STUDIES ON DIURETICS. II. THE RELATIONSHIP BETWEEN GLOMERULAR FILTRATION RATE, PROXIMAL TUBULAR ABSORPTION OF SODIUM AND DIURETIC EFFICACY OF MERCURIALS[1]

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According to Merrill (1) and Mokotoff, Ross and Leiter (2), renal plasma flow and glomerular filtration rate are characteristically low in congestive heart failure. These investigators infer that a reduction in the rate of delivery of sodium, chloride, and bicarbonate ions into tubules having essentially normal reabsorptive capacities favors retention of electrolyte and water. In line with this concept Weston and Escher (3) observed that patients who fail to exhibit a satisfactory diuretic response to intravenous mercurials often have exceptionally low filtration rates, and that the administration of aminophylline, which increases filtration rate, greatly enhances the diuresis. Others including Seymour (4), Briggs (5), and Sinclair-Smith (6) have expressed doubt that a reduction in filtration rate is either a constant or a significant finding in congestive failure, and have observed loss of edema without any accompanying increase in filtration rate or renal blood flow.

The difficulties in a clinical analysis of the role of reduced filtration rate in the pathogenesis of edema are evident. Chronic renal disease is often associated with congestive failure, and reduced filtration rate might in any given instance be more related to the former than to the latter. Furthermore, compensation is usually reestablished slowly and recovery of capacity to excrete salt and water might be more a function of readjustment of tubular absorptive capacity than of increased delivery of filtrate into the tubules. The present study on the dog was initiated with the view of establishing whether or not true glomerulo-tubular imbalance with relative overabsorption of water and salt could be induced by a reduction in glomerular filtration rate independent of changes in tubular function. Likewise it was hoped to determine whether a reduction in filtration rate would reduce the effectiveness of mercurial diuretics.

It has been found that a relatively minor (25%) reduction in glomerular filtration rate very seriously impairs the capacity of the dog to excrete a given load of water and electrolyte both under normal conditions and following mercurial diuretics. We infer from these experiments that insofar as filtration rate is reduced in congestive failure, this factor contributes to the incapacity of the individual to maintain fluid and electrolyte balance, and furthermore limits the efficacy of the commonly used mercurial diuretics. However, we recognize that such factors as increased venous pressure (7) and overactivity of pituitary and adrenal cortical water and salt conserving mechanisms (8, 9) may well play highly significant roles in the pathogenesis of edema and in the development of clinical mercurial resistance. No attempt has been made in this study to assess clinically the relative roles played by these several factors. We merely feel that we have demonstrated the fact that a reduction in filtration rate causes glomerulo-tubular imbalance, and that this imbalance must be considered as of some etiologic significance in any edematous patient who exhibits an acute reduction in filtration rate.

METHODS

Experiments included in this paper were performed on dogs lightly anesthetized with pentobarbital sodium (30 mg. per kg. intravenously) and on normal adult male subjects. In all experiments, the clearance of para-aminohippurate has been used as a measure of minimum effective renal plasma flow. In dogs the creatinine clearance, and in man the inulin clearance have been used as measures of glomerular filtration rate. Chemical methods employed have been noted in the previous communication (10).

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TABLE I

The effects of reduced renal arterial pressure on renal plasma flow, glomerular filtration rate and the absorption and excretion of sodium and water in an anesthetized dog

Total concurrent time	Renal circulatory status	Renal arterial pressure	Renal plasma flow	Glomerular filtration rate	Urine flow	Plasma sodium concentration	Sodium			
							Filtered*	Excreted	Reabsorbed	
mins.		*mm./Hg*	*cc./min.*	*cc./min.*	*cc./min.*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*Per cent of filtered*
15	control	122	181.7	78.6	1.35	148.2	11.06	0.228	10.83	97.94
30	control	124	175.3	79.5	1.73	146.5	11.06	0.302	10.76	97.27
45	control	129	171.5	80.4	1.77	146.1	11.15	0.292	10.86	97.38
60	aorta	70	161.1	70.3	0.60	147.3	9.84	0.072	9.77	99.26
75	clamped	60	137.7	61.3	0.57	147.3	8.58	0.035	8.54	99.59
90	control	137	169.6	75.4	4.53	147.0	10.53	0.294	10.24	97.21
105	control	134	161.2	76.8	6.43	149.1	10.81	0.379	10.43	97.51
120	aorta	60	143.1	61.7	1.63	147.9	8.67	0.052	8.62	99.40
135	clamped	50	118.1	53.3	0.80	146.7	7.43	0.022	7.41	99.70
150	control	138	167.8	79.8	7.93	149.4	11.32	0.580	10.74	94.88
165	control	147	147.8	77.4	7.44	149.4	10.98	0.594	10.39	94.60
180	aorta	55	132.0	59.8	1.07	148.8	8.46	0.065	8.39	99.23
195	clamped	50	129.2	57.4	1.00	149.1	8.12	0.045	8.07	99.45
210	control	143	164.1	82.9	8.40	148.2	11.66	0.838	10.82	92.82
225	control	147	154.9	83.4	7.70	149.7	11.86	0.851	11.01	92.83

