# Physiological Mechanisms Regulating Rate of Urinary Flow in Renal Disease.* (21003)

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Normally, maximal water diuresis constitutes approximately 15% of the filtered water load, and presumably represents that fraction of the renal tubular reabsorption of water ("facultative reabsorption") which is under the control of the neurohypophysial antidiuretic hormone(1). In patients with chronic renal disease as much as 40 to 60% of the filtered water load may be excreted in the urine(2-7). Two mechanisms have been proposed to explain such excessive excretion of water in chronic renal disease: a) osmotic diuresis(2,3) and b) tubular secretion of water(4,5).

In order to help decide between these possible mechanisms, it seemed of interest to investigate several aspects of the urinary excretion of solutes in patients suffering from renal disease. Although v. Koranyi measured the freezing-point depression of urine in such patients(8), no studies of the relation between the total urinary osmotic load and the rate of urinary flow in these cases have been reported; therefore, one aim of this communication is to describe such observations made here. In addition, data on the relationships among the glomerular filtration rate, clearance ratios, and urinary concentrations of solutes are presented.

*Methods.* The experimental subjects were 7 patients suffering from renal disease: 4 from chronic glomerulonephritis (I.G., F.S., C.L., and S.H.), one from acute glomerulonephritis (K.R.), one from chronic pyelonephritis (P.L.), and the seventh from polycystic kidneys with severe renal insufficiency (E.S.). Four healthy, young males served as control subjects. All subjects were permitted fluids *ad lib.* The patients with renal disease received a diet containing 200 mg sodium per day, unless otherwise indicated. Twenty-four-hour collections of urine were obtained, and in addition, one-half-hour or one-hour samples of urine, obtained by catheterization, were studied in some patients. Twenty-four-hour samples of urine were collected in a bottle containing 250 mg chloromycetin and 250 mg streptomycin in order to minimize bacterial decomposition of urea. *Creatinine chromogen* in serum and urine was measured by Peters' modification of the Folin method(9), urinary and serum sodium and potassium with an internal standard flame photometer(10), chloride by the Van Slyke-Hiller modification of Sendroy's iodometric method(11), and urea by the hypobromite method(12). Measurements of freezing-point depression ($\Delta$ F.P.) of urine and serum were made by means of a Beckmann thermometer. The "effective osmolarity" was calculated as: ($\Delta$ F.P. x 1000)/1.86 = mOsm/l. The "effective urinary osmotic load" (mOsm/min.) was obtained by multiplying the urinary effective osmolarity (mOsm/l) by the rate of urinary flow (1/min.). *Reproducibility and accuracy of measurements with the Beckmann*

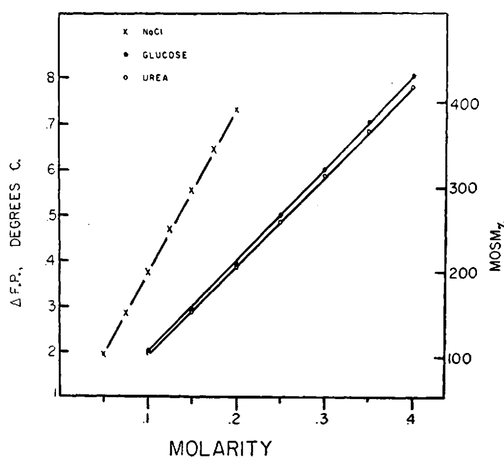


FIG. 1. Freezing-point depression of gravimetrically-standardized solutions of sodium chloride, glucose, and urea by means of the Beckmann thermometer. Each point represents mean of 10 readings on 3 independently-prepared solutions for a given concentration of each substance.

* Aided by a grant from the U. S. Public Health Service (H1245).

