# THE INFLUENCE OF GLOMERULAR FILTRATION RATE, SOLUTE EXCRETION AND HYDRATION ON THE CONCENTRATING MECHANISM OF THE EXPERIMENTALLY DISEASED KIDNEY IN THE DOG *

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Recent studies from this laboratory indicate that the concentrating ability of the diseased kidney in the dog is not markedly impaired when the contralateral kidney is intact and the internal environment remains essentially normal (1). These data suggested that the direct effects of the pathological processes on the structural integrity of the functioning nephrons did not render the concentrating mechanism impotent. The present studies represent an attempt to obtain additional information about the functional characteristics of the concentrating mechanism in the dog with experimentally induced renal disease. The majority of experiments have been performed on animals with one of several types of unilateral renal parenchymal disease. In addition, observations have been made on dogs with unilateral hemi-infarcted kidneys and with bilateral renal parenchymal disease.

## METHODS

Experiments were performed on young adult female dogs, maintained on standard dog chow with supplementary horse meat. The following experimental preparations were employed.

*1. Unilateral renal disease.* Three forms of chronic unilateral renal disease were induced: *a*) pyelonephritis; *b*) antikidney serum glomerulonephritis; and *c*) aminonucleoside-nephritis. The techniques for producing these lesions have been described in detail in previous publications (2–4). In each form of disease, the experimental kidney became contracted and demonstrated marked anatomical abnormalities of the remaining renal parenchyma. The nature of the histological changes varied with the type of underlying disease. In all animals, the contralateral control kidney remained free of significant disease.

*2. Unilateral hemi-infarcted kidney.* Unilateral hemi-infarction was produced by ligating one of the two major branches of one renal artery. The infarcted area was well delineated and involved the entire lateral half of the kidney. The experimental kidney ultimately became contracted but the persisting nephrons demonstrated no anatomical abnormalities. The contralateral kidney was unaltered.

*3. Bilateral renal disease.* Bilateral disease was produced by applying the method for the induction of unilateral pyelonephritis to both kidneys during the same operative procedure.

In all animals with unilateral renal disease or unilateral hemi-infarction, a preliminary bladder-splitting procedure was performed and two permanent hemibladders were constructed. Each of the latter drained urine from one kidney and permitted the simultanous study of the separate kidneys. The details of this preparation have been previously described (1, 4). When bilateral disease was produced, the urethra was ligated and divided and a permanent polyethylene cystotomy tube, similar to those used in the hemibladders, was employed. This resulted in permanent contraction of the bladder, thereby reducing bladder dead space; it also facilitated free drainage of urine with the dog in the standing position.

Preliminary clearance studies were performed prior to induction of disease. In the animals with divided bladders, only those with bilaterally equal functions were accepted for further study. Studies after induction of disease were performed from 7 to 240 days subsequent to initiation of the renal lesion. The majority of experiments were performed on unanesthetized, standing animals which were loosely supported by an abdominal sling. Certain of the experiments involving unilateral renal artery constriction were performed on anesthetized animals; however the effects of unilateral renal artery constriction and/or aortic constriction were also ob-

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TABLE I

*The differences in concentrating capacity, solute excretion, urinary sodium concentration and urinary osmolality between the diseased and intact kidneys of a representative dog during mannitol and vasopressin infusion**

| Clearance period | GFR | | $T^c_{H_2O}$/GFR | | $C_{osm}$/GFR | | $U_{Na}V/FL_{Na}$ | | $U_{Na}$ | | $U_{osm}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. |
| | *ml/min* | | % | | % | | % | | *mEq/L* | | *mOsm/kg $H_2O$* | |
| 1 | 18.0 | 53.0 | 4.7 | 6.1 | 16.1 | 12.6 | 9.7 | 5.4 | 113 | 109 | 420 | 574 |
| 2 | 18.5 | 50.3 | 4.9 | 7.2 | 16.6 | 14.8 | 9.0 | 5.4 | 102 | 95 | 422 | 582 |
| 3 | 17.3 | 52.6 | 4.9 | 6.7 | 17.5 | 14.3 | 10.0 | 4.9 | 102 | 84 | 420 | 568 |
| 4 | 17.0 | 53.0 | 5.6 | 6.4 | 18.8 | 14.1 | 9.4 | 4.3 | 92 | 74 | 430 | 559 |
| 5 | 18.7 | 53.1 | 5.3 | 6.5 | 17.3 | 14.1 | 7.8 | 3.8 | 86 | 65 | 441 | 567 |
| 6 | 20.1 | 55.0 | 5.4 | 6.6 | 17.6 | 14.9 | 8.0 | 4.2 | 90 | 70 | 440 | 547 |

* Dog Re (18.2 kg); aminonucleoside-nephritis, 100 days after induction. Exp. = experimental (diseased) kidney; Cont. = control (intact) kidney; $T^cH_2O$ = solute-free water abstracted in the concentration process; $C_{osm}/GFR$ = fraction of filtered solute excreted; $U_{Na}V/FL_{Na}$ = fraction of filtered sodium excreted; $U_{Na}$ = urinary sodium concentration; $U_{osm}$ = urinary osmolality. Mannitol was infused in a 12.5% solution at 5.0 ml/min; 100 mU of vasopressin was administered as a priming dose and 1 mU/min was infused in the sustaining solution.

served in unanesthetized dogs. Two techniques were used for renal artery constriction. *a*) The artery of the diseased kidney was exposed prior to initiation of clearance measurements and an arterial clamp was placed about it. This was then tightened under direct vision. *b*) A polyethylene band, which attached to an external screw clamp device, was placed about the renal artery several days in advance of clearance measurements. Aortic compression was also accomplished with a polyethylene band, placed about the aorta proximal to both renal arteries. The two ends of this constricting band were brought to the exterior posteriorly on either side of the spine and were permanently secured. Compression was accomplished with a screw clamp which attached reversibly to the band.

Further details of the experimental procedures employed have been described (1, 4). Creatinine was determined according to the method of Bonsnes and Taussky (5); para-aminohippurate (PAH) was determined according to the method of Smith and associates (6); osmolalities were measured using a Fiske osmometer; sodium and potassium were analyzed with an internally compensated Baird flame photometer, and urea was determined manometrically according to the method of Van Slyke and Kugel (7).

