

CHAPTER 19.

RELATIONSHIPS OF FILTRATION RATE, RENAL PLASMA FLOW, AND URINE VOLUME.

The conditions which determine filtration rate are now becoming clearer. The glomerular filtration pressure, or glomerular blood pressure less the osmotic pressure of the plasma proteins, is the motive force for production of glomerular filtrate, but the resistance against which this fluid is moved from Bowman's capsule is equally important in determining the flow rate. The factors influencing this resistance are the diameter of the renal tubule, the reabsorptive rate in the tubule, and the pressure which impedes the flow of fluid along the loop of Henle (and determining intra-renal pressure). These are all determined by complex inter-relationships of forces which are not easy to predict on every occasion. For example, the glomerular blood pressure depends not only on the systemic arterial blood pressure in the renal artery, but also upon the resistance offered by the afferent arteriole, and the linear velocity of blood in the glomerular capillaries, which in turn is greatly influenced by the resistance offered by the efferent arteriole and the post glomerular blood vessels. The resistance of the efferent arteriole is subjected to the influence of various hormones, of which the renin-hypertensin mechanism is best known, and is possibly also under some nervous control.

While the osmotic pressure of the plasma proteins may be predictable, one must also assume that the velocity of blood through the glomerulus is not so great that the blood has left the glomerulus before osmotic equilibrium is reached, leaving the filtration rate less than might have been predicted from the pressure figures alone. The linear velocity of fluid entering the renal tubule might also have a significant effect upon the reabsorptive rate for tubular fluid, and the linear velocity in turn will be related to the tubular diameter, to the amount of unabsorbable material in the filtered fluid, and to the pressure exerted upon the tubule at the cortico-medullary junction. Add to this the influence of the renal nerve supply, which tends to divert blood from the cortical to the juxta-medullary nephrons, and any prediction of the filtration rate involves so many variables that it becomes fairly speculative.

Nevertheless, provided the pressure in the glomerulus is maintained above the osmotic pressure usually exerted by the plasma proteins (i.e. above 40 mm.Hg. in most experiments designed to determine the minimum blood pressure compatible with urine formation) filtration rate is largely determined by the plasma protein concentration. Any dilution of this concentration by absorption of fluid into the circulation leads to increased filtration rate which is quantitatively greater than that produced by a rise in blood pressure in the glomerulus calculated to produce an equivalent rise in filtering pressure. This is presumably because of the associated pressure changes which an increase in blood perfusing pressure produces elsewhere in the renal circulation, and which have been discussed already.

These pressure changes are themselves subject to variation, for example by efferent vasoconstriction, which alters the differential pressure between the glomerular and juxta-medullary vessels. These variations have yet to be considered in a later section. At the same time any changes in plasma protein concentration is not without significance for fluid reabsorption further along the renal tubule. For if an increased volume of fluid is filtered in the

glomerulus, presumably the plasma proteins will have returned to about the previous level of plasma protein concentration which could have been expected in the same area if no haemodilution had occurred in the first place. Now the blood of the efferent arteriole divides into two sections, one of which passes to the proximal tubule and receives the fluid reabsorbed by the proximal tubule, which presumably dilutes the protein in the blood again to an appropriate level. The other section of blood from the efferent arteriole passes directly to the juxta-medullary region by way of the vasa rectae (spuria), where it is presumably diluted again by fluid reabsorbed in the vicinity of the loop of Henle. It has already been proposed that differential pressure exists in this area between the blood vessels and the tubules, and this could be expected to resist the passage of reabsorbed fluid into the blood vessels (whatever the reabsorptive capacity of the tubule cells might be) and if this differential pressure is great enough, help to retain fluid within the tubules where it would eventually pass to the collecting tubules producing diuresis of a greater degree than might otherwise occur. Such an effect would be independent of the presence or absence of the anti-diuretic hormone produced by the pituitary. It could be expected to be present whenever the 'intra-renal pressure' is increased, as in dilution and osmotic diuresis, and also as a contributing factor in water diuresis (in addition to the diminution of concentration of anti-diuretic hormone). With increased perfusion pressure on the other hand, there is little alteration of 'intra-renal pressure', and this effect on reabsorption would not be expected. A profuse diuresis does not occur in this condition, although sodium excretion is increased and urine volume may increase accordingly.

