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exclude other factors; in "renal" hypertension this process is initiated somehow by the kidney; similar examples might be invoked for other "forms" of hypertension. We plan to continue testing this working hypothesis.

SUMMARY AND CONCLUSIONS

Chronic excess salt ingestion will induce permanent hypertension in rats. Several biological factors modify the response to salt including: (a) the age at which salt-feeding is begun; (b) sex; (c) average daily amount of salt consumed; (d) duration of salt-feeding; and (e) variations in genetic sensitivity to salt.

The importance of the genetic factor(s) was demonstrated by the technique of selective inbreeding, with which two strains of rats were developed, one of which was very prone, the other very resistant, to the development of hypertension after chronic excess salt-feeding. Using these two strains of rats, similar marked differences in blood pressure response were observed both after a manipulation used to induce renal hypertension as well as after administration of salt plus desoxycorticosterone acetate (DOCA).

The genetic background critically controls the response to factors used to induce three "varieties" of experimental hypertension. Therefore, we suspect that this genetic-environmental interaction will prove true for other, possibly all, experimental models of the disease. Similar interactions probably operate in the hypertensive process of man.

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Sodium, Renal Arterial Distension and the Juxtaglomerular Apparatus

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SEVERAL lines of evidence indicate that the renin in a kidney is located in the juxtaglomerular apparatus. Therefore some consideration of the juxtaglomerular body is appropriate for this Symposium. In mammals, one part of the apparatus consists of cells with secretory granules in their cytoplasm. When stained with the Bowie stain, one can see that these cells actually lie in the medial layer of the afferent glomerular arteriole. Thus, if the wall of the afferent arteriole is distended, these cells will also be distended. Conversely, if the wall is underdistended, the cells will undergo a reduced stretch. Their anatomical position may have important implications. When one sees an abundance of juxtaglomerular granules in a section, it is usually a sign of hypersecretion. Conversely, when one sees few juxtaglomerular granules, it signifies a slow rate of secretion. Furthermore, various situations which would be expected to reduce the distension of the renal arterial bed tend to increase the granularity of these cells. And situations which increase the distension of the renal arterial bed tend to decrease their granularity. Thus, a diminished stretch of the cells appears to promote hypersecretion and an increased stretch is accompanied by a low rate of secretion. A few examples of underdistension of the renal arterial bed could be as follows:

First, adrenal insufficiency lowers blood volume and arterial pressure and increases the number of juxtaglomerular granules. The renal artery bed would tend to be underdistended in this situation.

Second, narrowing one renal artery decreases the distension of the arterial bed downstream from the constriction, especially during systole. This is often associated with an increased number of juxtaglomerular granules.

Third, if an ischemic kidney is removed in a rat with unilateral hypertension, the blood pressure comes down to normal and the extracellular fluid volume is probably somewhat less expanded. These effects should decrease the distension of the renal arterial bed. Concomitantly, the juxtaglomerular granules in the remaining kidney rapidly increase toward a normal abundance.

Fourth, many conditions associated with sodium retention and edema formation are also associated with increased juxtaglomerular granularity. Nephrotic edema in the rat, cirrhosis with a large amount of ascites in man, sodium retention following vena caval narrowing in the dog, congestive heart failure with edema in man, congestive heart failure in the dog due to an arteriovenous fistula, all of these are associated with an overabundance of juxta-

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glomerular granules. Moreover, in all five of these situations, there is reason to believe that there is an underdistension of the whole arterial tree including the renal arterial bed.

Fifth, either a drastic restriction of sodium intake or the administration of chlorothiazide increases juxtaglomerular granularity and also tends to produce a lowered blood volume. If this reduction in volume is shared by the arteries in the kidney, there should be a decreased stretch of the renal arterial bed associated with the abundant juxtaglomerular granules.

Sixth, an acute narrowing of the aorta just above the renal arteries causes an increase in the output of aldosterone within 10 minutes. Presumably this is caused by the release of an aldosterone-stimulating hormone from the juxtaglomerular apparatus. The acute constriction would be expected to diminish the stretch of the afferent arterioles with their granular juxtaglomerular cells.