## RESULTS

In Table I, values are shown for the concentrating ability of the diseased and normal kidneys of a representative animal with unilateral renal disease during mannitol and vasopressin infusion. Glomerular filtration rate (GFR) for the diseased kidney was decreased by approximately 65 per cent. Values for solute-free water abstracted per 100 ml of glomerular filtrate ($T^c_{H_2O}$/GFR) were within the normal range for a dog but were somewhat less for the diseased than for the normal kidney. Certain other differences existed between the two kidneys. Thus the diseased kidney excreted a greater fraction of its filtered solute ($C_{osm}/GFR$) and a *greater* fraction of its filtered sodium ($U_{Na}V/FL$) than did the normal organ. Moreover, the urinary sodium concentration ($U_{Na}$) of the diseased kidney was *greater* than that of the normal organ, whereas the urinary osmolality ($U_{osm}$) was *less*.

Results similar to those shown in Table I have been observed with a high degree of consistency during mannitol diuresis in animals with unilateral renal disease irrespective of the nature or pathological characteristics of the underlying renal lesion. Moreover an identical pattern has emerged during glucose diuresis, and with the exception of urinary sodium concentration, the same differences have been noted during the infusion of hypertonic saline.[1] A group plot of 30 experiments on 17 dogs undergoing solute diuresis is shown in Figure 1.

*Unilateral hemi-infarcted kidneys.* The general comparability of values between the diseased and normal kidneys of individual dogs, as well as the consistency of the differences, provide presumptive evidence against randomly distributed anatomical abnormalities. More direct evidence that structural damage need not be invoked to

[1] During hypertonic NaCl infusion, Na plus its attendant anions constitute over 90 per cent of total urinary solute, and the lower values for total solute concentration in the urine of the diseased kidney generally have been associated with lower values for $U_{Na}$. An explanation for higher urinary Na concentrations in the presence of lower $U_{osm}$ during mannitol and glucose diuresis is presented in the discussion.

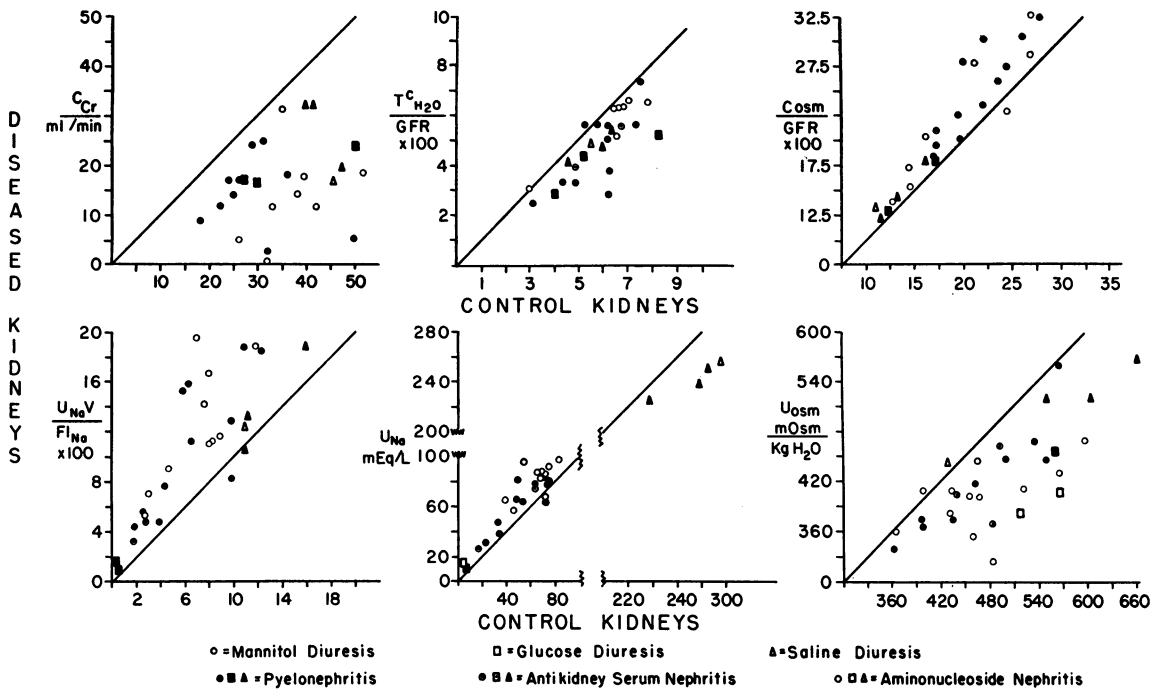


FIG. 1. SOLUTE DIURESIS IN ANIMALS WITH UNILATERAL RENAL DISEASE.

explain the differences has been obtained in experiments on animals with unilateral hemi-infarcted kidneys. The hemi-infarcted kidney is similar to the diseased kidney in that it has lost a significant fraction of its original nephron population and ultimately becomes contracted. However, it differs from the diseased kidney in one major respect: the residual functioning nephrons are not afflicted with a progressive renal disease and remain anatomically normal. Data obtained from a representative animal with unilateral hemi-infarction during mannitol and vasopressin infusion are shown in Table II. The differences between the hemi-infarcted and normal kidneys are essentially the same as those between diseased and normal kidneys.

*Arterial compression during mannitol diuresis.* Because of the known effects of GFR and solute excretion on urine concentration, experiments were performed in order to examine the interrelationships of the two former parameters and urinary concentrating ability of the diseased kidneys. Table III depicts the results of a representative study in which the GFR of the *diseased kidney only* was decreased experimentally in a dog with unilateral renal disease undergoing mannitol diuresis. During four control clearance periods, typical differences were noted between the dis-

TABLE II

*Differences between hemi-infarcted and intact kidneys of a representative dog during the infusion of mannitol and vasopressin**

| Clearance period | GFR | | $T^{c}_{H_2O}$/GFR | | Cosm/GFR | | $U_{Na}V/Fl_{Na}$ | | $U_{Na}$ | | Uosm | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. | Exp. | Cont. |
| | *ml/min* | | % | | % | | % | | *mEq/L* | | *mOsm/kg $H_2O$* | |
| 1 | 14.9 | 33.9 | 6.7 | 7.3 | 20.4 | 17.9 | 9.2 | 5.4 | 91 | 69 | 471 | 533 |
| 2 | 14.4 | 32.7 | 7.7 | 8.1 | 24.2 | 20.8 | 11.4 | 6.4 | 88 | 65 | 468 | 533 |
| 3 | 14.8 | 29.0 | 8.3 | 8.7 | 25.0 | 21.2 | 10.1 | 5.4 | 82 | 56 | 481 | 543 |
| 4 | 15.7 | 36.5 | 8.2 | 8.7 | 25.4 | 22.1 | 10.8 | 6.3 | 80 | 59.5 | 477 | 532 |

* Dog Ch (12.3 kg); 26 days after unilateral hemi-infarction.

