Studies of the Renal Circulation

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This work represents an attempt to confirm reported observations of a juxtamedullary by-pass in the kidneys of animals subjected to various physiologic procedures and to shock. Rabbits injected with epinephrine, pitressin, renin and hypertensin, made hypotensive by bleeding and inhalation of amyl nitrite, and after stimulation of one sciatic nerve, were injected with India ink. The kidneys were removed and studied for the paths of blood flow. No evidence of a by-pass mechanism through the juxtamedullary glomeruli was found.

Trueta and his co-workers have presented a new concept of the renal circulation. They believe that in certain physiologic and pathologic conditions the circulation of the blood through the renal cortex can be either diminished or totally arrested, while the circulation through the juxtamedullary glomeruli and medulla continues. The diversion of the blood from the cortex to the medulla is said to occur when there exist one or more of the following conditions: (1) constriction of the peripheral portions of the interlobular arteries; (2) dilatation of the vessels associated with the juxtamedullary glomeruli; (3) degeneration of the juxtamedullary glomeruli with the formation of arteriae rectae verae which are similar to "Ludwig’s arteries" in the remainder of the cortex; (4) obstruction of the glomeruli in the peripheral zones of the renal cortex.

The medullary circulation they term “the lesser circulation” or “medullary by-pass,” which consists of: (1) the most proximal portions of the interlobular arteries; (2) the first branches of the interlobular arteries, which are the afferent arterioles of the deep, or juxtamedullary, glomeruli; (3) the juxtamedullary glomeruli; (4) the efferent arterioles of the juxtamedullary glomeruli, which lie partly in the corticomedullary zone and partly in the subcortical zone of the medulla; (5) the arteriae rectae, and, probably to a lesser extent, the intertubular capillary network, which form part of the vasa recta system; (6) the venous components of the vasa recta which empty into (7) the proximal ends of the interlobular veins and the arcuate veins.

Trueta and collaborators state that in animals, under certain experimental conditions, they have demonstrated the existence of a “medullary by-pass” which is similar to physiologic and pathologic states occurring in man. They studied the course that the blood took in its passage through the kidneys by means of the injection of radio-opaque materials, various suspensions of dyes, ink, and colloidal substances. These were injected into the arterial and venous systems of the animals. Arteriograms of the kidneys were taken during life, radiographs of excised kidneys were made, and a method of taking microradiograms was devised.

During their experimental procedures many of the kidneys were exposed and their superficial surfaces and renal veins observed to determine the presence of the injected material. Blanching or paling of the surfaces of the kidneys occurred in the animals in many of their experiments, and, as a frequent accompaniment of this phenomenon, a pulsating arterial stream of blood was found in the renal vein, as was also a stream of the injected material. The blanching of the renal cortex, together with the observation of a pulsating arterial stream of blood in the renal veins, was interpreted by Trueta and his associates as a “by-pass” of the renal cortex by the blood and injected material. The renal pedicles were ligated; the kidneys were removed from the animals, sectioned, and examined to determine the route that the blood or injected mass traversed in its
passage through the kidneys. Frozen sections of the kidneys of varying thickness, both stained and unstained, as well as paraffin sections of the usual thicknesses were prepared. These sections were examined by means of the binocular dissecting microscope and single-objective microscope to determine the location of the blood or injected material in the kidneys. According to Trueta and his co-workers, the blood and injected materials were found occupying the vascular channels composing “the lesser circulation” of the kidneys when there existed, prior to the death of the animal, blanching of the renal cortex and a pulsating arterial stream of blood in the renal veins.

Trueta and his associates state that in the following experiments the circulation through the cortex of the kidneys was either diminished or totally arrested, while the circulation through the juxtamedullary glomeruli and medulla continued: (1) stimulation of the central end of the divided sciatic nerve; (2) after severe rapid hemorrhage; (3) after injections of adrenalin, pituitrin, and pitressin; (4) during inhalation of amyl nitrite.

They attributed the diversion of blood from the cortex to the medulla, in the first three series of experiments, to constriction of the peripheral portions of the interlobular arteries, while in the fourth experiment the diversion of blood was due to dilatation of the vessels associated with the juxtamedullary glomeruli. By these similar experiments Trueta and his co-workers believe they have shown that large numbers of glomeruli can be excluded from the circulating blood. The phenomenon of glomerular intermittence in the mammalian kidney may be on a vastly greater scale, according to these investigators, than in the amphibian, as reported by Richards. It is clear that the change in the course of the renal circulation outlined by Trueta and associates could be of great importance in the interpretation of normal renal physiology as well as of pathologic states due to diseases of the kidney, or of changes in other portions of the body, with secondary effects on the renal vascular pattern.

