63	72	80	40

1-16-60A

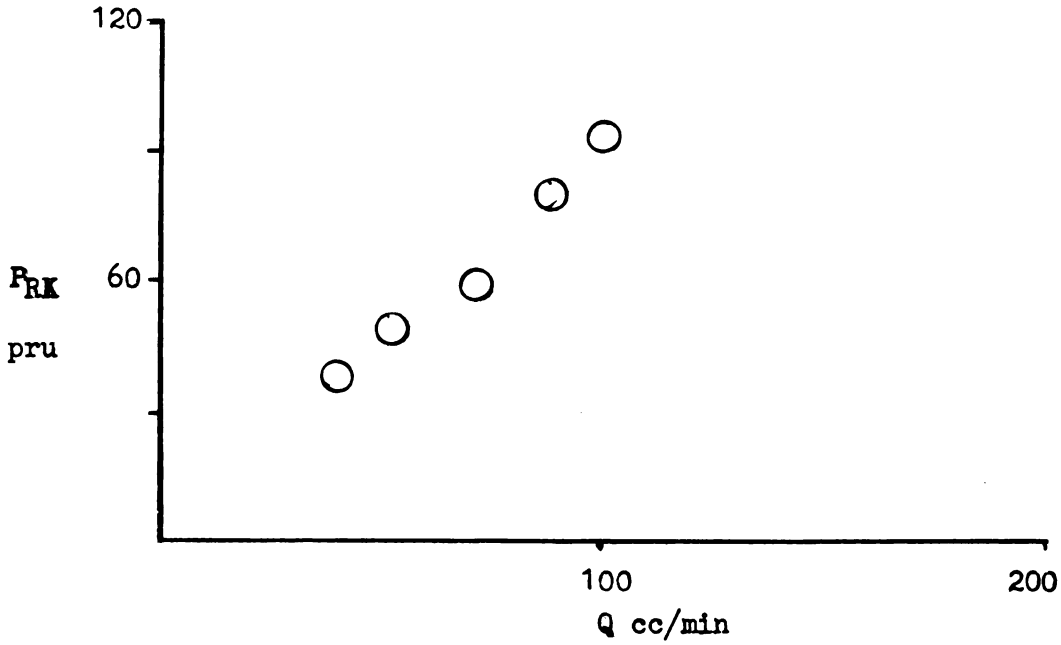
Figure 3



P_{RK}	42	52	61	81	97
Q	54	80	106	120	128

1-16-60B

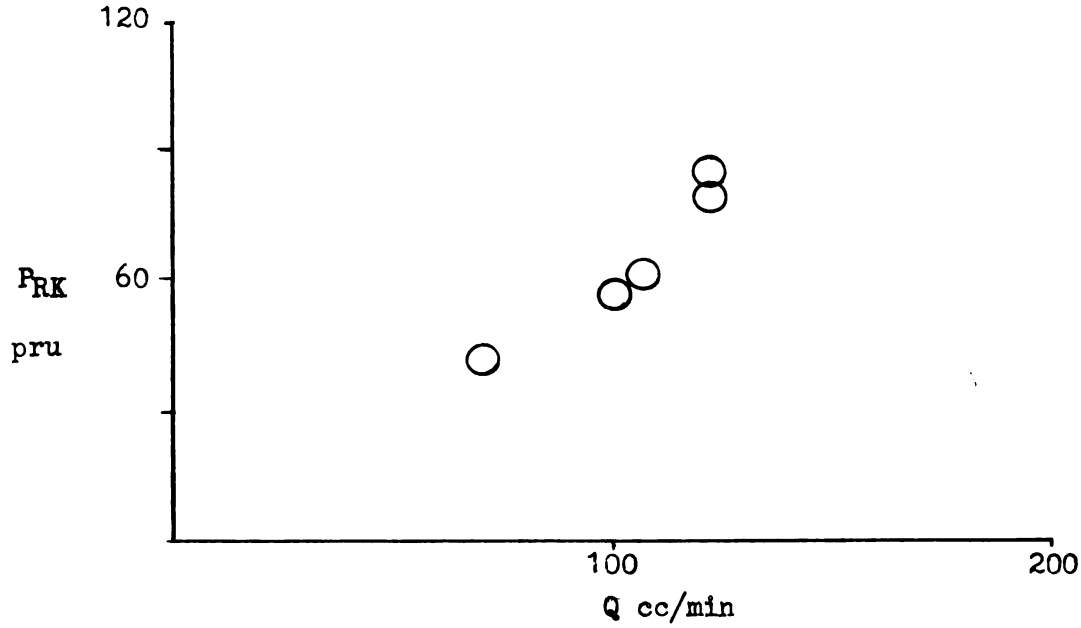
Figure 4



P_{RK}	36	48	59	78	93
Q	40	52	70	88	100

12-16-59

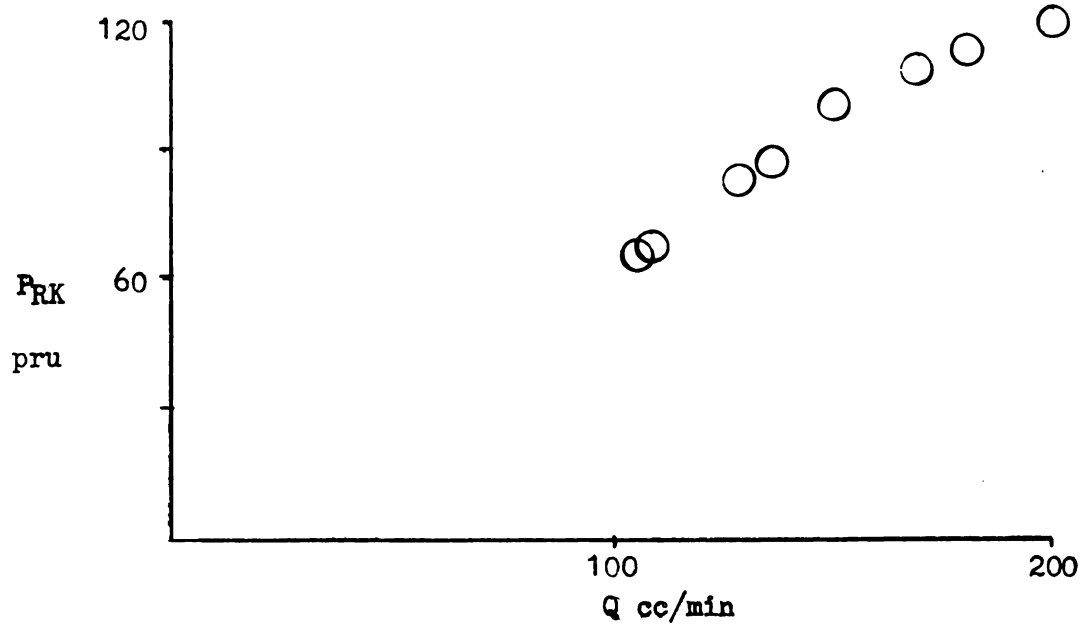
Figure 5



P_{RK}	62	78	84	39	57
Q	106	120	120	70	100

Figure 6

1-23-60

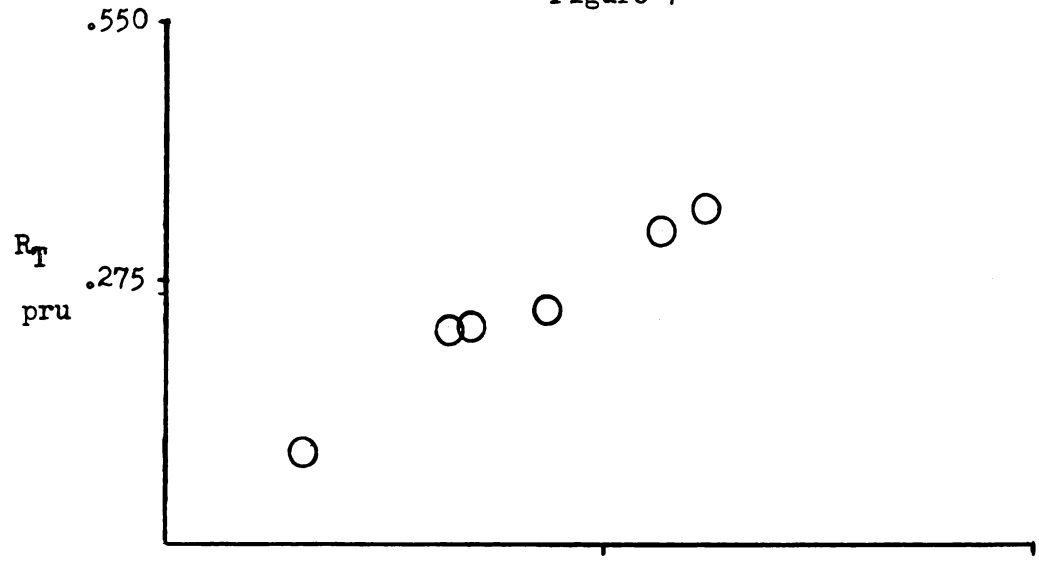


P_{RK}	66	67	82	86	99	108	112	118
Q	104	108	128	136	150	168	180	200

Figures 7-11 depict the relationship between mean peritubular capillary pressure and post-peritubular capillary resistance. In this group venous pressure was maintained at a constant value and changes in peritubular capillary pressure were achieved by elevating the arterial pressure. Figure 11 is a composite of the data obtained in four separate series of arterial pressure elevations in the same kidney at the same venous pressure.