TABLE III

*Effects of constriction of renal artery of diseased kidney on differences between diseased and normal kidneys of a representative dog during mannitol and vasopressin infusion**

| Clearance period | Time elapsed | GFR | | | $C_{osm}$/GFR | | | $U_{Na}V/FL_{Na}$ | | | $U_{Na}$ | | | $U_{osm}$ | | | $T^c_{H_2O}$/GFR ×100 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C |
| | *min* | *ml/min* | | | % | | | % | | | *mEq/L* | | | *mOsm/kg H₂O* | | | % | | |
| 1 | 0–9 | 13.3 | 18.5 | 0.72 | 32.2 | 25.4 | 1.27 | 18.9 | 10.1 | 1.87 | 81.4 | 60.8 | 1.34 | 366 | 402 | 0.91 | 2.0 | 2.7 | 0.74 |
| 2 | 9–18 | 14.6 | 20.2 | 0.72 | 33.2 | 27.1 | 1.23 | 18.2 | 10.5 | 1.73 | 80.0 | 60.8 | 1.32 | 379 | 409 | 0.93 | 2.9 | 4.2 | 0.69 |
| 3 | 18–25 | 15.2 | 21.7 | 0.70 | 33.8 | 28.9 | 1.17 | 19.2 | 12.0 | 1.60 | 78.5 | 61.2 | 1.28 | 387 | 413 | 0.94 | 2.4 | 3.8 | 0.63 |
| 4 | 25–34 | 14.5 | 19.6 | 0.74 | 32.1 | 29.3 | 1.10 | 14.0 | 7.9 | 1.77 | 62.3 | 44.3 | 1.41 | 405 | 464 | 0.87 | 3.6 | 6.6 | 0.55 |
| | Mean | | | 0.72 | | | 1.19 | | | 1.74 | | | 1.34 | | | 0.91 | | | 0.65 |
| | 38—Constrict renal artery of experimental kidney | | | | | | | | | | | | | | | | | | |
| 5 | 41–46 | 11.8 | 19.6 | 0.60 | 30.8 | 28.9 | 1.07 | 8.5 | 6.6 | 1.29 | 43.3 | 37.1 | 1.17 | 455 | 473 | 0.96 | 5.9 | 6.4 | 0.92 |
| 6 | 46–51 | 11.7 | 21.2 | 0.55 | 34.1 | 30.3 | 1.13 | 10.3 | 7.3 | 1.41 | 46.8 | 39.2 | 1.19 | 450 | 471 | 0.96 | 5.8 | 6.3 | 0.92 |
| 7 | 51–56 | 13.7 | 20.8 | 0.66 | 35.3 | 33.3 | 1.06 | 13.6 | 9.2 | 1.48 | 57 | 44.8 | 1.27 | 430 | 473 | 0.91 | 4.4 | 6.8 | 0.65 |
| 8 | 56–63 | 11.9 | 19.1 | 0.62 | 35.5 | 33.9 | 1.05 | 12.3 | 8.5 | 1.45 | 51.3 | 41.0 | 1.25 | 431 | 475 | 0.91 | 4.2 | 6.8 | 0.62 |
| 9 | 63–68 | 11.8 | 19.9 | 0.59 | 37.7 | 35.4 | 1.06 | 12.4 | 9.7 | 1.28 | 50.7 | 44.0 | 1.15 | 448 | 468 | 0.96 | 5.8 | 6.7 | 0.87 |
| | Mean | | | 0.61 | | | 1.07 | | | 1.38 | | | 1.21 | | | 0.94 | | | 0.80 |

* Dog Te (8.0 kg); unilateral pyelonephritis, 37 days after induction. Mannitol and vasopressin infusion was initiated 30 minutes before the beginning of period 1; E/C refers to the ratio of experimental to control kidneys.

eased and the normal kidneys. Subsequent to the fourth clearance period the renal artery of the diseased kidney was constricted, and a modest unilateral decrease in filtration rate occurred. In association with this, values for $C_{osm}$/GFR for the diseased kidney approached those for the contralateral kidney. Moreover the differences for all other parameters including $U_{osm}$ and $T^c_{H_2O}$/GFR diminished.

Animals with unilateral renal disease have also been subjected to aortic compression during mannitol diuresis. The results of two experiments on the same dog studied in the unanesthetized state are shown in Table IV. The first experiment (Table IV-A) was performed with the aortic clamp in place but without aortic constriction. The second experiment (Table IV-B) was performed on the following day with the aorta constricted sufficiently to permit approximation of maximal urinary osmolalities for the diseased and normal kidneys in the hydropenic state. The latter data are presented in detail in Table VII. In the absence of aortic constriction the typical differences between the diseased and normal kidneys existed. During aortic constriction, however, all of the differences were considerably reduced and in two of the five clearance periods, values for $T^c_{H_2O}$/GFR were essentially the same for the diseased as for the normal kidney.

*Arterial compression during urea diuresis.* The effects of compression of the renal artery and the aorta have also been examined during urea infusion. A representative experiment on a dog with unilateral renal disease subjected to constriction of the renal artery of the diseased kidney is shown in Table V-A. As in the mannitol experiments, arterial compression diminished the differences between the two kidneys, but the changes are not marked. However under identical experimental conditions, comparable results were obtained in the dog with a unilateral hemiinfarcted kidney (Table V-B) and also in the dog with two normal kidneys (Table V-C).

In the normal dogs subjected to unilateral renal artery compression during urea infusion, Levinsky, Davidson and Berliner have noted a marked rise in $U_{osm}$ of the experimental kidney relative to the contralateral control organ (8). The explanation for the discrepancy between these data and those presented in Table V-C is not im-

TABLE IV

*Effects of aortic constriction on differences between diseased and normal kidneys in a representative dog during mannitol and vasopressin infusion**