* Calculated with a Donnan factor of 0.95.

In the experiments performed on dogs a condition of pseudo-circulatory failure has been induced by the infusion of 0.85% sodium chloride at 10 cc. per minute for some two and one-half hours prior to and throughout the course of the experiment. Under these conditions water and salt are retained relative to the load administered and extracellular fluid reserves are progressively expanded over a period of hours. After two and one-half hours of infusion the animal exhibits hypervolemia, elevated venous pressure, distended and pulsating jugular

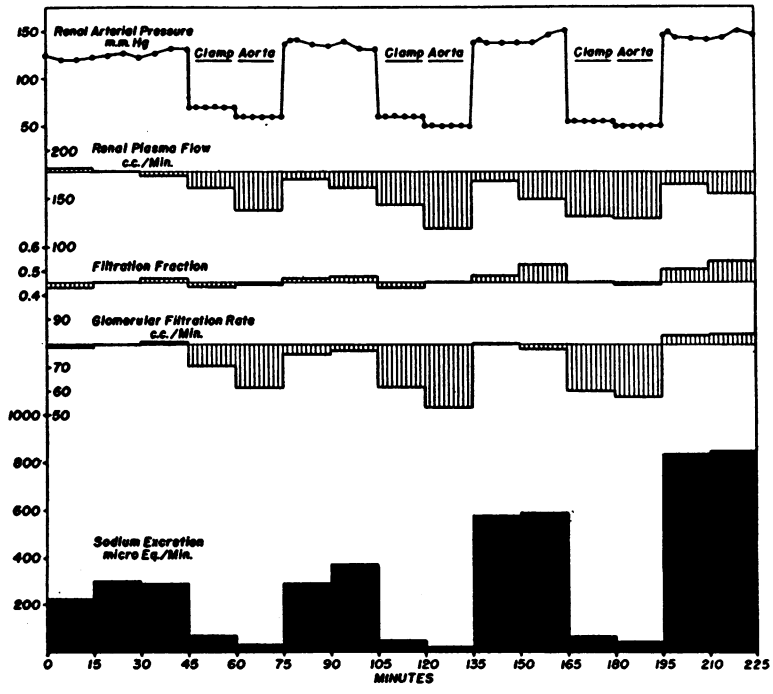

FIG. 1. THE EFFECTS OF REDUCED RENAL ARTERIAL PRESSURE ON RENAL PLASMA FLOW, GLOMERULAR FILTRATION RATE, FILTRATION FRACTION AND SODIUM EXCRETION IN THE SALT AND WATER LOADED ANIMAL

Data from Table I.

veins, moist râles in the lungs and some ascites. Several reasons may be advanced for the utilization of this type of preparation: (*a*) it mimics in some ways the state of congestive failure in man; (*b*) it permits the administration of large doses of mercurial diuretics without complicating renal circulatory disturbances; and (*c*) by ensuring a high rate of sodium and water excretion initially, it magnifies the effects of alterations in filtration rate.

The relationship between glomerular filtration rate and excretion of electrolyte and water in the animal in positive sodium and fluid balance

The experiment described in Table I and Figure 1 was performed on an anesthetized dog, in which an adjustable clamp was placed on the aorta above the renal arteries but below the origin of the coeliac axis. The clamp was introduced through a small lumbar incision and could be opened and closed at will by a screw control which projected from the flank of the animal. The pressure referred to as the renal arterial pressure was actually the mean femoral pressure (measured with a damped mercury manometer), for the abdomen was not opened and the kidneys were not disturbed. For two and one-half hours prior to, and throughout the course of the experiment, 0.85% saline containing creatinine and para-aminohippurate was infused at a constant rate of 10 cc. per minute. The animal was in marked positive sodium and water balance during the entire experiment, and exhibited the signs of "pseudo-circulatory failure" described under Methods.