*thermometer.* With respect to the reproducibility of measurements of freezing-point depressions by means of the Beckmann thermometer, the average deviation per specimen (for 174 readings on 58 specimens) was .002°C. Fig. 1 shows the freezing-point depressions of gravimetrically-standardized solutions of sodium chloride, glucose and urea, employing 7 concentrations of each substance. Each solution was prepared independently 3 times and 10 readings were taken on the 3 solutions of each concentration. Thus, the data in Fig. 1 were obtained from 210 readings. First, it will be noted that the freezing-point depressions for sodium chloride, glucose and urea are directly proportional to their concentrations, as demonstrated by the straight lines in Fig. 1. For glucose, the slope of the line in Fig. 1 is 2.01°C/mol. which exceeds the theoretical value of 1.86°C/mol. by 8.1%. The slope of the line for urea is 1.94°C/mol. which is 4.3% greater than the calculated 1.86°C. If sodium chloride were completely ionized and there were no ionic interactions, then the anticipated freezing-point depression would be 3.72°C/mol. which is 3.2% greater than the observed slope of the line in Fig. 1, 3.6°C/mol. According to the International Critical Tables the molal freezing-point depressions for a 0.2 M solution of sodium chloride should be 3.424°C; we obtained a value of 3.665°C which is 7.0% greater. Thus, because such a high fraction of plasma osmolarity results from its content of sodium salts, our measurements of the plasma freezing-point depression are within approximately 3% of the true value. In urine where urea composes approximately one-half the total solute, the determined "effective osmolarity" in these studies is thus approximately 2% in excess of the true value. We have not made any corresponding corrections of "effective osmolarity" because they would not alter the physiological conclusions.

*Results.* I. *General.* Table I contains representative measurements of urinary solutes and clearance ratios in the 7 patients suffering from renal disease and in the 4 normal subjects. The plasma concentrations of electrolytes may be calculated from the data presented. It will be noted that the 24-hour

TABLE I. Representative Values for Urinary* Solutes in Patients with Renal Disease and in Normal Subjects.

| Patient | $C_{Cr}$, ml/min. | V, ml/min. | Total solutes mOsm†/l | Total solutes mOsm/min. | Urea, mM/l | Na, mEq/l | Cl, mEq/l | K, mEq/l | Clearance ratios (%) $V/C_{Cr}$ | $C_{os}/C_{Cr}$ | $C_{Na}/C_{Cr}$ | $C_{Cl}/C_{Cr}$ | $C_K/C_{Cr}$ | $\frac{2(Na+K)}{\text{Total solutes}}$, % | BUN, mg % | Total solutes serum, mOsm†/l |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Renal disease | | | | | | | | | | | | | | | | |
| I.G. | 9 | 1.82 | 299 | .544 | — | 40.0 | 47.6 | 27.3 | 20 | 17.5 | 5.9 | 9 | 153 | 45 | 81 | 345 |
| I.G.‡ | 11 | 2.49 | 267 | .664 | — | 55.8 | 55.0 | 20.0 | 25 | 17.9 | 8.9 | 12 | 95 | 57 | 80 | 337 |
| F.S. | 9 | .31 | 389 | .121 | 318 | 15.3 | 22.4 | 36.4 | 3.4 | 4 | .4 | .9 | 21 | 27 | 65 | 330 |
| F.S.‡ | 11 | .86 | 235 | .202 | 67 | 32.9 | 30.5 | 41.0 | 7.8 | — | 1.8 | 2.2 | 68 | 63 | 38 | — |
| C.L. | 20 | 2.01 | 256 | .515 | — | 29.2 | 29.9 | 23.0 | 10 | 8 | 2.0 | 2.8 | 55 | 38 | 41 | 324 |
| P.L. | 57 | 1.09 | 415 | .452 | 166 | 50.8 | 43.0 | 32.0 | 1.9 | 2.6 | .7 | .9 | 8 | 36 | 18 | 310 |
| K.R. | 4 | 1.42 | 174 | .247 | 52 | 23.9 | 21.3 | 27.8 | 36 | — | 6.5 | 7.4 | 174 | 59 | 83 | — |
| S.H. | 20 | 1.41 | 382 | .539 | — | 50.5 | 47.7 | 38.0 | 7.1 | 8.1 | 2.5 | 3.2 | 61 | 46 | 62 | 333 |
| E.S. | 3 | .81 | 291 | .236 | 117 | 50.0 | 37.2 | 21.0 | 27 | 24 | 12 | 12 | 167 | 56 | 156 | 332 |
| Normal subjects | | | | | | | | | | | | | | | | |
| G.B. | 97 | .54 | 1017 | .550 | 356 | 162 | 168 | 97 | .6 | 1.8 | .7 | .9 | 14 | 51 | 22 | 312 |
| H.P. | 128 | .48 | 1290 | .622 | 472 | 231 | 207 | 109 | .4 | 1.6 | .6 | .7 | 9 | 53 | 19 | 304 |
| S.A. | 63 | .58 | 849 | .488 | 213 | 113 | 113 | 84 | .9 | 2.5 | .7 | — | — | 46 | 13 | 315 |
| R.R. | 107 | 1.58 | 484 | .765 | — | 50 | 69 | 50 | 1.5 | 2.3 | .5 | .9 | 12 | 41 | 11 | — |