| Clearance period | GFR | | | $C_{osm}/GFR$ | | | $U_{Na}V/FL_{Na}$ | | | $U_{Na}$ | | | $U_{osm}$ | | | $T^c_{H_2O}/GFR$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C | Exp. | Cont. | E/C |
| | *ml/min* | | | % | | | % | | | *mEq/L* | | | *$mO_{sm}/kg\ H_2O$* | | | % | | |
| | Exp. A. May 12, 1959; aortic clamp in place: unconstricted | | | | | | | | | | | | | | | | | |
| 1 | 16.7 | 24.8 | 0.67 | 16.9 | 17.2 | 0.98 | 1.6 | 0.2 | 8.0 | 15.4 | 2.8 | 5.5 | 343 | 525 | 0.65 | 3.1 | 8.3 | 0.37 |
| 2 | 17.5 | 28.0 | 0.63 | 18.1 | 18.1 | 1.0 | 1.6 | 0.3 | 5.3 | 15.7 | 3.8 | 4.1 | 363 | 525 | 0.69 | 4.2 | 8.5 | 0.49 |
| 3 | 18.0 | 27.7 | 0.65 | 19.7 | 17.5 | 1.1 | 1.9 | 0.3 | 6.3 | 16.6 | 3.9 | 4.3 | 383 | 484 | 0.79 | 4.8 | 7.2 | 0.67 |
| 4 | 15.9 | 28.0 | 0.57 | 21.8 | 18.9 | 1.2 | 1.6 | 0.3 | 5.3 | 13.5 | 4.0 | 3.4 | 413 | 525 | 0.79 | 6.6 | 8.5 | 0.78 |
| 5 | 16.4 | 28.5 | 0.58 | 21.8 | 20.6 | 1.1 | 1.6 | 0.5 | 3.2 | 14.3 | 5.2 | 2.8 | 425 | 525 | 0.81 | 6.9 | 8.8 | 0.78 |
| | Mean | | 0.62 | | | 1.1 | | | 5.6 | | | 4.0 | | | 0.75 | | | 0.62 |
| | Exp. B. May 13, 1959; aortic clamp constricted | | | | | | | | | | | | | | | | | |
| 1 | 15.5 | 24.7 | 0.63 | 12.8 | 13.3 | 0.96 | 0.6 | 0.4 | 1.5 | 11.5 | 7.9 | 1.5 | 495 | 567 | 0.87 | 5.2 | 6.4 | 0.81 |
| 2 | 13.9 | 24.0 | 0.58 | 16.3 | 14.5 | 1.1 | 0.9 | 0.6 | 1.5 | 13.2 | 10.0 | 1.3 | 491 | 552 | 0.89 | 6.3 | 6.5 | 0.97 |
| 3 | 14.2 | 23.2 | 0.61 | 16.4 | 16.7 | 0.98 | 0.9 | 0.7 | 1.3 | 12.6 | 9.9 | 1.3 | 488 | 547 | 0.89 | 6.2 | 7.4 | 0.84 |
| 4 | 13.8 | 23.0 | 0.60 | 17.0 | 16.3 | 1.0 | 1.2 | 0.8 | 1.5 | 13.9 | 11.1 | 1.3 | 451 | 493 | 0.91 | 5.4 | 6.1 | 0.89 |
| 5 | 13.9 | 24.0 | 0.58 | 19.3 | 18.4 | 1.0 | 0.9 | 0.9 | 1.0 | 10.5 | 10.4 | 1.0 | 500 | 527 | 0.95 | 7.3 | 7.5 | 0.97 |
| | Mean | | 0.60 | | | 1.0 | | | 1.4 | | | 1.3 | | | 0.90 | | | 0.90 |

* Dog Gi (13.2 kg); unilateral pyelonephritis, 21 days after induction. Both experiments were performed with the dog standing and unanesthetized. The rate of mannitol and vasopressin infusion was the same as in previous experiments (see Table I). The aortic clamp was constricted 2 hours before the beginning of Experiment B. The low rates of sodium excretion noted in both experiments were also observed in this dog during mannitol infusion prior to the surgical procedure for placing the aortic clamp.

TABLE V

*The effects of unilateral renal artery constriction during urea and vasopressin infusion**

| Clearance period | V | | GFR | | | $U_{osm}$ | | | $P_{urea}$ | $U_{urea}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exp. | Cont. | Exp. | Cont. | E/C | Exp. | Cont. | E/C | | Exp. | Cont. |
| | *ml/min* | | *ml/min* | | | *$mO_{sm}/kg\ H_2O$* | | | *mmoles/L* | *mmoles/L* | |
| Exp. A. Dog Su (17 kg); unilateral antikidney serum nephritis (59 days after induction) | | | | | | | | | | | |
| 1 | 1.23 | 1.99 | 15.4 | 36.2 | 0.43 | 590 | 717 | 0.82 | | | |
| 2 | 1.30 | 2.02 | 16.3 | 39.9 | 0.41 | 594 | 736 | 0.81 | 37.1 | 351 | 508 |
| 3 | 1.12 | 2.03 | 17.2 | 43.3 | 0.40 | 633 | 771 | 0.82 | | | |
| Constrict artery of diseased kidney | | | | | | | | | | | |
| 4 | 0.34 | 1.2 | 12.5 | 41.6 | 0.30 | 770 | 885 | 0.87 | 37.3 | 604 | 681 |
| 5 | 0.48 | 1.53 | 14.4 | 41.1 | 0.35 | 790 | 885 | 0.89 | | | |
| 6 | 0.56 | 1.54 | 16.6 | 46.1 | 0.36 | 810 | 900 | 0.90 | 37.8 | 539 | 620 |
| 7 | 0.67 | 1.70 | 14.2 | 39.5 | 0.36 | 880 | 950 | 0.93 | | | |
| 8 | 0.42 | 1.29 | 9.7 | 46.2 | 0.21 | 890 | 986 | 0.90 | 39.6 | 628 | 679 |
| 9 | 0.28 | 1.44 | 11.4 | 45.2 | 0.25 | 849 | 934 | 0.91 | | | |
| Exp. B. Dog Tr (14 kg); unilateral renal hemi-infarction | | | | | | | | | | | |
| 1 | 0.46 | 0.86 | 14.4 | 41.9 | 0.34 | 650 | 920 | 0.71 | | 513 | 680 |
| 2 | 0.48 | 0.91 | 14.8 | 39.6 | 0.37 | 656 | 908 | 0.72 | 18.8 | | |
| 3 | 0.46 | 0.96 | 16.8 | 45.7 | 0.37 | 654 | 942 | 0.69 | | 525 | 682 |
| Constrict artery of hemi-infarcted kidney | | | | | | | | | | | |
| 4 | 0.53 | 1.3 | 12.4 | 43.6 | 0.28 | 600 | 917 | 0.65 | 25.0 | 420 | 627 |
| 5 | 0.45 | 1.2 | 10.2 | 43.6 | 0.23 | 631 | 936 | 0.67 | 24.6 | 445 | 674 |
| 6 | 0.58 | 1.2 | 12.5 | 40.2 | 0.31 | 638 | 939 | 0.68 | | | |
| 7 | 0.55 | 1.2 | 12.5 | 36.8 | 0.34 | 652 | 966 | 0.67 | 24.8 | 488 | 750 |
| 8 | 0.47 | 1.3 | 10.6 | 41.2 | 0.26 | 646 | 964 | 0.67 | | | |
| 9 | 0.58 | 1.3 | 13.3 | 40.9 | 0.32 | 656 | 966 | 0.68 | 29.3 | 480 | 744 |
| Exp. C. Dog Fe (12 kg); two normal kidneys | | | | | | | | | | | |
| 1 | 3.2 | 3.3 | 18.1 | 17.3 | 1.05 | 410 | 393 | 1.04 | 44.3 | 179 | 174 |
| 2 | 2.6 | 2.6 | 19.5 | 18.9 | 1.03 | 438 | 433 | 1.01 | | | |
| 3 | 2.0 | 2.3 | 18.2 | 18.4 | 0.99 | 495 | 456 | 1.09 | | | |
| Constrict artery of right (experimental) kidney | | | | | | | | | | | |
| 4 | 0.86 | 1.8 | 9.2 | 19.8 | 0.46 | 576 | 568 | 1.01 | | | |
| 5 | 0.80 | 1.7 | 9.9 | 19.0 | 0.52 | 596 | 583 | 1.02 | 47.8 | 321 | 346 |
| 6 | 0.81 | 1.8 | 11.0 | 21.9 | 0.50 | 608 | 601 | 1.01 | | | |
| 7 | 0.52 | 2.2 | 6.8 | 26.1 | 0.26 | 661 | 651 | 1.01 | | | |
| 8 | 0.76 | 2.2 | 9.7 | 26.7 | 0.36 | 666 | 653 | 1.02 | 54.6 | 413 | 436 |
| 9 | 0.79 | 2.2 | 9.7 | 25.7 | 0.38 | 653 | 657 | 0.99 | | | |