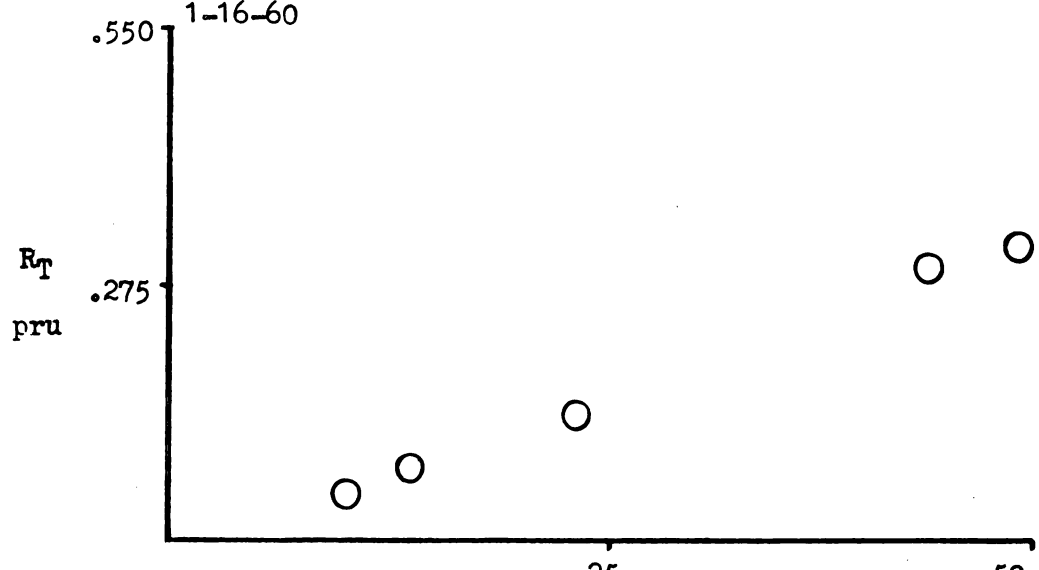
12-18-59

Figure 7



P_D	8	16	18	21.5	29	31
R_T	.100	.230	.233	.253	.346	.360

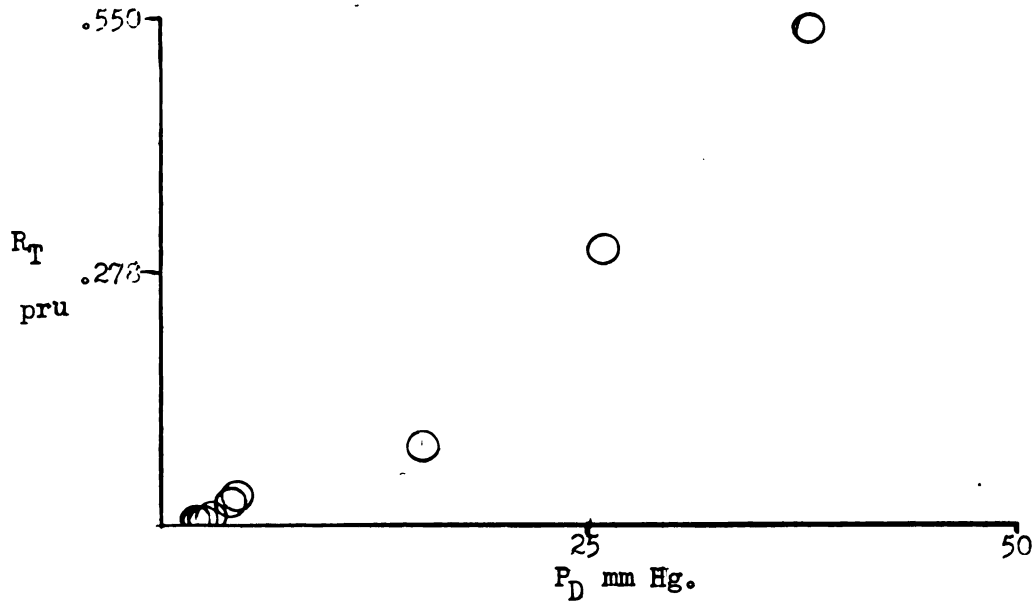
Figure 8



P_D	10	14	23.5	43.5	49
R_T	.054	.062	.136	.287	.313

11-25-59

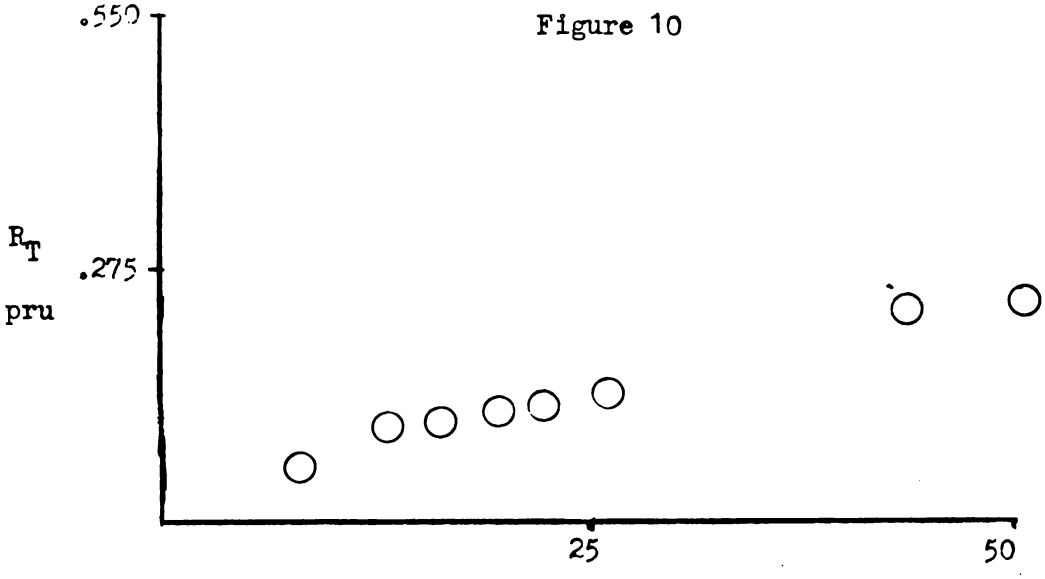
Figure 9



P_D	2	2.3	3.2	3.8	4.0	12	25.5	37
R_T	0	.004	.016	.024	.028	.085	.287	.530

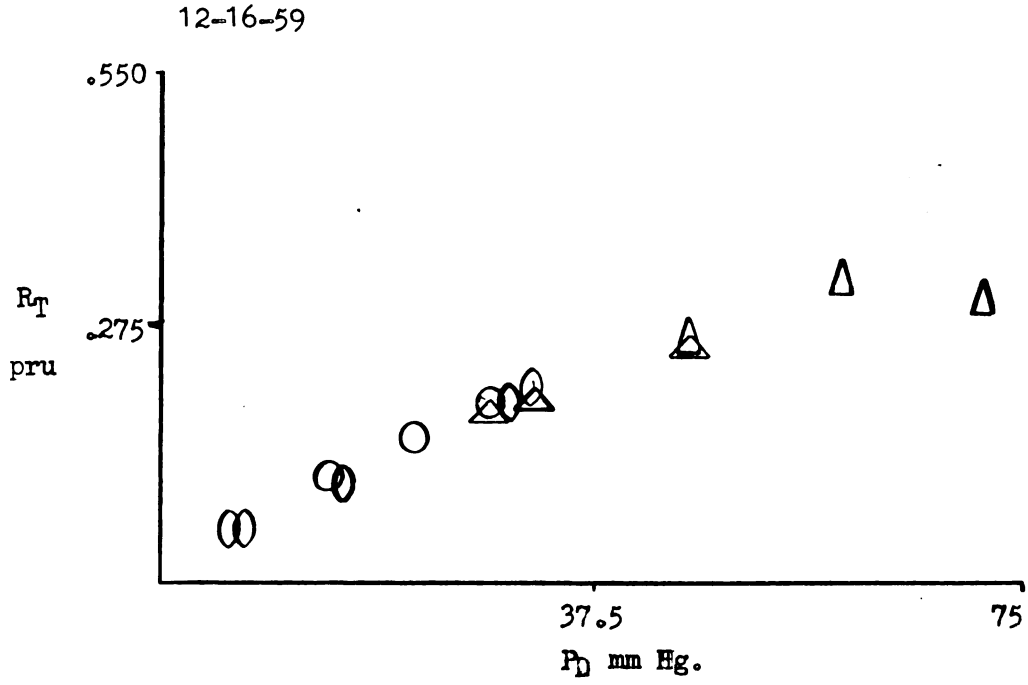
1-23-60

Figure 10



P_D	8	13	16	19.2	22	25.5	43	50
R_T	.058	.108	.108	.117	.126	.128	.223	.235

Figure 11



1st filling (○)

P_D	15	21.5	29
R_T	.113	.155	.216

2nd filling (△)

P_D	29	33.5	47
R_T	.192	.182	.245

3rd filling (◯)

P_D	6.5	8.5	17	32	33.5
R_T	.057	.057	.112	.195	.200

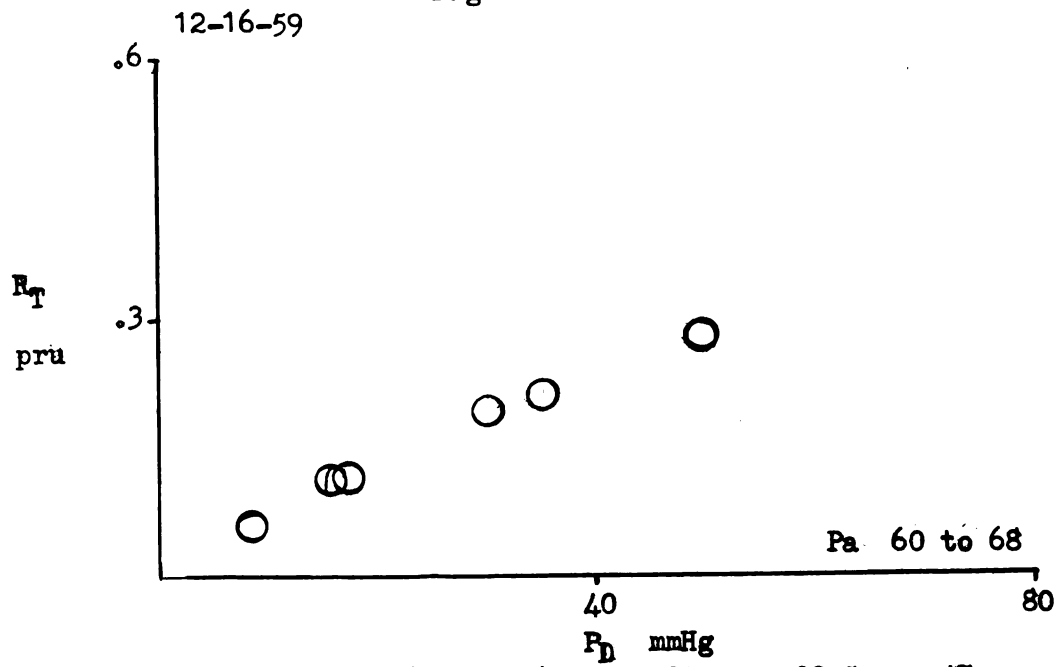
4th filling (△)

P_D	47	59	71.5
R_T	.260	.317	.320