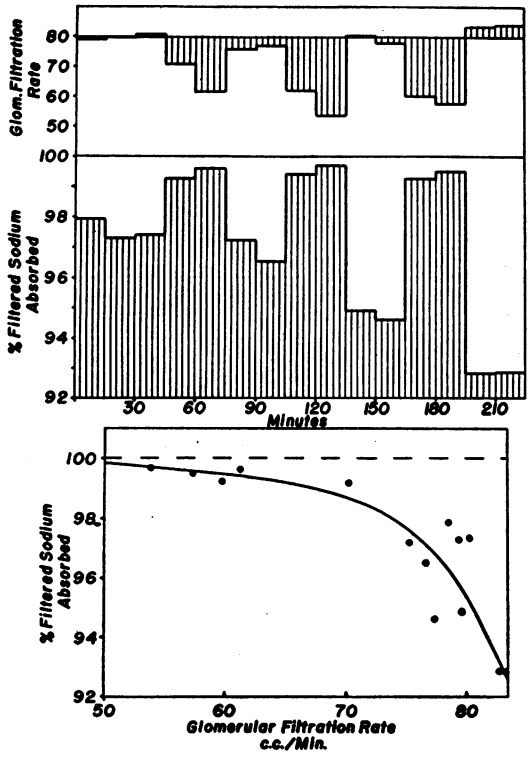

FIG. 2. THE RELATIONSHIP BETWEEN GLOMERULAR FILTRATION RATE AND THE PER CENT OF THE FILTERED SODIUM ABSORBED IN THE SALT AND WATER LOADED ANIMAL

Data from Table I.

After three control collection periods the clamp on the aorta was tightened to lower the mean femoral, and hence the mean renal arterial pressure, from 129 mm. Hg to 70 and then to 60 mm. Hg. On release of the clamp the pressure rose to or above the control level. In the succeeding two periods during which the aorta was clamped, arterial pressure was reduced to 60 and 50 mm. Hg, and then to 55 and 50 mm. Hg respectively. Pressures were held at these values by continual adjustment of the screw clamp.

It is apparent that renal plasma flow and glomerular filtration rate decreased during the intervals of reduced renal vascular pressure, but that the reductions were relatively small. On an average, plasma flow and filtration rate were reduced by one-quarter or less. In contrast, striking reductions in sodium and water excretion occurred during these intervals. With each reduction in renal arterial pressure, sodium excretion fell precipitously to a level only 1/10th to 1/20th that of the immediately preceding and succeeding periods.

It is evident from Table I that the absolute quantity of sodium reabsorbed was sharply reduced during each period of clamping of the aorta as a direct consequence of the reduced sodium load delivered into the renal tubules in the glomerular filtrate. However, the proportion of the filtered sodium reabsorbed increased during the periods in which filtration rate was reduced. This relationship is graphically shown in the upper part of Figure 2. In the lower portion of this figure, per cent of filtered sodium absorbed is plotted as a continuous function of filtration rate. As filtration rate decreased from 83 to 53 cc. per minute, the proportion of the filtered sodium absorbed increased from 93 to 99.7%.[2]

[2] The scatter of points in this chart indicates that uncontrolled factors complicate the relationship between