* Twenty-four hr collections of urine. Fluids permitted *ad lib.* † $\frac{\Delta \text{F.P.} \times 1000}{1.86}$. ‡ Supplemental sodium chloride administered orally.

$C_{Cr}$ = endogenous creatinine chromogen clearance; V = rate of urinary flow.

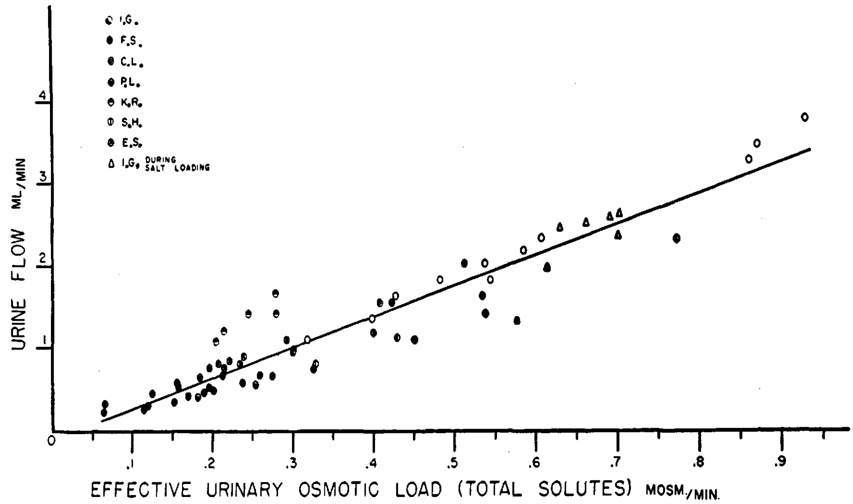


FIG. 2. Relation between rate of urine flow (ml/min.) and effective urinary osmotic load (total solutes) (mOsm/min.) in renal disease. Fluids permitted *ad lib.* K.R. is patient suffering from acute glomerulonephritis.

urinary volumes of the patients with renal disease represent much greater proportions of the daily filtered water load than those of the normal subjects (column $V/C_{Cr}$). The urine is hypotonic to plasma in patients I.G., F.S. (while receiving supplemental salt orally), C.L., K.R., and E.S. In all 7 patients the urinary concentrations of sodium and chloride are hypotonic to those in the plasma. It will be noted that $C_{os}/C_{Cr}$ approximates $V/C_{Cr}$ more closely than any other clearance ratio in the patients with renal disease. Using 2 (Na + K) mEq/l as a measure of the major portion of urinary electrolytes, the mean value for [2 (Na + K) mEq/l]/(total solutes, mOsm/l) in the patients with renal disease (47.4%) is approximately the same as the mean for the normal subjects (47.8%).

II. *Rate of urinary flow, effective urinary osmolarity, and effective urinary osmotic load.* A. *Flow versus osmotic load.* Fig. 2 shows a linear relationship between the urinary osmotic load (mOsm/min.) and the rate of urinary flow (ml/min.) in patients suffering from renal disease, including the periods during which I.G. and F.S. received supplemental salt orally. This holds for 24-hour collections of urine, as well as for one-half-hour and one-hour catheterized specimens of urine. The slope of the line, $\Delta y/\Delta x$, equals 1 ml/0.280 mOsm, indicating that the increase in urinary flow, associated with an increase in urinary osmotic load, is slightly hypotonic.