In the experiments of Sellwood and Verney on water and saline diuresis in the conscious dog which have been described previously, there was not only an increase in filtration rate which, at least initially, was probably induced by haemodilution, but also an increase in renal plasma flow so that the two phenomena appear to be associated at least in some degree, though differences appear which are more pronounced in the absence of the nerve supply. Increasing haemodilution can be presumed to occur until absorption of fluid from the gut is balanced by transfer of intravascular fluid to the extravascular compartment. Once absorption from the gut diminishes, equilibrium between intra-vascular and extravascular fluid will occur with some further haemoconcentration again until the intravascular volume is adjusted to the circulatory needs (as outlined in the first section of the book.)

Dilution of the plasma protein concentration seems to be the initiating factor in the production of these changes in the renal circulation, resulting in increased filtration rate and renal plasma flow. Now diuresis is associated with increased renal tubular diameter, and this presumably follows the increased filtration rate. If oxygen consumption in the kidney is linked to renal tubular diameter as suggested in earlier chapters, then an increase in tubular diameter will lead to a fall in renal oxygen tissue tension unless renal blood flow is increased. Such an increase in blood flow seems to occur with increased renal tubular diameter, and as in the general tissues of the body, this could well be in response to a fall in tissue oxygen tension in the active cells. It would mean dilatation of the afferent arterioles in the first instance, and these vessels are separated from the renal tubules by a considerable distance except in the region of the macula densa, where the distal tubule becomes closely associated with the afferent arteriole as it enters the glomerulus. The suggestion is that a hormone is produced in the renal cells in response to a fall

in oxygen tension, which is then conveyed in the fluid in the proximal tubule until it reaches the site of the macula densa, where it affects the musculature of the afferent arteriole and is then rapidly destroyed by the blood before it passes beyond the glomerular capillaries to the region of the efferent arteriole. Such a hormone has been found in normal urine (and other body tissues) which is only active in an acid environment such as is likely to occur when the oxygen tension falls and relatively 'anaerobic' metabolism might be expected to become more prominent, or acid metabolites accumulate. It is rapidly inactivated in the blood, so that its activity is purely local.

This substance was called "Kallikrein" by its discoverors (Frey and Kraut, 1926) and it has the properties which would make it suitable to act in this way. It is proposed then, that the increase in filtration rate produced by haemodilution, brings about increased tubular diameter, increased oxygen consumption, lowered oxygen tension, release of 'kallikrein type' substance into the tubule which then affects the afferent arteriole and increases blood flow, after a short time lapse. (Some of the dilator substance could pass further along the tubule, and appear in the urine).

This comparatively simple mechanism is not sufficient of itself to increase blood flow. On its own, the increase in pressure in the glomerular capillaries, does not alter blood flow unless the 'intra-renal pressure' is also increased. To increase the differential pressure between the vessels and the tubules in the juxta-medullary region, some dilatation of the efferent arterioles is also necessary, and this requires an entirely different mechanism which involves the renin-hypertensin system.

Renin is also released from the proximal convoluted tubule cells when tubular activity is restricted so that oxygen concentration is reduced. But a restricted tubular diameter does not mean a reduction in the reabsorptive work which the tubule performs. On the contrary, it is more likely to mean an increase in the rate of reabsorption of sodium and water, or in other words, an increase in the mechanical efficiency in performing reabsorptive work. If the reabsorptive rate for sodium and water increases, so does the filtration rate, while the oxygen consumption is related to tubular diameter. The ratio of sodium reabsorption / oxygen consumption will then become proportional to the ratio of filtration rate / renal plasma flow, or the filtration fraction (assuming that the haematocrit is constant, and that oxygen consumption, or tubular diameter is also proportional to renal plasma flow). The renin mechanism functions to regulate this relationship, so that the renal tubular diameter is maintained by regulating the filtration fraction through the degree of constriction of the efferent vessels, and also of the differential pressure between vessels and tubules in the juxta-medullary region. When the diameter of the proximal convoluted tubule is reduced, by whatever method, the ratio of sodium reabsorption / oxygen consumption is increased. The release of renin on the other hand, appears to follow a reduction of oxygen partial pressure relative to sodium reabsorption. Its shortest route to the glomerular vasculature is again by way of the renal tubule to the site of the macula densa, where it enters the afferent arteriole. Renin itself is an enzyme, and has no vasoconstrictor properties. By reaction with the blood proteins, it produces hypertensin, but by this time the blood has passed to the efferent arterioles, where vasoconstriction occurs. Any excess hormone is rapidly destroyed by normal renal cells, provided their oxygen content is sufficient. Dilatation of the proximal tubules reduces the ratio sodium reabsorption / oxygen consumption, but also reduces oxygen

concentration and increases renin production, which eventually allows an increase in filtration fraction by constriction of the efferent arteriole.