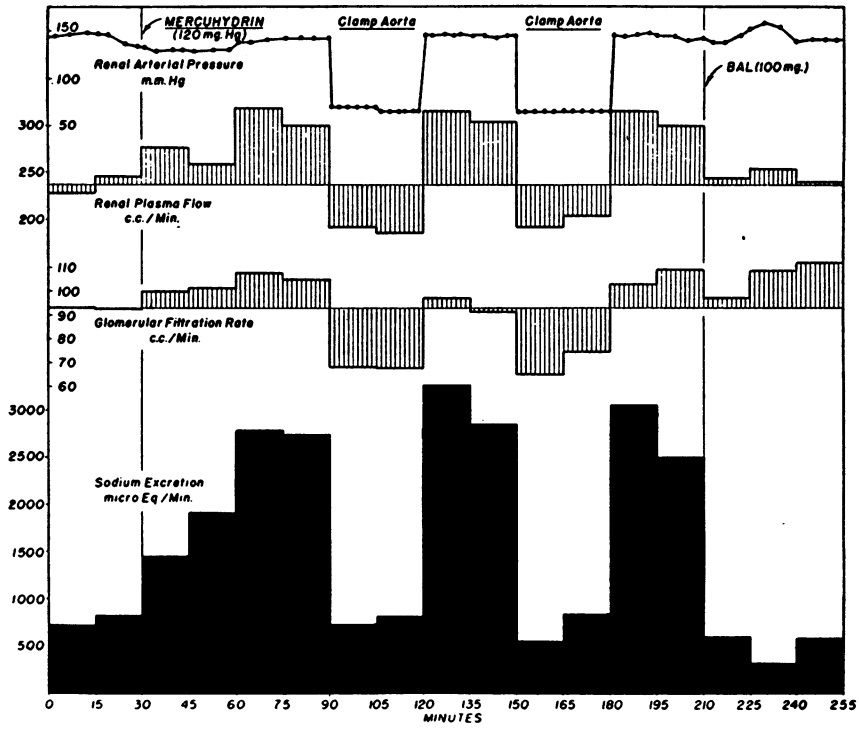

FIG. 3. THE EFFECTS OF REDUCED GLOMERULAR FILTRATION RATE ON SODIUM EXCRETION DURING MERCURIAL DIURESIS IN THE SALT AND WATER LOADED ANIMAL

The relationship between glomerular filtration rate and proximal tubular absorption of electrolyte and water

From the experiment just described and others of a similar nature,[8] it is evident that the lower the volume of filtrate delivered to the tubules the more completely is the sodium and water reabsorbed from that reduced volume of filtrate. Is this the consequence of more complete absorption in the proximal segment, perhaps as a result of reduced velocity of flow of tubular urine, or is it due to the fact that less sodium is passed on from the proximal to the distal segment, and that this lesser quantity is more completely reabsorbed?

Evidence presented in a preceding paper (10) suggests that an intravenous dose of 100 to 120 mg. Hg as mercuhydrin completely blocks the absorption of sodium by the distal segment of the renal tubule. If, as seems probable, distal tubular absorption is blocked in this manner, changes in tubular absorption which occur in consequence of alterations in glomerular filtration under such circumstances may be assigned to the proximal segment.

The experiment shown in Figure 3 was performed in a fashion similar to that of the one just described, *i.e.*, the dog was anesthetized with pentobarbital; an aortic clamp was placed in position above the renal arteries; and an infusion of saline was given at a rate of 10 cc. per minute for two and one-half hours prior to starting the experiment. After two control periods, 120 mg. Hg as mercuhydrin were administered intravenously. The excretion of sodium, which ini-

filtration rate and sodium absorption, probably those factors which underlie the progressive increase in sodium excretion which occurred during the course of the experiment. Although these factors have reduced any significance which could be attached to the form of the curve, it has not altered qualitatively the fact that completeness of reabsorption increases as filtration rate decreases.

[8] Qualitatively similar results were obtained in two additional experiments performed in identical fashion. In a number of additional experiments without salt loading, reduction in filtration rate has been observed to be attended by a reduction in sodium excretion. However, results in these experiments have been less striking because the initial rate of excretion has been lower; hence the magnitude of reduction has necessarily been less.

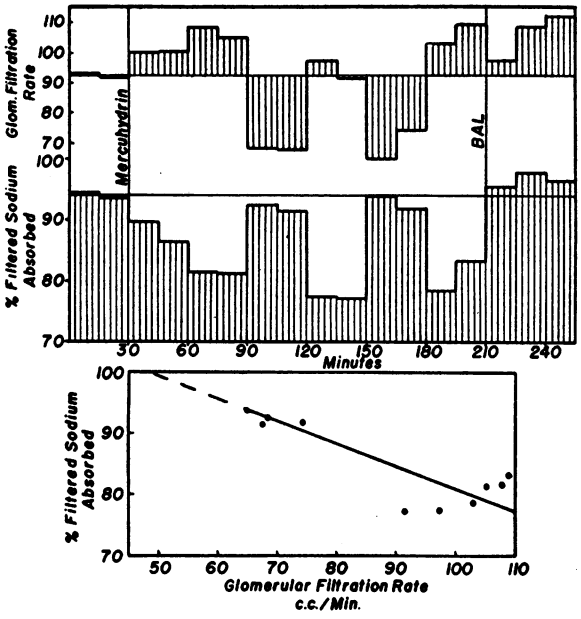

FIG. 4. THE RELATIONSHIP BETWEEN GLOMERULAR FILTRATION RATE AND THE PER CENT OF THE FILTERED SODIUM ABSORBED IN THE PROXIMAL TUBULE IN THE SALT AND WATER LOADED ANIMAL GIVEN MERCUHYDRIN