Because of the importance of the conclusions drawn by these authors, and our own interest in hypertension and renal circulation, we repeated some of their experiments. In addition, we used injections of renin and hypertensin, for the production of brief experimental rises in blood pressure, to determine whether these substances produce any changes in the pattern of blood flow through the kidneys during the periods in which the blood pressure is elevated. Thus, some of the physiologic conditions which are said to determine the by-pass of renal cortex were put to the test by means of these anatomic studies.

Experiments

Method.—Rabbits were used in all of our experiments during which they were anesthetized with intravenous Nembutal and given 1,000 units of heparin. One of the carotid arteries was cannulated and the blood pressure recorded on a moving drum. The contrast medium used for studying the vascular pattern of the kidneys was Higgins india ink, recommended by Trueta and colleagues. Fifty to 80 ml. of ink were injected under pressures averaging about 10 mm. Hg higher than the arterial pressure at the time of the injection into the distal portion of the abdominal aorta (below the renal arteries) through a cannula pointing towards the heart. The renal pedicles were ligated immediately after the injection was completed. The kidneys were then removed and placed in 10 per cent formalin. After two hours in formalin, the kidneys were sectioned and fixation was allowed to continue for twenty-four to forty-eight hours longer. Numerous specimens were taken from all portions of the kidneys. Blocks were embedded in paraffin, sectioned, and stained in the usual manner. Frozen sections of larger blocks of the kidneys were made and examined. We found that in our hands frozen sections of 100 to 200 micra were the most satisfactory. These sections were then run through the alcohols, cleared in xylol, and mounted in Clearite. Slides prepared in this manner could be examined either with the dissecting binocular microscope or the single-objective microscope with direct or transmitted light.

Experiment 1. Normal Controls.—Twelve control animals were used. Ink was injected into the distal end of the abdominal aorta. The renal pedicles were ligated immediately and the kidneys removed.
Result: In the 12 control animals all the glomeruli and the other structures of the cortex were well filled, but not intensely, with ink, while in the medulla only a few of the vasa recta contained ink (fig. 1).

Experiment 2. The Effect of Epinephrine.—Twelve animals were injected with epinephrine, 0.15 mg. per kilogram of body weight. Members of one group received only one injection, and, at the height of the rise of blood pressure, ink was injected and the animals were sacrificed. The animals of the other group received either repeated injections or a continuous intravenous infusion of epinephrine. India ink was injected, and some of the animals were sacrificed during the following stages: (1) while the blood pressure was rising, (2) while the blood pressure was being maintained at a moderately high level, and (3) during the period in which the blood pressure was falling.

Result: Although the venous pressure rose in the vena cava during the inhalation of the drug, there was no indication of a "medullary by-pass" at any stage after the injection, nor was there any evidence that a larger proportion of blood was passing through the medulla than in the normal animals.

Experiment 3. The Effect of Pitressin.—Twelve animals were given injections of pitressin, 0.75 to 2 units per kilogram of body weight. They were injected with ink and sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

Result: The animals which had received injections of pitressin differed from the controls and other experimental groups of animals (except those that received injections of renin or hypertensin) in that the cortex, medulla, and juxtedemalular glomeruli and their efferent arterioles were well filled with ink. The vasa recta in the medulla were distinct and their arterial, venous, and capillary components were also well filled with ink (fig. 2).

Experiment 4. The Effect of Amyl Nitrile Under Ordinary Conditions.—Ten animals were given amyl nitrile by inhalation, and the kidneys injected with ink at the following stages: (1) while the blood pressure was falling, (2) at the time that the blood pressure had reached its maximum drop, and (3) when the blood pressure began to rise, after the administration of the drug had been stopped.

Result: The kidneys from the group of animals which received inhalations of amyl nitrile differed from the kidneys of the other animals in two respects: (1) The entire vascular bed of the cortex, including the glomeruli, was greatly dilated and filled with a large amount of ink. (2) The large and abundant venous channels in the subcortical zone of the medulla were also strikingly filled with ink. The entire cortex and the subcortical medullary zone contained more injected material than did the corresponding areas in any of the other groups. The vasa recta were empty (fig. 3).

Experiment 5. The Effect of Amyl Nitrile Under Special Conditions.—To eliminate any change in the vascular pattern of the kidneys due to a rise in venous pressure, 4 more rabbits were given amyl nitrile by inhalation. When the blood pressure had dropped significantly, following the administration of the drug, the renal vein of one kidney (the left) was clamped near the vena cava and cut between the kidney and the clamp while the right renal vein was tied off immediately after the injection of the ink. The injection of the india ink was begun simultaneously with the section of the renal vein. Although the renal vein was cut across, there was but little bleeding from it, and but little ink came through in this blood.