III. *Relationships among the glomerular filtration rate, clearance ratios, and urinary concentrations of solutes.* A) *$C_{Cr}$ versus $C_{os}/C_{Cr}$, $V/C_{Cr}$ and $C_{Na}/C_{Cr}$.* These relationships are depicted in Fig. 3. Each of these clearance ratios appears to be related to the glomerular filtration rate in a curvilinear fashion. The graph for $C_{os}/C_{Cr}$ vs. $C_{Cr}$ approximates that for $V/C_{Cr}$ vs. $C_{Cr}$ more closely than the one for $C_{Na}/C_{Cr}$ vs. $C_{Cr}$. Both maximum $C_{os}/C_{Cr}$ and maximum $V/C_{Cr}$ exceeded 40% in this series of patients with renal disease. B) *V/GFR versus glomerular* filtration rate (GFR). Data for $V/C_{Cr}$ vs. $C_{Cr}$ vs. $C_{Cr}$ obtained in the present studies are plotted in Fig. 4 along with those of Nickel *et al.*(3) who employed the clearance of inulin ($C_{in}$) as a measure of the glomerular filtration rate, and those of Roscoe(5) who used $C_{Cr}$. There is a general agreement of the results obtained in the three series of studies, in which maximum V/GFR exceeds 60% and appears to be related to the GFR in a curvilinear manner. V/GFR exceeds 15% when the GFR decreases to approximately 10 ml/min. C) *$C_K$/GFR versus GFR.* Fig. 5 presents the collected data on $C_K$/GFR vs. GFR of the present studies, as well as those of Nickel *et al.*(3) and of Roscoe(5). Again there is

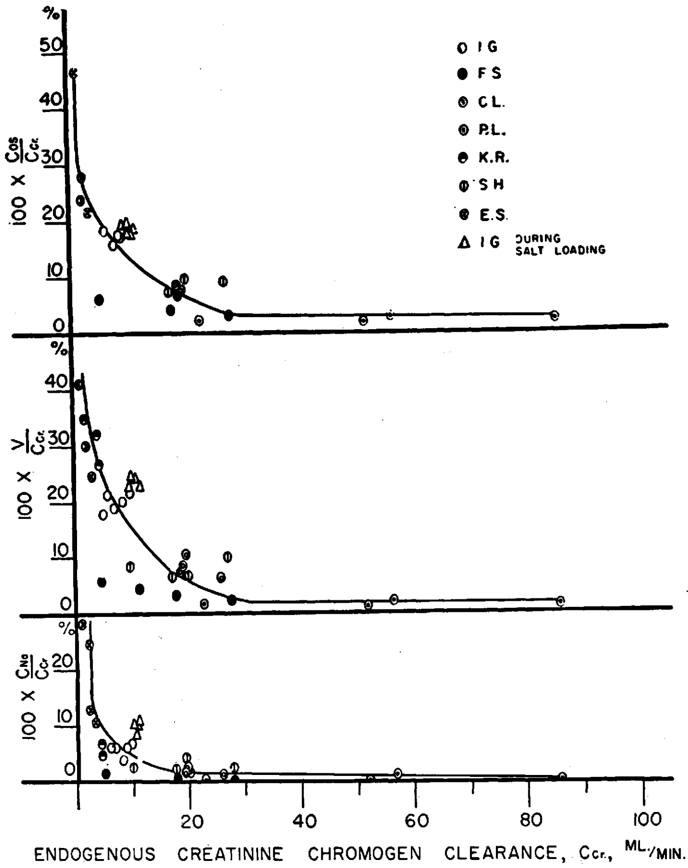


FIG. 3. Relation of clearance ratios of total solutes and sodium to glomerular filtration rate (measured by endogenous creatinine chromogen clearance). Clearance ratio of water exceeds 15% when $C_{Cr}$ decreases to approximately 10 ml/min. or less. $C_{os}/C_{Cr}$ vs $C_{Cr}$ approximates $V/C_{Cr}$ vs $C_{Cr}$ more closely than does $C_{Na}/C_{Cr}$ vs $C_{Cr}$.