tially averaged 750 microequivalents per minute, rapidly increased to 2,700 to 2,800 microequivalents per minute within the next hour. Clamping the aorta moderately reduced renal plasma flow and glomerular filtration rate but very greatly reduced sodium excretion. Toward the end of the experiment the intramuscular administration of 1 cc. of 10% BAL in oil inhibited the action of the mercurial diuretic and sodium excretion returned to the control level.

Analysis of the relationship between glomerular filtration rate and per cent of filtered sodium absorbed is presented in Figure 4. From the upper graph it is evident that some 94% of the filtered sodium was absorbed during the two control periods, and that following the mercurial diuretic, absorption fell to 80% (*i.e.*, 120 mg. Hg blocked roughly 15% of sodium absorption). Each time filtration rate was reduced the per cent of sodium absorbed increased. If, as seems probable, absorption in the distal tubule is blocked under these conditions (10), it follows that the proportion of the filtered sodium absorbed in the proximal segment varies as an inverse function of glomerular filtration rate. Qualitatively similar results have been obtained in two additional experiments performed in identical fashion.

In the lower graph of Figure 4 the 10 values for per cent of sodium absorbed between 60 and 210 minutes, *i.e.*, those obtained during maximum action of the mercurial, are plotted against filtration rate. It is by no means certain that the true relationship is a linear one, but if extrapolation were justifiable, it is evident that sodium absorption would be essentially complete at a filtration rate of about 50 cc. per minute. Under such conditions one might expect urine flow to drop to extremely low values.

The relationship between glomerular filtration rate and diuretic efficacy of mercurials in normal man

One would anticipate from the results just presented that if glomerular filtration rate were to be low initially, or if it were to fall during the course of action of the drug, diuretic efficacy of the mercurial would be reduced. It has been observed in the normal dog in experiments in which no supporting infusion of saline was administered that the loss of large quantities of water and electrolyte early in the course of action of a mercurial so compromises circulating blood volume that there results a fall in filtration rate and curtailment of diuresis after some 60 to 120 minutes. It is probable, as claimed by Weston and Escher (3), that excessively low filtration rate is at least one significant causative factor in the resistance to mercurial diuretics occasionally observed clinically. Our own results on normal man are in agreement with this concept.

Three experiments on a single normal individual are presented in Figure 5. In the first two experiments no hydrating procedures were employed other than the ingestion of 500 cc. of water prior to the experiment. In the third experiment 0.85% saline was infused at a rate of 10 cc. per minute for two and one-half hours prior to and throughout the course of the experiment. All experiments were performed with the subject in the post-absorptive state. In each instance 2 cc. of mercuhydrin (78 mg. Hg) were given intravenously following the second control period. In the first experiment glomerular filtration rate dropped significantly following the mercurial, and the rate of elimination of sodium was only moderately increased. In the second experiment filtration rate dropped immediately after the mercurial, but soon