Figures 12-15 also illustrate a relationship of the mean peritubular capillary pressure to the post-peritubular capillary resistance. However, in these cases, elevations of peritubular capillary pressure were obtained by elevating the venous pressure while the arterial pressure remained constant. In the previous group of plots the arterial pressure was varied.

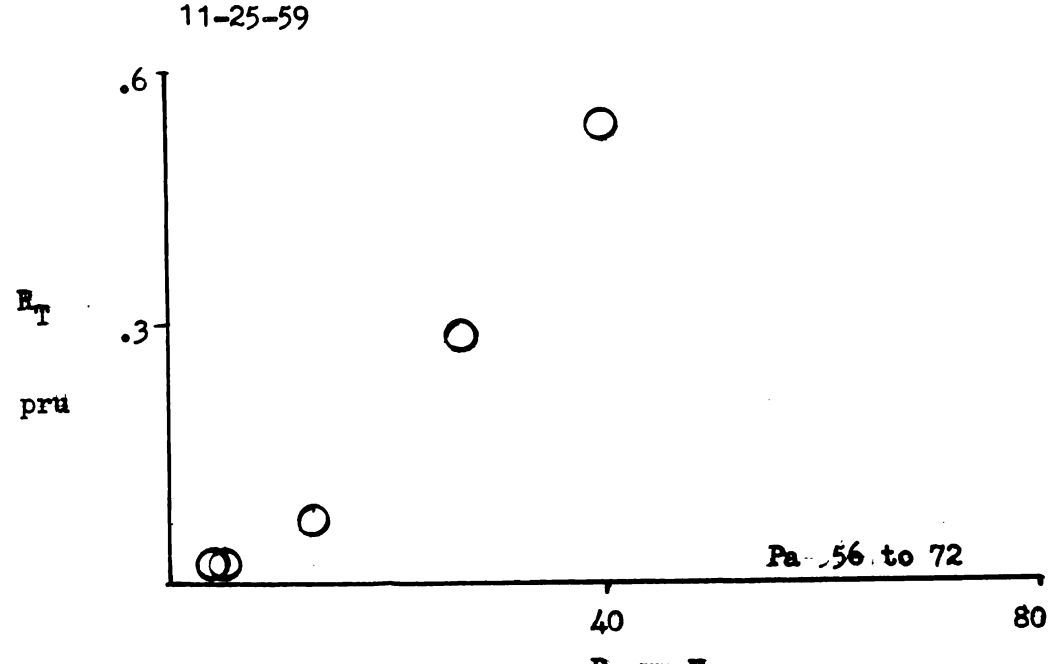
Figures 12 and 14 are composites of all data obtained on one dog at arterial pressures of 60-68 and 81-87 mm Hg respectively. At no other arterial pressure was there a sufficient grouping of data from this animal to justify another figure. Figure 15 is derived from data obtained similarly from another animal. Data plotted in figure 13 were obtained at a fairly steady arterial pressure (56-72) and during a single filling of the kidney.