Applying this hypothesis to the differences in the response of the renal circulation to water and saline diuresis in the conscious dog, an explanation becomes possible for these observations. When saline solution is given to the animals with intact renal innervation, haemodilution occurs and in turn produces a dilution diuresis. An increase occurs in the filtration rate, but without any overall pressure changes in the kidney of any significance, because the increased filtrate is isotonic saline solution, which is rapidly reabsorbed without significant change in tubular diameter or volume. There is then little change in renal plasma flow, any increase in tubular diameter being more than matched by increased reabsorption of sodium and water, so that any slight afferent dilatation is matched by a slight efferent constriction from increased renin production. Most of the increase in filtration rate and filtration fraction is mechanical, following haemodilution, as is the increase in urine flow, the pressure differential between the ends of the proximal tubule having been increased as increasing filtration rate reduces blood volume proceeding to the efferent arteriole and beyond, and allowing more of the filtrate to reach the distal tubule. Any tendency for dilatation of the renal tubule is restricted by the action of the renal nerve supply on the afferent arterioles. Removal of the renal nerve supply, removes this restriction from the afferent arterioles, and both glomerular filtration rate, and renal plasma flow increase accordingly, but without any further increase in filtration fraction which is still largely mechanically determined by haemodilution, as is the increase in urine flow. The ratio of kallikrein type hormone to renin type hormone is presumably increased after denervation, because the tubules have been able to dilate, the oxygen consumption to increase, and the subsequent fall in oxygen tension prevented in some degree by increased blood flow.

The picture after water administration is different because of the different composition of the glomerular filtrate. Haemodilution occurs in the same way, and the glomerular filtration rate increases to the same degree, as it does following saline administration in the normally innervated animal. The filtration fraction is little changed because there is now also an increase in renal plasma flow. If the renal innervation limits any increase in tubular diameter, the increase in plasma flow must result from efferent dilatation. This implies that though the tubular diameter is unaltered, sodium reabsorption has been reduced because the glomerular filtrate now has more water and less salt than after saline administration, and sodium reabsorption is reduced as the filtrate becomes a more dilute salt solution. The ratio of sodium reabsorption / oxygen consumption is then reduced, while oxygen concentration is maintained and renin production partly inhibited, and efferent vasodilatation eventually follows. The diuresis is greater than that seen after saline, because it is a classical water diuresis from inhibition of anti-diuretic hormone from the pituitary. When the nerve supply is removed, all of these changes are accentuated because the tubules can now increase in size to a greater degree. The oxygen utilisation may increase and the oxygen tension fall initially, so that the vasodilator hormone of the kallikrein type is increased. But sodium reabsorption is still reduced because the glomerular filtrate remains hypotonic, sodium reabsorption / oxygen consumption becoming further reduced.

Provided oxygen partial pressure is maintained, renin production is further inhibited, and the filtration fraction falls, while renal plasma flow increases to an even greater degree. The water diuresis may be augmented still further by these mechanical changes. The result of denervation of the kidney on the circulatory changes occurring in the kidney during water diuresis is to increase renal plasma flow and reduce filtration fraction, while the glomerular filtration rate is little altered. With saline administration on the other hand, denervation allows an increased filtration rate and renal plasma flow, but with little change in filtration fraction, from the normally innervated state. These complicated adjustments occur through interaction of hormonal and mechanical mechanisms, and they are further modified by the presence of the normal renal innervation.