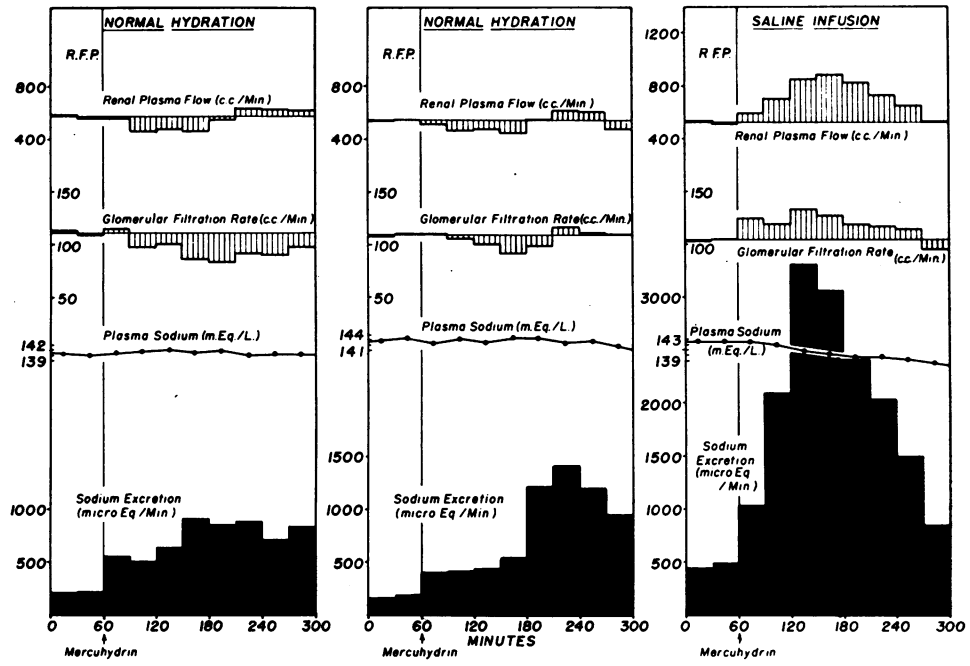

FIG. 5. THE RELATIONSHIP BETWEEN RENAL CIRCULATORY DYNAMICS AND DIURETIC EFFICACY OF A MERCURIAL IN A NORMAL MAN

Subject R. F. P.

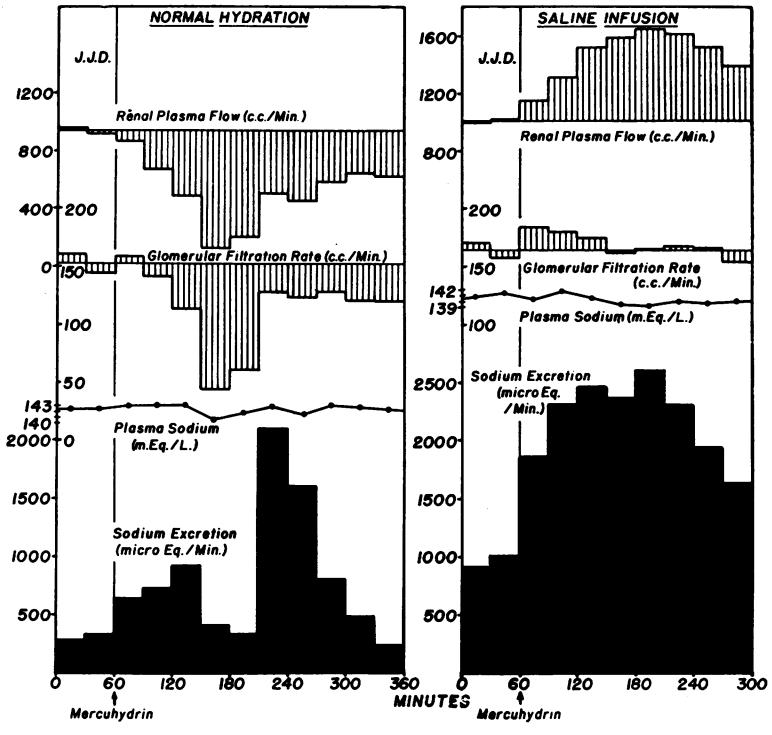

FIG. 6. THE RELATIONSHIP BETWEEN RENAL CIRCULATORY DYNAMICS AND DIURETIC EFFICACY OF A MERCURIAL IN A NORMAL MAN

Subject J. J. D.

recovered to the control level, and sodium excretion was somewhat enhanced. In the third experiment in which saline was administered, filtration rate increased following the mercurial and large quantities of sodium were poured out in the urine.

In a second series on another normal subject shown in Figure 6, peripheral circulatory collapse occurred some 60 minutes after the mercurial.[4] Renal plasma flow dropped from 943 to 136 cc. per minute and glomerular filtration rate decreased from 153 to 45 cc. per minute. The accompanying reduction in sodium excretion is reminiscent of that observed on clamping the aorta in the dog experiments. In the second experiment in which saline was infused, renal hyperemia and increased filtration rate resulted from the mercurial. Sodium excretion was much enhanced in consequence of the well maintained filtration rate.