Result: Although the venous pressure rose in the vena cava during the inhalation of the drug, there was no rise in venous pressure in the left kidney because of section of the renal vein. No indication of a "medullary by-pass" was demonstrated in either kidney of any of these 4 animals. In the sections taken from the left kidneys, there were ink-free areas in the cortex, and areas in which the glomeruli and intertubular capillary network were moderately well filled. It was found that the un.injected areas of the cortex were supplied by the interlobular arteries arising from the distal portions of the "arcuate arteries," while the ink-filled cortical areas were...
supplied by the interlobular arteries arising from the proximal portions of these vessels (fig. 4).

Experiment 6. The Effect of Low Blood Pressure Due to Bleeding.—Ten animals were bled from the carotid artery. The blood was allowed to flow from a T tube inserted into the tubing which connected the cannula in the carotid artery with the mercury manometer. The amount of blood removed from the animals varied from 50 to 75 cc. The animals were injected with ink when their blood pressures had dropped significantly.

Result: In all 10 animals the ink was normally distributed throughout the cortex and medulla, but there was a marked decrease in the amount of injected ink. There was no indication of a medullary by-pass (fig. 5).

Experiment 7. The Effect of Stimulation of the Central End of the Severed Sciatic Nerve.—In 11 ani-

FIG. 2.—Appearance of the cortex and medulla in a rabbit injected with ink at the time of maximum rise of blood pressure following an injection of pitressin (X5).

Fig. 3.—Appearance of cortex and medulla at the time of the greatest fall of blood pressure following the inhalation of amyl nitrite and injection of ink (X4).

mals the central end of the severed sciatic nerve was stimulated by faradization for periods varying from one and one-half to five minutes, during which time they were injected with ink and sacrificed.

Result: Eight of the 11 rabbits, in which the central ends of the cut sciatic nerves were stimulated by faradic current, had a normal distribution of ink in the cortex and medulla of the kidneys.

In the 3 remaining animals the peripheral portions of the renal cortex were not filled with ink. Many of the glomeruli in the deep zone of the cortex, and many of the juxtamedullary glomeruli were well filled, as were their efferent arterioles and the capillary beds of their corresponding medullary rays. The ink in the medulla was present in radially arranged vessels constituting the arteriae rectae of the corresponding ink-filled juxtamedullary glomeruli, the venae rectae, and, to a lesser extent, the intertubular capillary network comprising the remaining vascular bed of the vasa recta system. Ink-free areas in the deep zone of the cortex alternated with ink-filled areas. In many places the medulla beneath the unfilled cortex was also free of ink. In these 3 animals there was marked vasoconstriction of the main renal arteries and their branches, including their arcuate portions, with a consequent reduction in the size of the renal vascular bed (fig. 6).

The marked contraction of these vessels was best seen in paraffin sections stained with hematoxylin and eosin, or with a combination of Weigert's and van Gieson's stain. In such sections the lumen is
greatly constricted, the internal elastic membrane is wrinkled, and the media is thickened, due to the contraction of the smooth muscle. The lumen of the interlobular arteries, on the other hand, is dilated, their walls are thin, the internal elastic lamina is not wrinkled, and the smooth muscle of the media is not contracted.

*Experiment 8. Effect of Renin.*—Twelve rabbits received varying amounts of renin by intravenous injection. Renin and hypertensin were prepared by the method of Katz and Goldblatt. Ink was injected

and the animals were sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

*Result:* No "medullary by-pass" was recognized in any animal. All of the cortical glomeruli were well filled, as was the cortical intertubular capillary network. The juxtamedullary glomeruli were prominent, as were also their large efferent arterioles. All of the components forming the vasa recta system in the
medulla were well filled. The vessels in the outer zone of the medulla (Peters) contained more injected material than did the corresponding areas in any of the animals subjected to the other experiments. When the blood pressure was elevated as a result of

Experiment 9. Effect of Hypertensin.—Twelve rabbits received varying amounts of hypertensin by intravenous injection. They were injected with ink and sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the

height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

Result: In none of these animals was any anatomic indication of a “medullary by-pass” found. All of the cortical glomeruli were well filled with ink.

Fig. 6.—Sagital section of the kidney of a rabbit injected with ink during stimulation of the central end of severed sciatic nerve (X3).

Fig. 7.—Appearance of the cortex and medulla after ink injection at the time of the maximum rise of blood pressure following the administration of renin. Note the marked filling of the vasa recta systems in the medulla and the prominent juxtamedullary glomeruli (X6).
The cortical intertubular capillary network was only moderately well filled with ink. The juxtamedullary glomeruli were prominent and large and their efferent arterioles were also well filled. The animals that received hypertensin differed from all the other groups in that the ink in the glomeruli was more concentrated. If the renal vein was not ligated immediately after the injection of the ink, the intertubular capillaries of the cortex and vasa recta system in the medulla began to clear, while the glomeruli remained well filled and contrasted markedly with the poorly filled intertubular capillaries of the cortex. This latter observation suggests that there is constriction of the efferent arterioles of the glomeruli after the administration of hypertensin. This is consistent with the finding of Corcoran and Page that the intertubular capillary network were ink-filled. In the 3 rabbits in which at least a part of the superficial cortex was not filled it is difficult to interpret of what importance, if any, was the exclusion of this portion of the cortex from the renal circulation, since it occurred only during stimulation of the nerve.