Figure 12



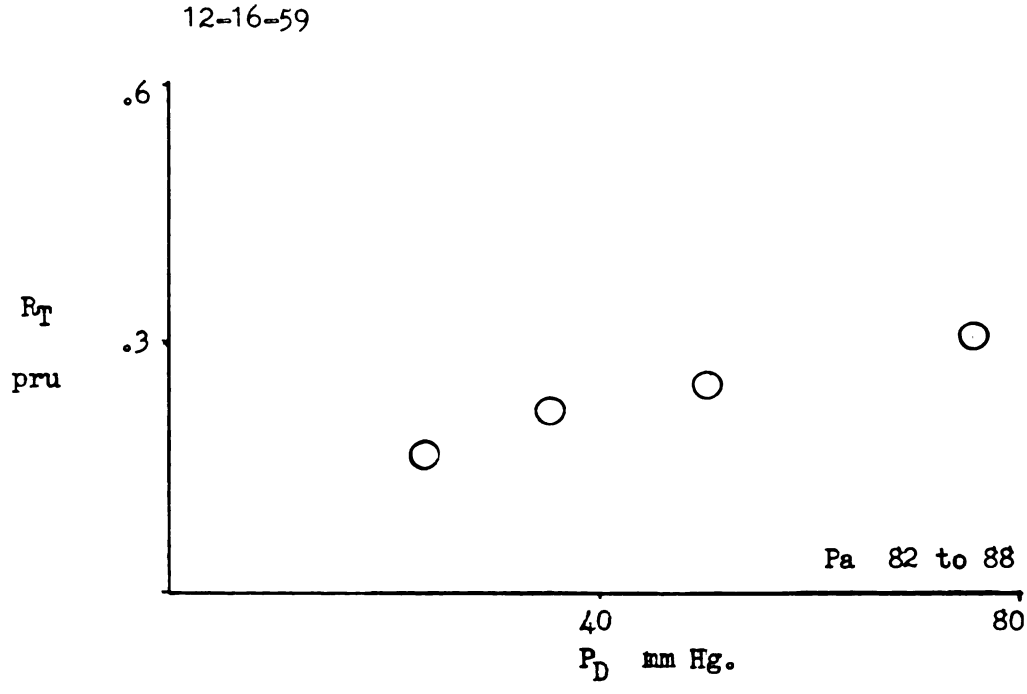
P_D	8.5	15	17	29	33.5	47
R_T	.057	.113	.112	.192	.182	.260

Figure 13



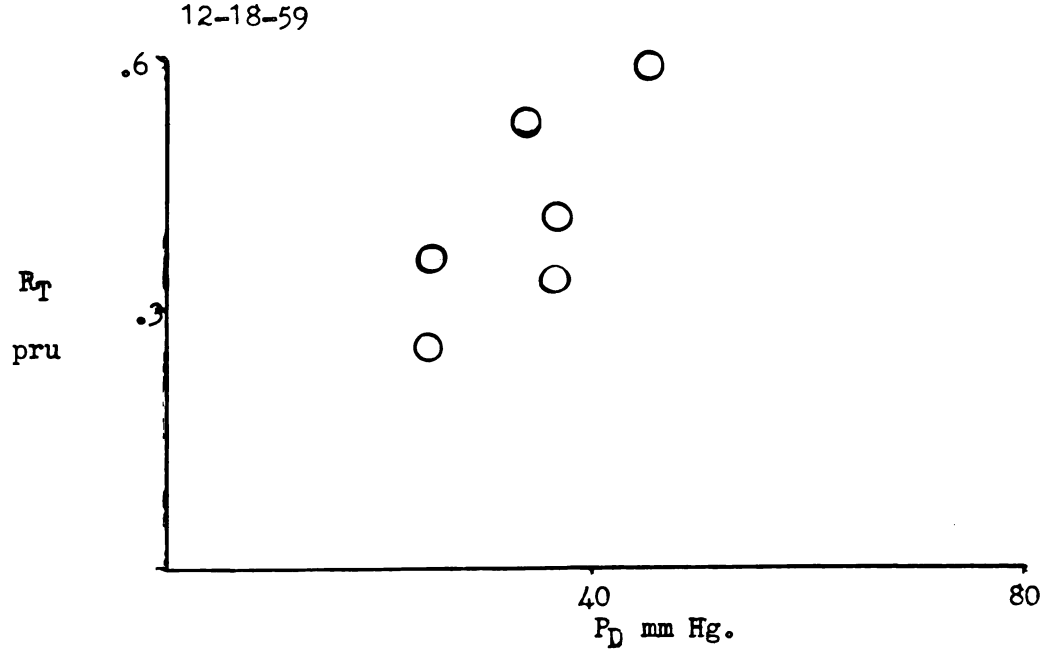
P_D	3.8	4	12	25.5	37
R_T	.024	.028	.083	.287	.530

Figure 14



P_D	21.5	33.5	47	71.5	
R_T	.155	.200	.245	.302	

Figure 15

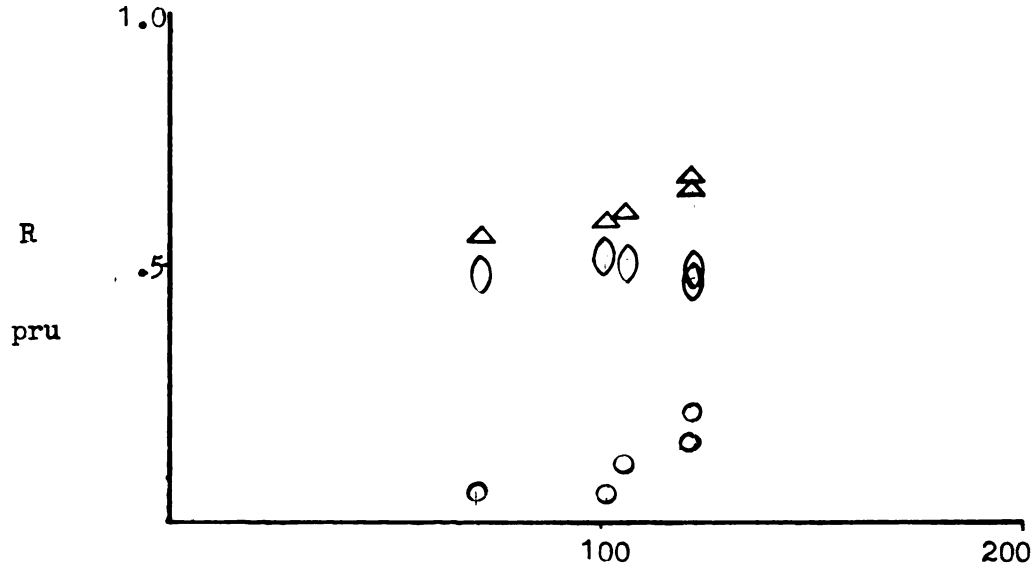


P_D	21.5	21.5	31	34	34	41
R_T	.362	.253	.510	.410	.340	.577

If the renal resistance is separated into two components, the pre- and post-peritubular capillary resistances, as described in Theoretical Principles, it should be possible to show the relative contribution of each to the total resistance under varying flow conditions. The following 6 figures (16-21) show these relationships.