The volume of urine produced must depend on the production of an adequate volume of glomerular filtrate and also on the reabsorptive and/or excretory function of the renal tubule. While the production of glomerular filtrate, and the main circumstances which affect it have been examined, the factors which determine tubular reabsorption require further discussion. In the case of water diuresis the dominant position occupied by the anti-diuretic hormone of the posterior pituitary gland in determining the volume and composition of the urine is clearly established. In other forms of diuresis, mechanical factors play a more dominant role. These same factors are present in water diuresis and have already been described, but they are overshadowed in importance by the effect of the pituitary hormone. In pressure diuresis on the other hand, mechanical conditions acting upon the renal cells and blood vessels and affecting the release of the renal hormones occupy a more prominent position. When the pressure rises in the glomerulus, without any accompanying change in the osmotic pressure of the plasma proteins, there may be no change in glomerular filtration rate or renal plasma flow, because changes in pressures in the tubules and vessels which act to prevent any change in these parameters, will have the effect of producing increased diameters of the proximal renal tubules, with subsequent increases in renal oxygen consumption and reduced sodium reabsorption. In the absence of the renal nerve supply, this allows a greater volume of filtrate which contains more sodium as well as water, because of the reduced rate of reabsorption. Although many modifications to its composition still occur in the distal tubule, the amount of sodium excreted is increased together with additional water, so that the final result is an increased volume of urine, but with an equal concentration of sodium as before the pressure was raised. Raising the pressure (and diameter) of the tubules inhibits reabsorption and increases the excretion of urine, provided the pressure is not sufficient to reduce the filtration rate. A similar mechanism probably also operates during dilution diuresis and also during osmotic diuresis. In dilution diuresis, continuing dilution of the plasma increases the urine flow and sodium excretion while the dilution is increasing and still producing increasing dilatation of the renal tubules. (v.infra.)

With osmotic diuresis, the distention of the tubules with unabsorbable material, not only ensures a greatly increased volume of fluid passing to the distal tubule, but also greatly increases the oxygen consumption of the kidney (Barcroft and Straub, 1910). In effect then, increasing the diameter of the renal tubules has a significant effect in increasing the volume of urine which is produced. All this is greatly modified by the renal innervation, although the effect is not

uniform, and affects the more peripheral cortical nephrons to a greater degree than those in the juxta-medullary region, and this will be further discussed in a later chapter.

Before leaving the subject of osmotic diuresis, the special position occupied by urea needs to be mentioned. This product of the deamination of amino-acids is the main nitrogenous excretion product in primates as it is in most other mammals, and the control of the level of urea, together with the regulation of extracellular fluid volume is a very important function of the kidney. It is not surprising then that these two are closely associated functions, and difficulty in controlling one is frequently accompanied by some abnormality regarding the other. Urea is excreted by filtration in the glomerulus and concentration in the distal tubule, where it acts as an osmotic diuretic, but in the proximal tubule it diffuses readily through the tubular cells, so that its concentration in the reabsorbed fluid is the same as that remaining within the tubules. The amount excreted therefore depends both on the filtration rate, and also (as a consequence) upon the linear velocity of fluid in the proximal tubule. When the reabsorptive rate of sodium and water in the proximal tubule is increased, so is the absorption of urea. If filtration rate is reduced, while sodium reabsorption is high, the urea concentration of the blood will be increased, until the level of blood urea is sufficiently high to allow the excretion of all the urea produced. A raised blood urea is found when the filtration rate is reduced, particularly when the sodium reabsorptive rate is high. This state of affairs is most likely to appear when the extra-cellular fluid volume is depleted. On the other hand filtration rate is increased and a greater quantity of sodium excreted, when the extra-cellular fluid volume is increased, as in saline administration. For this reason saline and urea excretion often appear to be associated, and both require an adequate extra-cellular fluid volume, if the kidney is to maintain a satisfactory blood level of each. The circulatory conditions which need to be fulfilled so that the kidney is enabled to perform this function, are of fundamental importance to the further consideration of blood pressure maintenance. That the diameter of the renal tubules needs to be regulated so that a proper balance is maintained between the reabsorptive work and the oxygen consumption, becomes increasingly evident as the forces within the kidney are analysed. In order to maintain that balance, the neural, hormonal, and mechanical factors which have been outlined, all have a part to play, but of these the osmotic pressure exerted by the plasma proteins, is probably the key factor, once an adequate perfusion pressure has been provided to allow filtration to take place.

In the next chapter an investigation is described, which became the basis of the relationship which has been shown to exist between reabsorption, oxygen consumption and filtration fraction in the kidney of the rabbit, after the effect of the renal nerve supply had been removed by the prior use of hexamethonium.