On the other hand, an increased distension of the renal arterial bed seems to be associated with a diminished number of juxtaglomerular granules and, therefore, with a decreased rate of secretion by these cells. The following are some examples of this:

First, either desoxycorticosterone plus salt or large amounts of salt alone decrease JG cell granularity. Both of these ministrations would be expected to increase blood and ECF volume and therefore increase the distension of the renal arterial bed.

Second, three forms of an experimental hypertension cause a diminished juxtaglomerular granularity. These include metacorticoid hypertension, adrenal regeneration hypertension, and the hypertension which remains after the late removal of an "ischemic" kidney. All three of these types of experimental arterial hypertension probably increase the stretch of the renal arterial bed.

Third, the kidney which is contralateral to a kidney with a narrowed renal artery always gets a great reduction in granules. This kidney may be exposed to hypertension, but not necessarily in all cases. However, the ischemic kidney retains sodium and water which this contralateral kidney is obliged to excrete. This retention of salt and water tends to expand ECF and blood volume, which in turn would tend to increase the distension of the renal arterial bed and the JG cells in the contralateral kidney.

Fourth, isolated kidneys which have been mechanically perfused for two hours at a high pressure show considerable degranulation. Such a perfusion undoubtedly stretches the renal arterial bed and the JG cells.

In this compilation of examples, situations which understretch the juxtaglomerular cells are associated with hypersecretion and situations which overstretch them are all associated with a low secretory level. The granular cells thus appear to act as stretch receptors which vary their rate of secretion with different degrees of stretch. In this way they influence the rate of aldosterone secretion and release varying amounts of renin into the blood and lymph. We were interested in other possible actions of the kidney which might be controlled by varying degrees of distension of the renal arterial bed. The signal for such actions could come from the granular juxtaglomerular cells. I would like to describe two such actions.

In one of these experiments, an isolated normal kidney from one rat was connected to the circulation of another rat and received blood from it. The perfusing rat had neither kidneys nor adrenals. The isolated kidney was perfused for 55 minutes, a so-called "preparatory" perfusion, and was then put through a stop-flow procedure. In half the experiments, the isolated kidney was perfused at 170 mm. Hg during the preparatory perfusion. In the other half of the experiments, the isolated kidney was perfused at 100 mm. Hg during the preparatory perfusion. In all the experiments, the isolated kidneys were perfused at 100 mm. Hg during the "stop" period of the stop-flow procedure. Thus the hemodynamics of the actual stop-flow procedure were the same in all the experiments, even though the conditions for the preparatory perfusions differed. At the end of the "stop" period, the clamp on the ureter was released and each drop of issuing urine was analyzed for its sodium concentration. The characteristic dip in sodium concentration was seen in all these experiments; and the lower the dip in sodium concentration, the greater the net transport of sodium out of distal tubular urine.

The results indicated that after a 55-minute perfusion of the isolated kidneys at 170 mm. Hg, the tubular cells in the distal part of the nephron have a relatively limited ability to effect a net transport of sodium out of the distal tubular urine in a "stop-flow" situation. In a series of experiments utilizing this high perfusion pressure, the lowest concentration of sodium in the stop-flow studies averaged 14 mEq./kg. of urine. Contrariwise, after a 55-minute perfusion at 100 mm. Hg, the distal tubular cells have a relatively enhanced ability to effect a net transport of sodium out of the distal urine. In a series of experiments utilizing this lower perfusion pressure, the lowest concentration of sodium in the stop-flow studies averaged 8 mEq./kg., a significantly different level.

This difference in net transport of sodium seems related more to the perfusion pressure than to the rate of blood or urine flow. Renal hemodynamics and the rate of flow in the renal tubules during the "stop" period can not account for the difference. The difference in net sodium transport does not

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depend upon a changing rate of aldosterone secretion or upon neurogenic reflexes from the central nervous system. It would appear that changing the distension of the renal arterial bed by altering perfusion pressure somehow influences the ability of the distal tubular cells to effect a net transport of sodium, underdistension increasing transport and overdistension decreasing it.

The author would like to speculate that the varying levels of perfusion pressure are sensed by the juxtaglomerular cells, acting as stretch receptors. The juxtaglomerular apparatus (granular cells + macula densa cells) then appropriately responds by changing its rate of secretion. The concentration of these secreted substances in the fluids of the kidney then regulates the net transport of sodium out of the distal convoluted tubule and collecting duct, acting in concert with the tissue levels of aldosterone. This mechanism is probably active in various sodium-retaining situations associated with the underdistension of the arterial tree. It may also partly explain the phenomenon of the Howard test.