12-16-59

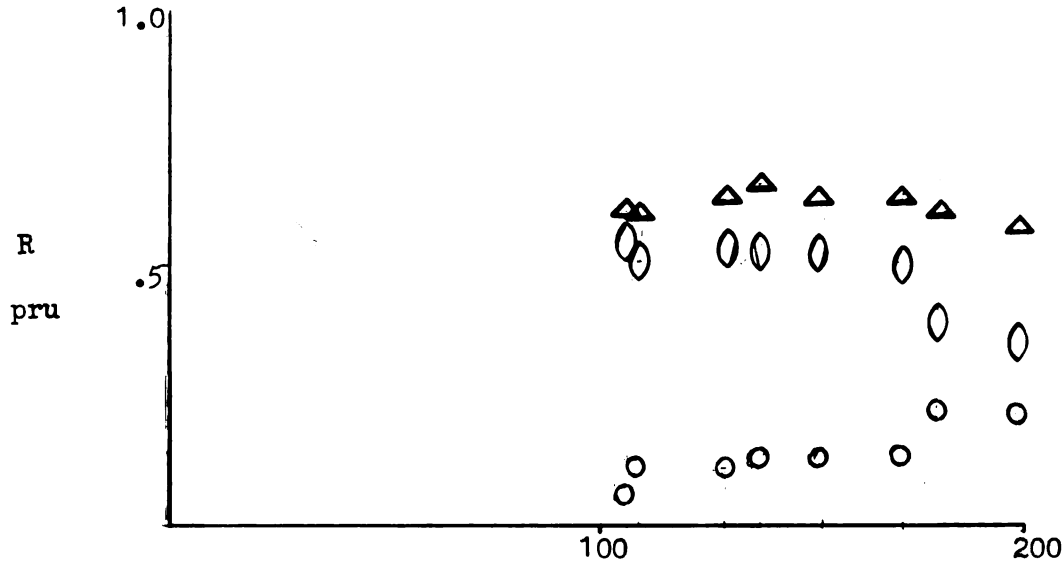
Figure 16



Q	106	120	120	70	100
R_T(○)	.113	.155	.216	.057	.057
R_P(◯)	.517	.495	.484	.503	.533
R_K(△)	.630	.650	.700	.560	.590

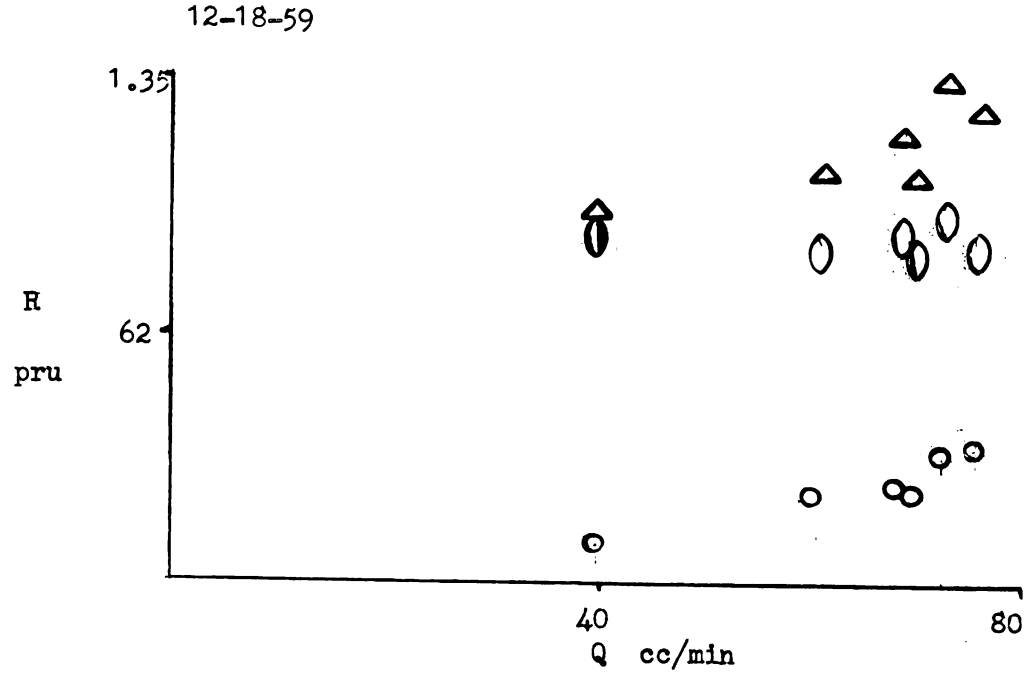
Figure 17

1-23-60



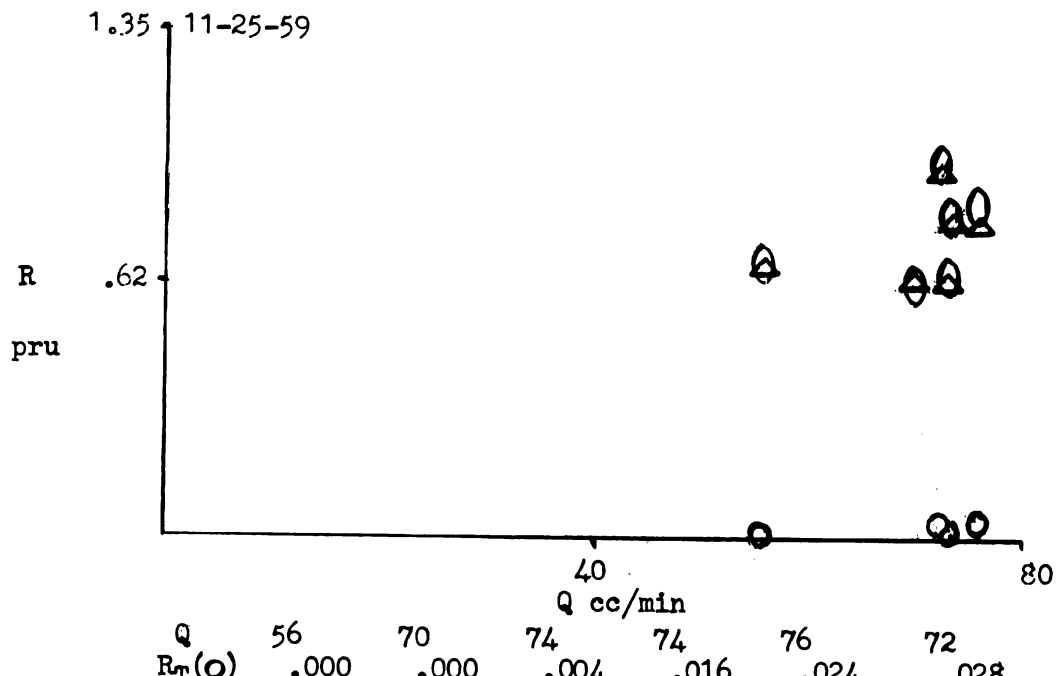
Q	104	108	128	136	150	168	180	200
R_T(○)	.058	.108	.108	.119	.126	.128	.223	.235
R_P(◯)	.574	.514	.532	.551	.526	.512	.399	.355
R_K(△)	.632	.622	.640	.670	.652	.640	.622	.590

Figure 18



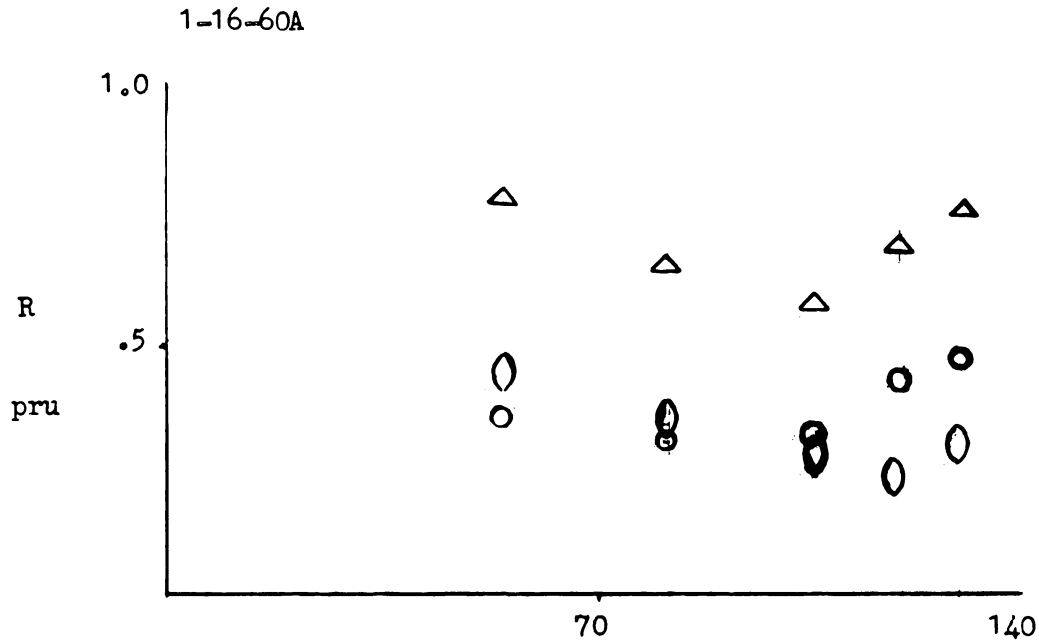
Q	40	52	60	69	72	75
R_T(o)	.100	.230	.233	.253	.346	.360
R_P(())	.900	.850	.867	.917	.974	.890
R_K(△)	1.00	1.08	1.10	1.17	1.32	1.25