a general agreement among the 3 laboratories, and $C_K$/GFR exceeds 100% when the GFR decreases to approximately 10 ml/min. D) *Relation of Pitressin antidiuresis to GFR.* In order to amplify the interrelationships between the glomerular filtration rate and renal function in patients suffering from renal disease, Table II presents data on the antidiuretic response of 5 other patients with chronic renal disease to a single intravenous dose of Pitressin (0.57 mU/Kg) administered during continuous intravenous hydration with 5% glucose in water(7). There is a distinct difference in the antidiuretic response between the 3 patients (S.S., W.D., Y.S.) with a GFR of 14 ml/min. or less, and the other 2 (G.F., J.W.) in whom the GFR was 19 and 24 ml/min., respectively. E) *Urinary concentrations of sodium potassium and total solutes versus $V/C_{Cr}$.* 1. *Sodium* Fig. 6 presents data on the relation of the urinary concentration of sodium to $V/C_{Cr}$. The points have also been differentiated with respect to values of $C_{Cr}$ greater or less than 10 ml/min. There is a tendency toward a linear relationship for those instances in which $C_{Cr}$ is less than 10 ml/min. (hollow dots), but such a relationship is not suggested for the cases with a $C_{Cr}$ greater than 10 ml/min. (solid dots). 2. *Potassium.* Fig. 7 is a scatter diagram of the relation of the urinary concentration of potassium to $V/C_{Cr}$. Again the points have been differentiated with reference as to whether $C_{Cr}$ is greater or less than 10 ml/min. A linear relationship between K (mEq/l) and $V/C_{Cr}$ is possibly more apparent for those patients with $C_{Cr}$ less than 10 ml/min. (hollow dots), but is not striking in any case. 3. *Total solutes.* Fig. 8 shows the nature of the interrelationship between the effective urinary osmolarity and $V/C_{Cr}$, with the points also indicating whether the respective $C_{Cr}$ is greater or less than 10 ml/min. The plateau of urinary osmolarity for the points (hollow dots) representing values of less than 10 ml/min. for $C_{Cr}$ is apparent.

*Discussion.* 1. *Rate of urinary flow, effective urinary osmolarity and osmotic load.* A. *Flow versus osmotic load.* The observed linear relationship between the urinary osmotic load (mOsm/l) and the rate of urinary flow (ml/min.) (Fig. 2) suggests that osmotic diuresis is the major physiological mechanism regulating the rate of urinary flow in these patients with renal disease. The exact extent to which normal renal function must be depressed by disease for this physiological mechanism to become apparent remains to be determined. Although it has been suggested that the excessive excretion of water in patients with renal disease may be related to impaired reabsorption of electrolytes(2) or of sodium(3), reference to Table II and Fig. 3 shows a closer parallelism between $V/C_{Cr}$ and $C_{os}/C_{Cr}$ than between the clearance ratio of water and that of sodium or any other single solute, thus emphasizing that the excretion of total solute is a more important determinant of the excretion of water in these patients with renal disease than is the excretion of sodium.

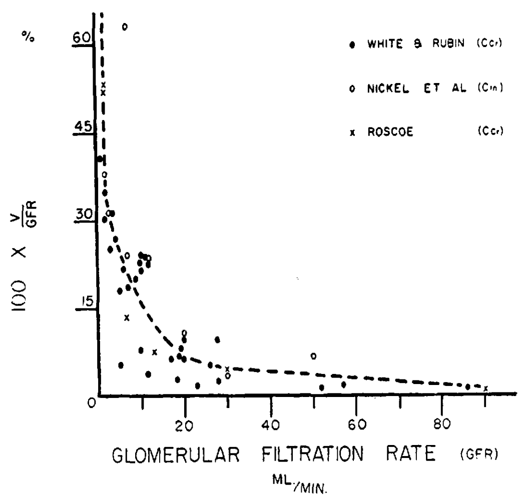


FIG. 4. Relation of clearance ratio of water to glomerular filtration rate. V = urine flow (ml/min.).

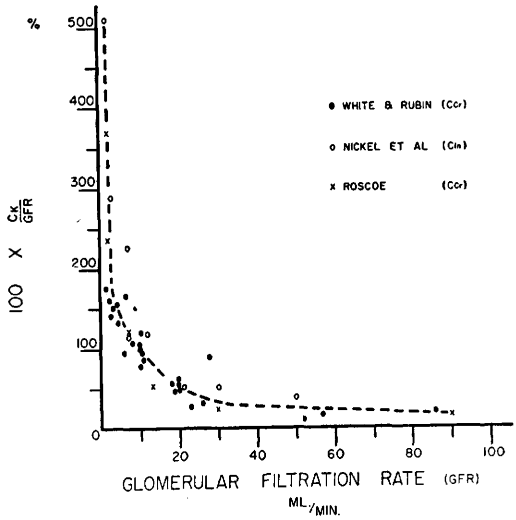


FIG. 5. Relation of clearance ratio of potassium to glomerular filtration rate.