In the other experiment to be described, an isolated kidney from a normal rat was connected to the circulatory system of a rat with hypertension that has resulted from a narrowed renal artery in its one remaining kidney. The isolated kidney was connected artery-to-artery and vein-to-vein.

In 11 such experiments, the isolated normal kidney was perfused with the full force of the hypertensive levels of blood pressure. In 13 other experiments, a variable resistance in the arterial connection to the isolated kidney allowed us to perfuse the isolated kidney at low normal levels of pressure (85-95 mm. Hg). When the normal kidney was perfused with the higher arterial pressure for two hours, there was a distinct drop in the arterial pressure of the hypertensive rat to a level one-third of the way toward normal (see Fig. 1). When the normal kidney was perfused at low normal pressures, virtually no drop in the arterial pressure of the hypertensive rat occurred. Apparently the antihypertensive mechanism of a normal kidney behaves appropriately, being brought into action by a high arterial pressure and being held in check by low normal pressures. This would appear to be a feed-back arrangement designed to maintain normal arterial pressures. It is quite possible that the varying levels of perfusion pressure are sensed by the granular juxtaglomerular cells of the isolated kidney. These cells could then appropriately change their rate of secretion, and thereby regulate the antihypertensive action of the isolated kidney.

It is possible that the actions of the sympathetic nervous system amplify the signal which is received by the stretch receptors of the juxtaglomerular apparatus. It is known that an acute loss of

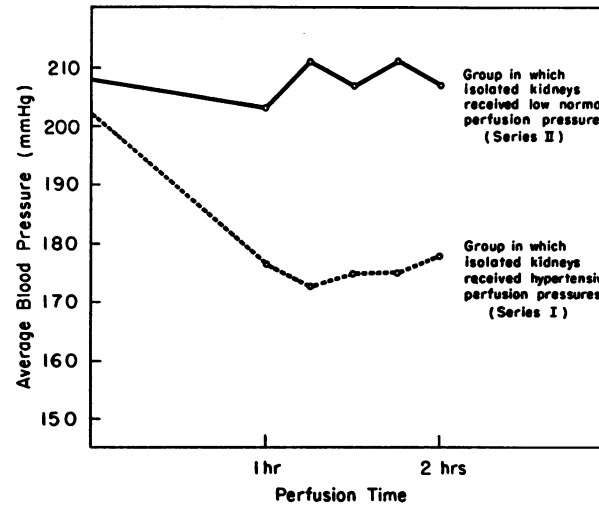

Fig. 1.—The average arterial pressure of two groups of rats with renal hypertension during a two-hour period in which an isolated normal kidney is connected to their circulatory system.

blood will stimulate the release of renin from the kidney. If an adult human subject lost only 200 c.c. of blood, the juxtaglomerular cells would become somewhat less distended but the change in distension would be minimal. However, the loss of this much blood would also stimulate the receptors in the aortic arch and carotid sinus. This would bring about an increased number of sympathetic nerve impulses arriving along the length of the afferent glomerular arteriole. If this arteriole were to become somewhat constricted, its increased resistance to flow would further decrease the pressure in the terminal part of the afferent arteriole just before it joins the glomerular tuft. This decreased pressure caused by the constriction would reinforce the effect of the original blood loss to provide even less distension of the juxtaglomerular cells. In such a way the signal to the juxtaglomerular cells may be amplified to provide even closer regulation of arteriolar distension.

The denervation experiments of Dr. Taquini lend support to the probability of this mechanism. He reports that a denervated kidney contains 40% less renin than the opposite kidney with its nerves intact. These observations were made three weeks after the denervation procedure. This timing would indicate that the denervated kidney was secreting less renin. The denervation procedure would prevent sympathetic nerve impulses from reaching the afferent glomerular arteriole. This should result in a relative dilatation of the afferent arteriole and a decrease in its resistance to flow. Thus, the arterial pressure at the juxtaglomerular end of the afferent arteriole would be relatively higher and would increase the distension of the granular juxtaglomerular cells. This would decrease the storage and secretion of renin by these cells. This experiment seems to implicate the nervous system as a factor in determining the distension of the JG cells.