Figure 19



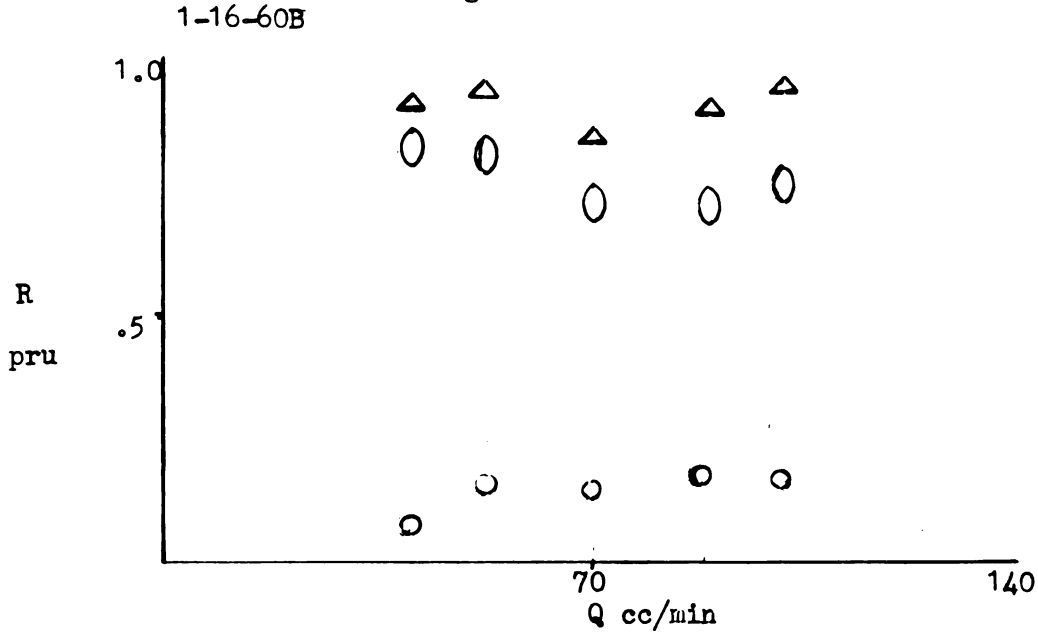
Q	56	70	74	74	76	72
R_T(o)	.000	.000	.004	.016	.024	.028
R_P(())	.733	.655	.701	.849	.856	.972
R_K(△)	.733	.655	.705	.865	.880	1.00

Figure 20



Q	54	80	106	120	128
R_T(O)	.350	.300	.300	.435	.455
R_P(())	.425	.350	.275	.245	.300
R_K(△)	.775	.650	.575	.680	.755

Figure 21



Q	40	52	70	88	100
R_T(O)	.058	.127	.128	.175	.175
R_P(())	.842	.793	.712	.710	.755
R_K(△)	.900	.920	.840	.885	.930

DISCUSSION

Autoregulation was present in some degree in most kidneys studies. However, Figure 6 shows no tendency toward an increase in resistance to blood flow at high flow rates, and consequently no autoregulation. The presence of autoregulation in Figure 4 is questionable. Note that Figure 4 is from data obtained on a second perfusion of the kidney of dog 1-16-60. In an earlier perfusion, this organ showed a marked ability to autoregulate (Figure 3). Previous studies on isolated perfused dog kidneys have revealed that autoregulation varied in intensity and in some cases it was absent altogether (Haddy *et al.*, 1958). Weiss *et al.* (1959) reported that prolonged perfusion of isolated dog kidneys resulted in the loss of autoregulation. The absence of this phenomenon was explained by Haddy *et al.*(1958) as death of the organ.

This hypothesis is reinforced by studies showing the abolition of autoregulation by treatment of the organ with cyanide. In this study however, no perfusions were carried out in which there was not a noticeable color difference between arterial and venous blood. This observation does not rule out the possibility of the structures responsible for autoregulation being dead, but it does indicate that there was oxygen uptake in some portion of the organ.

Figures 7 through 15 illustrate the relationship between

mean peritubular capillary pressure and post-peritubular capillary resistance.

There are several possible explanations of this phenomenon. The rise in post-peritubular capillary resistance could be brought about by a reflexly induced vasoconstriction. The pressure sensitive receptors would then be located in the peritubular capillary bed. Such a reflex was proposed by Lochner and Ochwadt (1954) although he did not locate the receptors. Further studies will be necessary before this theory can be adequately evaluated. The observation that peritubular capillary pressure is essentially identical with interstitial pressure (Gottschalk, 1956) allows explanation of the data from figures 7-15 on the basis of partial collapse of the intrarenal veins by the interstitial pressure. The degree of collapse is dependent upon the interstitial pressure and the resultant reduction in vessel lumina are responsible for the increase in resistance (Replogle, 1960). Hinshaw et al. (1959) has recently reported a close relationship between interstitial pressures as measured by renal puncture and total renal resistance.

Figures 16-21 are presented to demonstrate the relative contributions of the pre- and post-peritubular capillary resistance to the total renal resistance. In every case in which autoregulation is seen, the rise in total resistance (R_K) is derived from increases in post-peritubular capillary resistance (R_T) (Figures 16, 18, 20). The pre-peritubular capillary re-

sistance (R_p) tended to remain constant, or to decrease with increased blood flow. Theories explaining autoregulation as renal arteriolar constriction (Forster and Maes, 1947, Shipley and Study, 1951, Thompson et al., 1957, Haddy et al., 1958) would place the resistance increases of autoregulation proximal to the peritubular capillary bed. Such theories are incompatible with the findings presented in figures 16-21.

Pappenheimer's plasma skimming theory (Pappenheimer and Kinter, 1956) would place the resistance rise in shunts parallel to the peritubular capillaries. At high flows the blood presented to the veins draining the peritubular capillaries would be relatively cell poor and thus less viscous. This should result in a lower apparent resistance in the post-peritubular capillary vessels. The data presented in figures 16-21 appear to be in sharp disagreement with this theory. The resistance in question appears to be elevated, if anything.

Lochner's theory that autoregulation was due to an intrarenal reflex did not specify the location of the pressure sensitive structures nor the site of the reflex vasoconstriction. In order for this theory to fit the findings of this study, the location of the vasoconstriction must be somewhere in the vascular system beyond the peritubular capillary bed, and the pressure sensitive structures located in the peritubular capillaries. The sparcity of muscle in the vein walls would cast doubt on theories crediting autoregulation to generalized renal vein constriction and no well

differentiated renal vein sphincters have been described. Histological evidence of peritubular capillary pressure receptors is also lacking.

Replogle's theory of partial collapse of the intrarenal veins by interstitial pressure is in agreement with these findings, however, a precise explanation of the physical principles involved has not yet been accomplished.

The venous sinusoidal cushions (Koester et al., 1955), by virtue of their location and structure, should also be considered as a possible source of this changing resistance. If these structures were to become engourged, and distend into the vascular lumina as the interstitial pressure was increased, the resultant reduction in venous lumina could account for the resistance rise.

None of these theories offer a ready explanation of the effect of cyanide on the kidney. It is known that cyanide abolishes autoregulation (Lochner and Ochwadt, 1954) but little is known of the mechanism by which this is accomplished.

The two cases of lack of autoregulation (Figures 17, 21) appear to have little in common. In Figure 17 there is a rise in the post-peritubular capillary resistance as the blood flow increases, but this is offset by a similar drop in pre-peritubular capillary resistance. Figure 21, however, shows very little change in pre- or post-peritubular capillary resistances at flows above 50 cc/min. No explanation is offered for the lack of post-peritubular capillary resistance response to peritubular capillary pressure increases in this perfusion.