* Urea was infused at the rate of 2,900 μmoles; the priming and sustaining doses of vasopressin were the same as in the mannitol infusions (see Table I); V = urine flow; $P_{urea}$ = plasma urea concentration; $U_{urea}$ = urine urea concentration.

TABLE VI

*The effects of aortic compression during urea infusion on urine concentration in a dog with bilateral pyelonephritis**

| Clearance period | Time | GFR | $C_{PAH}$ | $C_{osm}/GFR$ | $U_{Na}V/FL_{Na}$ | $U_{Na}$ | $U_{osm}$ | $T^{c}_{H_2O}/GFR$ | $P_{urea}$ | $U_{urea}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | *min* | *ml/min* | *ml/min* | *%* | *%* | *mEq/L* | *$mO_{sm}$* | *%* | *mmoles/L* | *mmoles/L* |
| 1 | 71–82 | 41.3 | 164 | 13.4 | 4.5 | 84 | 590 | 5.9 | 28.2 | 274 |
| 2 | 82–92 | 36.7 | 142 | 13.3 | 4.2 | 81 | 600 | 6.0 | | 251 |
| 3 | 92–102 | 33.6 | 134 | 12.0 | 3.4 | 75 | 604 | 5.4 | 30.2 | 303 |
| | 105 | Aortic constriction | | | | | | | | |
| 4 | 131–143 | 29.9 | 129 | 10.2 | 1.3 | 37 | 765 | 5.8 | | 556 |
| 5 | 143–153 | 32.7 | 139 | 9.5 | 0.4 | 15.5 | 800 | 5.6 | | 487 |
| 6 | 153–173 | 28.1 | 127 | 11.7 | 0.4 | 12.8 | 805 | 6.0 | 31.2 | 480 |

* Dog Wi (16 kg); glomerular filtration rate in control studies prior to induction of pyelonephritis was 63.4 ml/min. $C_{PAH}$ = clearance of *p*-aminohippurate.

TABLE VII

*Effects of aortic constriction on maximal urinary osmolality from diseased and normal kidneys of dog with unilateral pyelonephritis following 18 hours of water deprivation**

| Collection period | Time | $U_{osm}$ Exp. | $U_{osm}$ Cont. | $U_{osm}$ Exp./Cont. |
|---|---|---|---|---|
| | *min* | *$mO_{sm}/kg\ H_2O$* | | |
| 1 | 0–36 | 1313 | 1601 | 0.82 |
| Pitressin tannate in oil; 4 pressor units i.m.; time 60 min | | | | |
| 2 | 70–86 | 1038 | 1377 | 0.75 |
| 3 | 100–120 | 956 | 1405 | 0.68 |
| 4 | 126–140 | 1321 | 1471 | 0.90 |
| 5 | 140–150 | 1061 | 1276 | 0.83 |
| Mean 1–5 | | | | 0.79 |
| Aortic constriction at time 151 | | | | |
| 6 | 154–170 | 1440 | 1469 | 0.98 |
| 7 | 170–182 | 1118 | 1334 | 0.84 |
| 8 | 182–192 | 1344 | 1477 | 0.91 |
| 9 | 192–203 | 1372 | 1414 | 0.97 |
| 10 | 230–256 | 1442 | 1576 | 0.91 |
| Mean | | | | 0.92 |
| Additional aortic constriction at time 257 | | | | |
| 11 | 269–280 | 1149 | 1321 | 0.87 |
| 12 | 280–304 | 1129 | 1286 | 0.88 |
| 13 | 304–355 | 1228 | 1188 | 1.03 |
| 14 | 355–365 | 1051 | 1064 | 0.99 |
| 15 | 365–403 | 1175 | 1281 | 0.92 |
| Mean | | | | 0.94 |

* Dog Gi (13.2 kg); unilateral pyelonephritis (26 days after induction).

mediately apparent. However, the experimental design of the two studies was different in that Levinsky and co-workers studied unanesthetized dogs in which an inflatable balloon had been placed about the renal artery in advance of the experiments, whereas the present animals were anesthetized and the renal artery clamp was placed within one to two hours of the start of urine collections. For purposes of this discussion, the similarity of response between the dog with unilateral renal disease and those with unilateral hemi-infarction and two normal kidneys seems worthy of emphasis.

In Table VI, the effects of aortic compression are shown in an unanesthetized animal with bilateral pyelonephritis during urea infusion. Three control clearance periods were obtained following which the aortic band was tightened. Subsequent to constriction of the aorta, filtration rate diminished by approximately 30 per cent and values for $C_{osm}/GFR$, $U_{Na}V/FL_{Na}$ and $U_{Na}$ all decreased, whereas values for urinary osmolality increased.