DISCUSSION

The observation that a moderate reduction in glomerular filtration rate very greatly restricts the capacity of the kidney to eliminate water and salt, constitutes experimental evidence for the concept that glomerulo-tubular imbalance may well be a significant factor in the pathogenesis of edema (11). According to this view, the delivery of a reduced quantity of filtrate into tubules having essentially normal reabsorptive function leads to the retention of electrolyte and water. Merrill (12) maintains that edema accumulates in patients with reduced cardiac reserve when filtration rate falls below 70 cc. per minute, *i.e.*, below 60% of the normal. In the experiments on dogs reported above, a 25% reduction in filtration rate reduced excretion of salt and water by more than 90%. Obviously these results cannot be applied quantitatively in a consideration of fluid and electrolyte metabolism in disease because of the abnormally high salt and water loads imposed. Nevertheless the observation that a reduction in filtration rate leads to glomerulo-tubular imbalance and relative overabsorption of sodium is qualitatively significant. Indeed these findings and those recently reported by Selkurt and his associates (13) constitute the only direct experimental evidence that a fall in filtration rate *per se* induces significant glomerulo-tubular imbalance.

A more serious criticism may be directed against the *acute means* by which these results were obtained, for edema characteristically accumulates and recedes gradually. Whether tubular preponderance occurring in consequence of a reduction in filtration rate is sustained over relatively long periods of time cannot be answered in experiments of this type. It is possible that increased secretion of antidiuretic and adrenal cortical hormones and increased venous pressure play more significant roles in maintaining glomerulo-tubular imbalance in congestive failure (7, 9, 11) than does reduced filtration rate. Furthermore reduced hormone secretion and reduced venous pressure may be more significant for the reestablishment of balance than increased filtration rate (5, 6). However, it is evident from the instantaneous changes in the rates of excretion of salt and water that variations in hormone activity played no role in our experiments, and that such changes as occurred were solely related to alterations in arterial circulatory dynamics. We infer that if a reduction in filtration rate occurs during the accumulation of edema, that occurrence will *per se* contribute to the establishment of positive salt and water balance. We do not infer that it is the sole etiological factor nor even the most significant one in the pathogenesis of edema.

The finding that the per cent of filtered sodium absorbed in the proximal tubule is inversely related to glomerular filtration rate is at variance with the view expressed by Wesson, Anslow and Smith (14) that a constant fraction of the filtered load is absorbed in the proximal segment. The validity of our interpretation depends directly upon the validity of the conclusion that large doses of mercurial diuretics completely block the distal tubular absorption of sodium (10). Although conclusive proof is lacking, we feel that the weight of evidence is presently in favor of this concept. It is significant that Shannon (15) some years ago considered that reduced velocity of flow of tubular urine through the proximal segment favors

[4] This reaction, accompanied by pallor, faintness, chilliness, and nausea, was undoubtedly a manifestation of mercurial toxicity not of salt and water loss *per se*. Toxicity of the mercurial is probably also the cause of the reduction in filtration rate in the first two experiments on R. F. P. However the infusion of saline either protected against or in some manner compensated for toxicity in both subjects.

absorption of electrolyte, and that as filtration decreases to subnormal levels, absorption of sodium becomes essentially complete within this portion of the tubule.

If we accept the fact that proximal tubular absorption is more complete at subnormal than at normal filtration rates, it is evident that a given decrease in filtration rate would cause a supraproportional decrease in the quantity of electrolyte and water delivered to the distal segment. Hence even were mercurial diuretics to block completely distal tubular absorption of sodium, little would appear in the urine if the rate of glomerular filtration were low. Our experiments support this view and provide a rational explanation for the finding of Weston and Escher (3) that those patients who are clinically resistant to mercurial diuretics have exceptionally low filtration rates, and that a satisfactory diuresis will result if filtration rate can be increased by the administration of aminophylline. It is, however, possible that excessive hormonal stimulation of tubular absorption plays a significant or even in some instances a dominant role in mercurial resistance.

CONCLUSIONS

It has been demonstrated in the dog that a moderate reduction in glomerular filtration rate very greatly restricts the capacity of the kidney to eliminate water and electrolyte. We interpret our evidence as indicating that this reduction in excretory capacity is largely due to relative overabsorption of salt and water in the proximal segment in consequence of prolonged contact of the filtrate with the tubular epithelium. If filtration rate is significantly below normal, absorption in the proximal segment may be so nearly complete and such small quantities of sodium may reach the distal segment that even were complete blockage of absorption by a mercurial diuretic to result, an insignificant increase in sodium excretion would occur. The relation of these findings to the pathogenesis of edema and to the problem of clinical mercurial resistance is discussed.

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