SUMMARY AND CONCLUSIONS

(1) Isolated dog kidneys were perfused with the dogs' own blood at varying arterial and venous pressures. Direct measurement of arterial and venous pressure, and blood flow, and a n indirect measurement of the mean peritubular capillary pressure allowed calculation of the total renal resistance to blood flow and the resistances imposed by its pre- and post- peritubular capillary segments. These resistances were calculated at a variety of blood flow rates.

(2) Autoregulation as manifest by rise in resistance at high flow rates, was present in the majority of the kidneys perfused.

(3) The data indicate a linear relationship between the mean peritubular capillary pressure and the post-peritubular capillary resistance.

(4) Simultaneous determinations of pre- and post-peritubular capillary resistances at varying flow rates supplied evidence that post-peritubular capillary resistance changes are the cause of renal autoregulation. This mechanism furnishes a new explanation for the autoregulation phenomenon.

APPENDIX 1

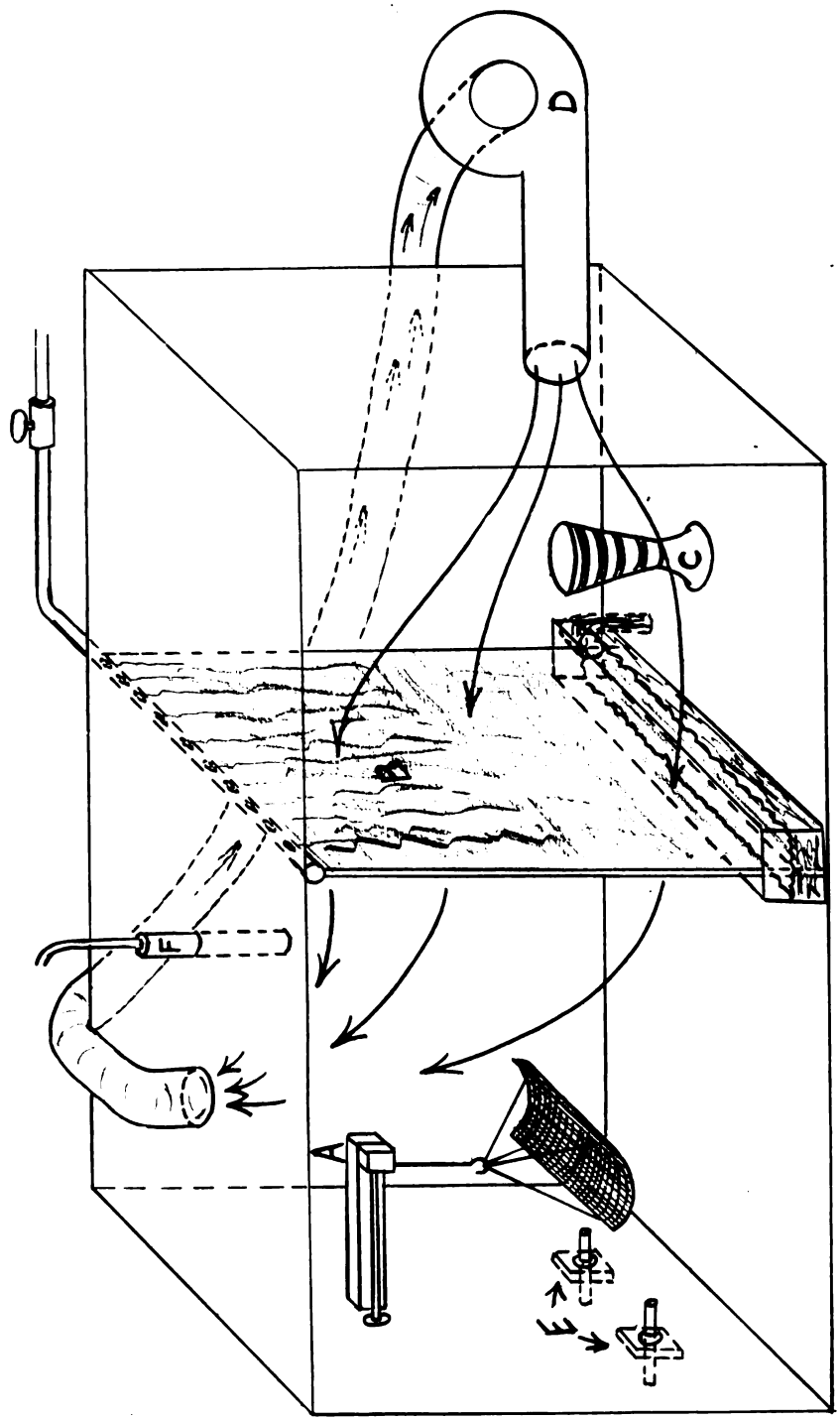
PERFUSION CHAMBER

The perfusing chamber was designated to bathe the kidney in an atmosphere of 100% relative humidity at 38°C. The air was continuously recirculated through a blower powered duct system. Steam was introduced into the duct to saturate the air at that point. A wet burlap screen separated the chamber into two compartments. All circulating air was forced through this screen and evaporation from it contributed to atmospheric saturation with water vapor.

Temperature control was accomplished by use of an electric heater placed on the side of the screen opposite the kidney. The heater was controlled by a thermostat placed in the roof of the chamber above the kidney.

The weight transducer was mounted in the roof of the chamber with the kidney in a wire basket suspended from it.

The pressure transducers were mounted on the exterior of the perfusing chamber and connected to the cannulae by polyethylene T tubes. Polyethylene extentions of the femoral cannula and venous draining apparatus were rigidly attached to the wall of the chamber at the height of the kidney and provided points for attachment of the renal vascular cannulae.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APPENDIX 2

VENOUS BUBBLE TRAP

The overflow drain from the venous pressure apparatus to the Sigma Motor Pump was open to the atmosphere and consequently air was mixed with the blood being pumped back to the animal. This mixture was pumped into a reservoir which drained into the donor dog's femoral veins. The bottom of the reservoir narrowed to a 1 cm inside diameter polyethylene tube that was placed vertically so that its lower most portion was at the level of the animal's spine. From here cannulae ran upward to the femoral veins. Under static conditions the level of blood in this vertical tube was determined by the animal's venous pressure. The animal would have to develop a strong negative venous pressure in order to lower the blood level in the reservoir sufficiently for entry of air into the vascular system.

APPENDIX 3

AN APPARATUS FOR THE REGULATION OF VENOUS PRESSURE

Venous pressure was maintained by the level of a column of blood with relation to the kidney. The tubing used was of sufficient diameter that its resistance to blood flow was negligible. The pressure was maintained at a constant value by delivering the blood to a point beneath the surface of a reservoir which was open to the atmosphere. This fluid level was governed by an overflow tube. By adjusting the height of the overflow reservoir venous pressure could be altered.

APPENDIX 4

Table 1.

PRESSURE, FLOW, WEIGHT MEASUREMENTS

P_A	P_V	P_D*	Dgm.	D%*	Qcc/min	R_T*	R_K*
		Dog 1-16-60A Kidney Weight 73.4 gm					
40/30	-9	10	9.9	13.5	54	.351	.775
50/40	-9	14	12.6	17.1	80	.300	.650
57/50	-9	23.5	17.9	24.4	106	.300	.475
80/70	-9	43.5	27.3	37.2	120	.435	.680
95/85	-9	49	29.9	40.7	128	.458	.755
		Dog 1-16-60B Kidney Weight 73.4 gm					
45/37	4	6.3	5.9	8.05	40	.058	.900
55/50	4	10.6	9.9	13.5	52	.127	.920
70/60	4	13	11.3	15.4	70	.128	.840
87/80	4	19.4	15.3	20.8	88	.175	.885
100/95	4	21.5	16.6	22.6	100	.175	.930
		Dog 1-23-60 Kidney Weight 80 gm					
85/60	2	8	24	30	104	.058	.630
87/60	2	13	28	35	108	.108	.622
96/80	3	16	30	37.4	128	.108	.640
108/90	3	19.2	32	40	136	.119	.670
115/95	3	22	34	42.5	150	.126	.652
121/108	4	25.5	36	45	168	.128	.640
125/110	3	43	40	50	180	.223	.622
132/115	3	50	42	52.5	200	.235	.590
		Dog 11-25-59 Kidney Weight 59 gm					
45/40	2	2	3.75	6.6	56	.00	.733
50/45	2	2	3.5	6.2	70	.00	.655
55/52	2	2.3	4.5	7.9	74	.004	.705
68/61	2	3.2	5.5	9.7	74	.016	.865
71/65	2	3.8	6.5	11.5	76	.024	.880
77/69	2	4	7	2	72	.028	1.00
75/70	6.5	12	9	16	66	.083	1.05
70/65	14	25.5	12.0	21	40	.287	1.35
65/52	20	37	14.5	25.5	32	.530	1.33