*Aortic compression during hydropenia.* Following water deprivation, the diseased kidney in the animal with unilateral renal disease characteristically has retained the ability to elaborate a hypertonic urine (1). However, the values for $U_{osm}$ have been somewhat less for the diseased

TABLE VIII

*Effects of hydration on concentrating capacity of diseased and normal kidneys during mannitol and vasopressin infusion**

| Clearance period | GFR Exp. | GFR Cont. | $T^c_{H_2O}/GFR$ Exp. | $T^c_{H_2O}/GFR$ Cont. | $C_{osm}/GFR$ Exp. | $C_{osm}/GFR$ Cont. | $U_{Na}V/FL_{Na}$ Exp. | $U_{Na}V/FL_{Na}$ Cont. | $U_{Na}$ Exp. | $U_{Na}$ Cont. | $U_{osm}$ Exp. | $U_{osm}$ Cont. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *ml/min* | | % | | % | | % | | *mEq/L* | | *$mO_{sm}/kg\ H_2O$* | |
| Dog Ai (11.8 kg); antikidney serum nephritis | | | | | | | | | | | | |
| Exp. A. Hydropenic | | | | | | | | | | | | |
| 1 | 5.0 | 47.2 | 5.4 | 6.8 | 18.5 | 15.8 | 5.8 | 3.6 | 60.8 | 54.1 | 456 | 563 |
| 2 | 5.0 | 51.4 | 5.6 | 6.7 | 21.4 | 16.7 | 7.7 | 4.1 | 65.7 | 55.8 | 444 | 548 |
| 3 | 5.3 | 51.9 | 5.3 | 7.2 | 22.1 | 18.3 | 8.0 | 4.7 | 66.5 | 52.8 | 439 | 545 |
| 4 | 5.1 | 50.6 | 5.6 | 6.9 | 23.7 | 18.3 | 9.0 | 5.2 | 64.8 | 52.8 | 440 | 539 |
| Exp. B. Hydrated | | | | | | | | | | | | |
| 1 | 7.6 | 44.3 | 0.7 | 2.3 | 11.5 | 13.2 | 3.5 | 4.5 | 41.8 | 53 | 346 | 397 |
| 2 | 8.4 | 45.8 | 1.2 | 2.6 | 12.5 | 15.2 | 4.0 | 4.7 | 44.0 | 50 | 362 | 419 |
| 3 | 9.5 | 46.0 | 1.4 | 3.5 | 13.2 | 15.3 | 4.4 | 4.3 | 47 | 46 | 373 | 427 |
| 4 | 10.2 | 46.3 | 1.7 | 4.2 | 12.8 | 15.9 | 4.3 | 3.9 | 48 | 42 | 382 | 451 |

* Hydration was accomplished by the intragastric administration of 50 ml of water per kg and the infusion of hypotonic saline at 5.0 ml/min during 4 preliminary clearance periods. Mannitol and vasopressin infusion was initiated 45 minutes before the beginning of period I.

TABLE IX

*The effects of renal artery constriction on maximal urinary osmolality after 40 hours of water deprivation in a dog with unilateral pyelonephritis following contralateral nephrectomy**

| Collection period | Time | V | $U_{osm}$ |
|---|---|---|---|
| | *min* | *ml/min* | *$mO_{sm}$/kg $H_2O$* |
| 1 | 0–32 | | 872 |
| 2 | 32–61 | 0.26 | 936 |
| 3 | 61–81 | 0.27 | 998 |
| 4 | 117–168 | 0.24 | 950 |
| | Arterial constriction at 211 | | |
| 5 | 212–222 | 0.34 | 1,090 |
| | Further constriction at 227 | | |
| 6 | 240–252 | 0.40 | 1,065 |
| | Further constriction at 330 | | |
| 7 | 360–378 | 0.18 | 575 |
| 8 | 433–525 | 0.06 | 500 |

* Dog To (14.2 kg); pyelonephritis was induced in the left kidney 98 days before these studies were performed. The right kidney (i.e., the control kidney) was surgically removed 12 days before the experiments. Two days before the experiments a band was placed about the renal artery of the left kidney which could be constricted with the dog in the unanesthetized state. Glomerular filtration rate of the two kidneys prior to induction of unilateral renal disease was 47 ml/min. Glomerular filtration rate of the remaining pyelonephritic kidney was 16.0 ml/min. Plasma creatinine was 0.84 mg/100 ml in the control state and 1.73 mg/100 ml at the time of the experiment.

than for the normal kidney. In Table VII, the effects of aortic compression on maximal urinary osmolality are shown for the diseased and normal kidneys of a hydropenic animal during low rates of solute excretion. During five periods prior to constriction of the aorta, values for $U_{osm}$ were greater for the normal kidney.[2] Subsequent to aortic constriction the differences between the diseased and normal kidneys were diminished, and during several urine collection periods values for $U_{osm}$ were essentially equal bilaterally.

*Hydration and marked arterial compression.* In the foregoing experiments, attempts have been made to increase the concentrating ability of the diseased kidney by experimental manipulation. Experiments have also been performed employing techniques known to diminish concentrating ability in the normal kidney.

Epstein, Kleeman and Hendrikx (9) have shown that hydration decreases values for $T^c_{H_2O}$ during mannitol and vasopressin infusion in the normal subject. Table VIII depicts the results of mannitol and vasopressin infusion in a representative animal with unilateral renal disease in the hydropenic state (A) and in the hydrated state (B). Hydration was associated with a decrease in $T^c_{H_2O}$/GFR for both kidneys and in this animal as well as in the majority of other dogs on which this experiment was performed, the suppression of $T^c_{H_2O}$/GFR was more marked in the diseased kidney.

In the normal hydropenic dog marked constriction of the renal artery during low rates of urine flow results in a decrease in urinary osmolality (8). In Table IX, the effects of renal arterial constriction are shown in an unanesthetized dog with unilateral pyelonephritis in which the intact kidney had been removed surgically 12 days in advance of the study. The GFR of the remaining kidney was 16 ml per minute whereas the combined GFR of both kidneys in preliminary control studies was 47 ml per minute. With moderate arterial constriction $U_{osm}$ increased; however, with more marked constriction $U_{osm}$ diminished and remained depressed.

## DISCUSSION

Recent observations by Wirz (10), Ullrich (11), Berliner, Levinsky, Davidson and Eden (12) and Gottschalk and Mylle (13) have established the fact that the concentration of urine in the mammalian kidney involves the elaboration of a hypertonic interstitial fluid in the renal medulla and the subsequent diffusion of water out of the collecting ducts into the hypertonic milieu. The elaboration of the hypertonic medullary interstitium appears to depend in large part upon the reabsorption of sodium presumably in the ascending limb of the loop of Henle; the diffusion of water across the collecting ducts is facilitated by the action of antidiuretic hormone (ADH) on the water permeability of this segment. The vasa recta are thought to contribute to the maintenance of a hypertonic medullary fluid by virtue of a countercurrent exchange mechanism oper-

[2] It may be noted that, during the control periods, osmolalities tended to decrease bilaterally. Similar observations have been recorded by Levinsky and colleagues (8) on normal dogs, but the reasons for these spontaneous changes are unknown.

ating between the two limbs of the hairpin capillary loops.[3]

Within the framework of these concepts, a number of specific factors may contribute to a diminished ability to concentrate the urine in chronic renal disease. These include: *1*) impaired transport of sodium into the inner medulla; *2*) impaired permeability of the collecting ducts to the passive diffusion of water despite maximal ADH activity; *3*) alterations in the spatial relationship between the loops of Henle, the collecting ducts and the vasa recta in the inner medulla; *4*) continuing high rates of solute excretion per functioning nephron; *5*) failure to achieve osmotic equilibrium between the urine and the medullary interstitium despite anatomical integrity of the constituent parts; and *6*) augmented rates of vasa recta blood flow.