It is our opinion that vasoconstriction in the distal portions of the arcuate arteries resulted in the exclusion of the ink from the cortex supplied by the interlobular arteries arising from this portion of these vessels. Blood continued

![Fig. 8.—Appearance of the cortex and medulla following ink injection at the time of the maximum rise of blood pressure after the injection of hypertensin. Note the prominence of the ink-filled glomeruli (×8).](image)

dition of hypertensin produces a rise in the glomerular filtration fraction (fig. 8). The marked concentration of ink in the glomeruli occurred also in the rabbits that received renin and were sacrificed during the period in which the blood pressure was rising.

**Discussion**

The results which we obtained, with the exception of those in some of the animals in the group in which the proximal end of the severed sciatic nerve was stimulated, were not in agreement with the reports of Trueta and collaborators. In none of the animals was the existence of a true “medullary by-pass” demonstrated. In most of the animals the superficial and deep cortical glomeruli as well as the cortical intertubular capillary network were ink-filled. The animals that received hypertensin differed from all the other groups in that the ink in the glomeruli was more concentrated. If the renal vein was not ligated immediately after the injection of the ink, the intertubular capillaries of the cortex and vasa recta system in the medulla began to clear, while the glomeruli remained well filled and contrasted markedly with the poorly filled intertubular capillaries of the cortex. This latter observation suggests that there is constriction of the efferent arterioles of the glomeruli after the administration of hypertensin. This is consistent with the finding of Corcoran and Page that the intertubular capillary network were ink-filled. In the 3 rabbits in which at least a part of the superficial cortex was not filled it is difficult to interpret of what importance, if any, was the exclusion of this portion of the cortex from the renal circulation, since it occurred only during stimulation of the nerve.

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areas in the renal cortex. A few of these involved the whole width of the cortex, but the majority were composed of only the superficial, most peripheral glomeruli and subcapsular intertubular capillary network. In the latter instance, the distal portions of the interlobular veins in the areas containing no injected fluid were filled with ink. It is our opinion that the injected ink had already passed from the glomeruli and intertubular capillaries into the veins. In the first instance, in which the whole width of the cortex contained no injected fluid, we have found that these areas were supplied by the interlobular arteries arising from the first por-

tion of the arcuate vessels. The ink, therefore, passed through this portion of the cortex first, and, when the kidneys were examined, it was found in the arcuate veins and the venous channels of the corticomedullary zones which drain these regions (fig. 9).

We think that the increased amount of ink in the venous channels which occurs during the administration of amyl nitrite is due to the rise in venous pressure which occurs simultaneously with the fall in the arterial pressure. The most significant effect of this drug on the renal circulation appears to be on the venous side, with marked dilatation of the cortical intertubular capillary network. The injected ink passes through the arterial side of the renal circulation into the dilated venous capillaries and is impeded in its flow from the interlobular and arcuate veins by the rise in venous pressure. Large amounts of the injected ink, therefore, collect in the venous components of the vasa recta, the venous channels in the juxtamedullary zone, and in the venous components of the cortical intertubular capillary network, and there may occur some retrograde flow of ink from the venous channels of the subcortical zone of the medulla into the interlobular veins in the cortex.

In the 4 animals in which amyl nitrite was administered and the renal vein cut, we think that the fall in arterial pressure resulted in the injected ink being carried through only the proximal portions of the “arcuate arteries” and the interlobular branches arising from these segments. Ink was present in the vascular bed of the deep zone of the cortex, between the patches of cortex that were ink-filled and those containing no injected fluid. The ink was found in the arcuate arteries, the proximal ends of the interlobular arteries, the glomeruli arising from these segments, the intertubular capillary network, and the juxtamedullary glomeruli and their efferent arterioles and the corresponding vasa recta in the medulla. There was no evidence of a “by-passing” of the cortex by the blood or injected material through a “medullary by-pass” produced by dilatation of the vessels associated with the juxtamedullary glomeruli.

**Summary**

1. We were unable to demonstrate the existence of two potential circulations in the kidneys of rabbits. No “medullary by-pass” or independent circulation through the medulla occurred.

2. From our observations it would appear that the arterial blood entering the kidneys through the renal arteries passes first through the cortex and then into the medulla.

3. In the kidneys of rabbits in which the blood pressure is elevated as a result of hyper-
tensin, and in which the blood pressure is rising following the injection of renin, there is a concentration of ink in the glomeruli. This observation suggests that there is constriction of the glomerular efferent arterioles.

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