* = calculated values

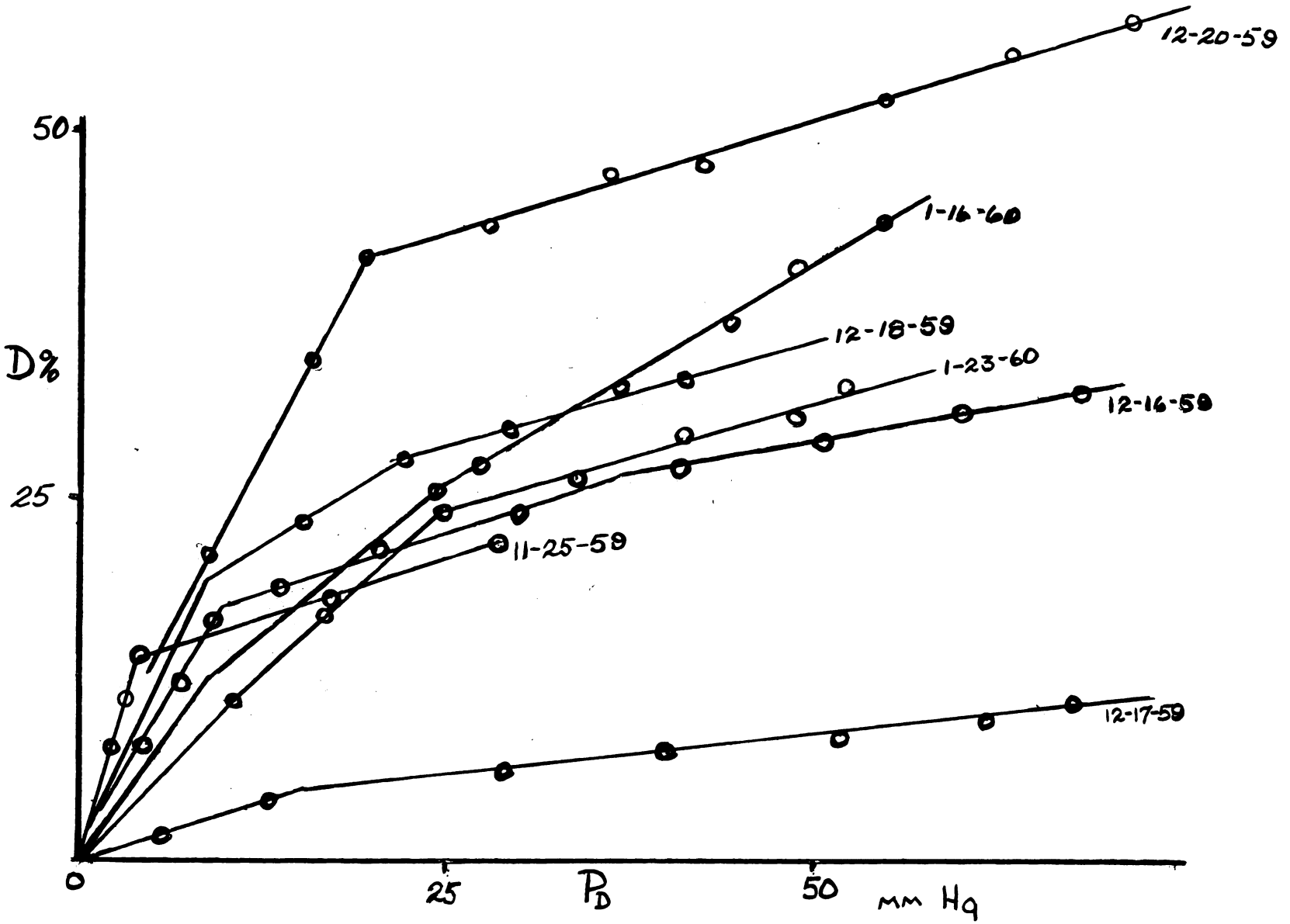
P_A	P_V	P_D*	Dgm.	D%	Qcc/min	R_T*	R_K*
		Dog 12-16-59 Kidney Weight 85 gm					
75/60	3	15	16	19	106	.113	.630
92/75	3	21.5	18	21	120	.155	.650
100/80	3	29	20	23.5	120	.216	.700
50/37	2.3	6.5	11	13	70	.057	.560
75/55	2.8	8.5	14	16.5	100	.057	.590
80/60	9	17	16.5	19.5	78	.112	.840
90/70	9	32	21	24.5	118	.195	.420
95/77	9.5	33.5	21.5	25	120	.200	.690
70/55	9.2	29	20	23.5	104	.192	.580
75/65	19	33.5	21.5	25	80	.182	.850
92/77	20	47	24	28	110	.245	.745
72/60	20	47	24	28	104	.260	.615
80/65	33.5	59	26	30.5	80	.317	.875
97/83	34	71.5	28	33	124	.302	.720
		Dog 12-18-59 Kidney Weight 58 gm					
48/42	4	8	11	19	40.5	.100	1.00
65/58	4	16	14	24	52	.230	1.08
75/68	4	18	14.5	25	60	.233	1.10
90/82	4	21.5	16	27.5	69	.253	1.17
105/95	4	29	17	29.5	72	.346	1.32
105/95	4	31	17.5	30	75	.360	1.25
70/62	11	31	17.5	30	72	.277	.905
72/62	28	41	19	33	60	.216	.940
95/85	0	21.5	16	24.5	58	.362	.660
88/77	4.5	31	17.4	30	52	.520	.650
90/80	11	34	18	31	56	.420	.675
90/82	16	34	18	31	50	.360	.585
90/80	20	41	19	33	44	.577	.532

Table 2.

STATIC WEIGHT AND DISTENDING PRESSURE MEASUREMENTS

P_D	Dgm.*	D%**	P_D	Dgm.*	D%**
Dog 11-25-59 Kidney wt 57gm			Dog 12-18-59 Kidney wt 58gm		
1.0	2.5	4.5	8.0	11.0	19.0
2.0	4.0	7.0	22.0	16.0	28.0
3.0	5.5	9.5	30.0	17.0	29.5
4.5	7.9	13.0	38.0	18.2	31.5
12.0	9.5	16.0	46.0	19.5	34.0
19.0	10.5	18.5	72.0	22.5	39.0
Dog 12-16-59 Kidney wt 85 gm			Dog 1-16-60 Kidney wt 73.4gm		
0.0	2.0	2.3	6.0	1.9	2.6
3.5	7.0	8.2	10.0	9.8	13.5
8.0	13.0	15.3	14.0	12.6	17.2
16.0	16.0	19.0	18.0	14.0	19.0
25.0	18.7	22.0	24.0	18.5	25.3
33.0	21.0	25.0	28.0	20.0	27.2
42.0	23.0	27.0	34.0	21.0	28.9
54.0	25.0	29.5	40.0	25.0	34.5
59.0	26.0	30.5	47.5	28.5	39.0
72.0	28.0	33.0	54.0	32.5	44.5
84.0	29.0	34.0	61.0	35.4	48.1
Dog 1-23-60 Kidney wt 80 gm					
3.0	2.0	2.5			
10.0	9.0	11.2			
19.0	15.0	18.7			
27.0	19.5	24.5			
35.0	21.0	26.3			
43.0	23.0	28.7			
50.0	24.0	30.0			
58.0	27.0	33.8			

* Dgm = the increase in weight due to the distending pressure.
** D% = per cent increase in weight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12-16-59
11-25-59
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D%
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