The present observations permit an evaluation of the significance of certain of these factors in the dog with experimental renal disease.

1. The possibility that sodium transport out of the tubular urine and into the inner medulla was markedly impaired is considered unlikely for the following reasons. *a*) In the animals with unilateral renal disease, the diseased kidneys have retained the ability to elaborate a urine distinctly hypertonic to the plasma. Presumably the osmolality of the medullary interstitial fluid was at least as great as that of the final urine; and it may be assumed that the medullary hypertonicity was produced primarily by means of sodium transport into the medulla. *b*) Present evidence suggests that the dilution of urine involves active reabsorption of sodium in the loop of Henle (and probably in the distal segments) without simultaneous removal of water. Studies previously reported from this laboratory (1) have demonstrated that the diseased kidney in the animal with unilateral renal disease not only can dilute the urine effectively but the values for free-water clearance per unit of glomerular filtrate characteristically have been greater for the diseased kidney than for the contralateral normal organ.

2. The possibility that pathological changes rendered the collecting ducts impermeable to back-diffusion of water seems unlikely in view of the continuing ability of the diseased kidneys to elaborate a urine of high osmolality during conditions of hydropenia. Moreover, during high rates of urine flow induced by mannitol, urea, glucose or sodium chloride infusion, the existence of values for $T^c_{H_2O}/GFR$ within the normal range provides strong evidence in favor of the continuing permeability of the collecting ducts to water.[4]

3. The persisting ability of the diseased kidneys to concentrate the urine in the present experiments also militates against the possibility that the spatial relationships between loops of Henle, vasa recta and collecting ducts were severely distorted as a consequence of fibrosis or other pathological changes in the inner medulla.

4. The present data are not inconsistent with the possibility that continuing high rates of solute excretion (per nephron) may represent a major factor in the genesis of the concentrating changes of chronic renal disease. In all animals, the slightly decreased concentrating ability of the diseased kidney (relative to the normal kidney) was associated with the excretion of a greater fraction of filtered solute by the diseased organ. Moreover, during experimentally induced osmotic diuresis, values for $U_{osm}$ decreased predictably toward the plasma osmolality in the diseased as well as in the normal kidney. Because the total nephron population (i.e., diseased plus normal kidney) invariably exceeded 50 per cent of the

[3] A detailed discussion of these concepts is contained in a recent review by Smith (14).

[4] It is implicit in this assumption that marked absolute falls in $T^c_{H_2O}$ in the diseased kidneys do not represent decreased concentrating capacity if they are proportional to falls in GFR. The basis for this contention may be briefly considered. The decrease in values for GFR in the experimentally diseased kidneys has been accompanied by proportional falls in values for a number of tubular functions. Thus the ratios for $GFR/Tm_{PAH}$, $GFR/Tm_{glucose}$ and $GFR/Tm_{phosphate}$ remain the same in the diseased kidneys as in the contralateral normal kidneys. Preliminary observations also indicate that ammonia and titratable acid excretion per unit of glomerular filtrate remain equal bilaterally (15). These data suggest that the values for GFR in the diseased kidneys provide an index of the population of residual functioning nephrons; and absolute values for $T^c_{H_2O}$ must decrease as the nephron population decreases. Using $T^c_{H_2O}/GFR$ as a means of comparing the concentrating power of different kidneys, ranging from normal to severely contracted chronically diseased organs, it is apparent that $T^c_{H_2O}$ does decrease in proportion to GFR (see Figure 1). That other factors may influence $T^c_{H_2O}$ in the diseased kidney (e.g., GFR per nephron, solute excretion, and so forth) is evident, and the present studies represent an attempt to delineate these factors.

original number, the continuing solute diuresis, which is seen under basal conditions in advanced chronic bilateral renal disease, did not occur. However, it is well documented that in the presence of solute diuresis the maximal attainable urinary osmolality decreases toward isotonicity as the rate of solute excretion increases, even if all constituent parts of the concentrating process are capable of normal operation (i.e., in the normal kidney).[5]

5. The possibility that under certain conditions osmotic equilibrium may fail to occur between the urine and medullary interstitium, despite the anatomical integrity of the constituent parts of the concentrating process, is suggested by recent observations on normal individuals (16, 17). These studies have demonstrated that extremely high rates of solute excretion induced by mannitol infusion may be associated with *decreasing* values for $T^c_{H_2O}$. Perhaps the best explanation for this phenomenon is that the flow rate through the nephron is so brisk that the urine does not return to isotonicity in the distal tubule, and hypotonic urine enters the collecting ducts. The subsequent removal of water from the collecting ducts might then occur without raising the final osmolality of the urine to values appreciably in excess of plasma. Under these conditions it is likely that osmotic equilibrium between the collecting ducts and the medullary interstitium fails to occur.

In the present animals the number of functioning nephrons was never diminished sufficiently to evoke basal rates of solute excretion (per nephron) comparable with those achieved during massive osmotic diuresis in the normal animal or human. However, it is conceivable that, in bilateral renal disease, isotonic or even hypotonic urine could result, in the presence of ADH, despite the intrinsic integrity of the concentrating mechanism.

6. The possibility that vasa recta blood flow was increased in the experimentally diseased kidneys could not be evaluated with existing experimental techniques. However, there are certain considerations which suggest that this phenomenon may have occurred. It has long been suspected that glomerular filtration rate increases in the surviving nephrons of the diseased kidney as an adaptive change (18, 19) and certain of the observations in the present studies are consistent with the thesis that GFR per nephron might be greater in the diseased kidneys than in the contralateral control organs.[6] If GFR per nephron is indeed increased, renal plasma flow per nephron must also be increased because of the fact that filtration fractions typically have been the same for the diseased kidneys as for the normal organs. Finally, if total renal plasma flow per nephron is increased, it is conceivable that vasa recta blood flow may share in this increase. If the flow of blood through the vasa recta was increased in the diseased kidneys, the osmolality of the medullary interstitium would have been diminished despite a constant and maximal transport of sodium from the tubular urine into the inner medulla. This would contribute to a lowering of maximal urinary osmolaltiy.[7] It also seems reasonable that vasa recta blood flow may be increased (perhaps markedly) in bilateral renal disease, particularly when the latter is advanced and associated with a continuous solute diuresis. In this regard, Gottschalk has noted an increased velocity of blood flow through the vasa recta of the exposed hamster papilla during high rates of solute excretion (20).

In the present studies it is apparent that the structural alterations of three forms of experi-

[5] The mechanism of this phenomenon has been discussed in detail by Levinsky and Berliner and associates (8, 12).

[6] These observations include: *a*) Greater values for $C_{osm}/GFR$ and for $U_{Na}V/GFR$ for the diseased than for the control kidneys. *b*) The narrowing of all differences between the diseased and normal kidneys during mannitol diuresis by decreasing the GFR of the diseased organ. *c*) Similar narrowing of differences by aortic constriction during the latter experiments. (If GFR per nephron were greater in the diseased than in the control kidney, the decrease in hydrostatic pressure produced by aortic compression might be expected to diminish the difference.) *d*) In the dog with two normal kidneys, experimental reduction of GFR to one kidney (by renal artery compression) is attended by the emergence of differences between the two kidneys for $C_{osm}/GFR$, $U_{Na}V/GFR$, $U_{osm}$ and $U_{Na}$ (8). The values for the control kidney, which may be assumed to have the greater GFR/nephron, bear the same relationship to the contralateral kidney as do the values for the diseased kidney to its contralateral organ in the present studies.

[7] Berliner and co-workers (12) have postulated that the maximal concentration of the urine is inversely proportional to some power of the vasa recta blood flow between 1 and 2.

mental renal disease did not result in marked impairment of urine concentrating ability. However, the diseased kidneys, when compared with the contralateral normal organs, did exhibit a limited decrease in concentrating capacity. The experimental observations therefore may be examined for information relevant to the nature of this alteration in function.

During high rates of solute excretion, values for $U_{osm}$ and $T^c_{H_2O}/GFR$ have been somewhat lower for the diseased than for the normal kidneys. On the other hand, the fraction of filtered solute (and of filtered sodium) excreted by the diseased kidneys has been greater; and despite the presence of lower urinary osmolalities, values for urinary sodium have been greater. The fact that similar differences existed between the hemi-infarcted kidneys and the contralateral normal kidneys suggests that the differences need not relate to structural abnormalities in the residual nephrons of the contracted organs. Moreover, the fact that all of the differences could be reduced experimentally by decreasing the filtration rate of the diseased kidney suggests that they may relate, at least in part, to functional adaptations in a kidney with a diminished population of nephrons.

Theoretically a greater filtration rate per nephron in the contracted kidney than in the contralateral intact organ could account for the majority of these differences.[8] Thus a greater GFR per nephron would be expected to result in a greater volume of intratubular urine entering each segment of the nephron. Sodium and water reabsorption might proceed isosmotically in the proximal tubules of both kidneys, but the volume of urine entering the loops of Henle would be greater in the diseased kidney. Within the loops, the rate of sodium transport from tubular urine to medullary interstitium may be comparable bilaterally, and equivalent amounts of sodium may also be reabsorbed in the distal segments. Moreover, under the influence of ADH, water may diffuse out of the distal tubules of both kidneys until the urine becomes isosmotic. However, the fluid entering the collecting ducts of the diseased kidney would be greater in volume, and in the presence of an unreabsorbed solute such as mannitol or glucose, it would have a higher sodium concentration.[9] Free-water might then diffuse out of the collecting ducts and into the medullary interstitium until osmotic equilibrium occurred bilaterally. The diseased kidney thus would excrete a greater fraction of its filtered solute and of its filtered sodium; its final urine would have a lower osmolality and the urinary sodium concentration might be greater.

The foregoing sequence of events should result in higher values of $T^c_{H_2O}$ *per nephron* in the diseased organ than in the contralateral intact kidney. The fact that values for $T^c_{H_2O}$ *per unit of GFR* were consistently less for the diseased kidney (and for the hemi-infarcted kidney) must thus be explained. If GFR per nephron is increased in the diseased kidney relative to the intact organ, derived values for $T^c_{H_2O}/GFR$ would be decreased. This, however, would not appear to be a major factor particularly in view of greater values for $C_{osm}/GFR$, sodium clearance/GFR and, as has been noted previously, for free-water clearance/GFR (1). Thus one or more additional factors must be involved to explain the lower values for $T^c_{H_2O}/GFR$ in the presence of higher values for $C_{osm}/GFR$. Among these, increased vasa recta blood flow may be of particular importance.

## SUMMARY AND CONCLUSIONS

The present observations, in concert with studies previously reported (1) provide evidence that the concentrating ability of the experimentally

[8] It is also possible to explain the differences on the basis of a greater filtration rate per unit of tubular function (e.g., an unchanged GFR with suppressed tubular function). However, the consistency of the relationships between GFR and solute excretion in the diseased kidneys (relative to the normal kidneys), as well as previous observations on the interrelationships of glomerular and tubular functions (21) would require a remarkably uniform degree of tubular suppression. Moreover, because of the identity of functional patterns in each of the three lesions studied, this would have to be independent of the histological details of the underlying disease.

[9] This is due to the fact that the unreabsorbed solute (e.g. mannitol) obligates an osmotic equivalent amount of water. The reabsorption of sodium and water isosmotically would therefore serve to decrease the concentration of sodium in the tubular urine. If more filtrate enters the nephrons of the diseased kidney than of the contralateral organ, and if sodium reabsorption is essentially the same bilaterally, there will be more unreabsorbed sodium per unit volume of residual urine in the nephrons of the diseased kidney.

diseased kidney in the dog is not markedly impaired when the contralateral kidney is intact and the internal environment remains essentially normal. Comparison of the concentrating ability of the diseased kidney with that of the normal kidney, however, did reveal certain differences. In the hydropenic state this was reflected by a lower value for maximal urinary osmolality; and during high rates of urine flow induced by mannitol infusion, values for $T^c_{H_2O}/GFR$ were less for the diseased kidney. The slightly lower values for $T^c_{H_2O}/GFR$ characteristically were associated with the excretion of a greater fraction of filtered solute and sodium, lower urinary osmolalities and higher urinary sodium concentrations. These same differences have been noted between hemi-infarcted kidneys (in which the residual nephrons are free of a progressive renal disease) and the contralateral normal kidneys. Moreover, the differences could be diminished substantially by decreasing the filtration rate to the diseased kidney through experimental constriction of the renal artery and also by constriction of the aorta. The data indicate that the structural abnormalities of the three forms of experimental renal disease did not render the concentrating mechanism impotent. It has also been suggested that the modest diminution in concentrating ability (and the associated changes in solute excretion) in the diseased kidneys may have been related, at least in part, to functional adaptations in intact residual nephrons.

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