II. *Relationships among the glomerular filtration rate, clearance ratios, and urinary concentrations of solutes.* A. Before discussing these relationships, a comment may be in order concerning the reliability of the endogenous creatinine chromogen clearance as an estimate of GFR in patients with severe kidney disease. Table II, based on some of our earlier data(7), shows that the mean $C_{Cr}/C_{In}$ for 5 similar patients was 1.03. Furthermore, in Fig. 4 and 5 we have plotted data taken from Nickel *et al.*(3) who employed inulin clearance to measure GFR, and

TABLE II. The Relation of Pitressin Antidiuresis to Glomerular Filtration Rate.*

| | GFR | | Pitressin antidiuresis | |
|---|---|---|---|---|
| Patients | $C_{In}$, ml/min. | $C_{Cr}$, ml/min. | % inhibition | Duration Pitressin effect, min. |
| S.S. | 8.0 | 6.4 | 5.4 | 36 |
| W.D. | 13 | 11 | 6.5 | 30 |
| Y.S. | 14 | 14 | 0 | 0 |
| G.F. | 19 | 19 | 24.2 | 49 |
| J.W. | 24 | 33 | 31.8 | 46 |

* Data from White, Kurtz and Rubin(7).

$$\% \text{ inhibition} = \frac{\text{Expected diuresis minus observed diuresis} \times 100}{\text{Expected diuresis}}.$$

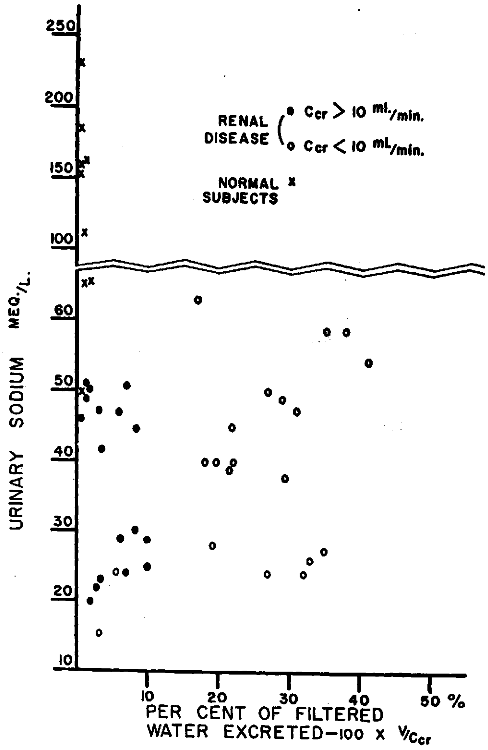


FIG. 6. Relation of urinary concentration of sodium (mEq./l) to $\frac{V \times 100}{C_{Cr}}$. A linear relationship between these variables is possibly more apparent for those patients with $C_{Cr}$ less than 10 ml/min. (hollow dots).

it is evident that their observations are entirely consistent with ours based on $C_{Cr}$, as well as with Roscoe's employing $C_{Cr}$. It must be acknowledged that at very low glomerular filtration rates any means of estimation of the GFR may be in error. B. An interesting parallelism in the relationships between V/GFR and GFR and $C_K$/GFR vs. GFR, is depicted in Fig. 4 and 5. The two curves are superimposable, but whether or not this is a happenstance or represents some similarity in the handling of water and potassium by the diseased kidney must be a very speculative point with the evidence at hand. It is of interest that V/GFR exceeds 15% and $C_K$/GFR exceeds 100% when the GFR decreases to approximately 10 ml/min. Roscoe(5) observed that "in two normal subjects and five cases of renal failure the urinary concentrations of sodium, chloride, potassium, phosphorus, urea and protein varied with the ratio (filtration rate)/(urine volume), the relationship in each case being of the form: urine concentration = A. (filtration rate)/urine volume + B". In Fig. 6, 7 and 8 are plotted similar calculations for sodium, potassium and total solute, employing data obtained from our patients with renal disease. Inspection of these scatter diagrams does not seem to demonstrate the linear relationships described by Roscoe(5).

*Summary and conclusions.* 1. A linear relationship was observed between the urinary osmotic load (mOsm/min.) and the rate of urinary flow (ml/min.) in 7 patients suffering from renal disease. This suggests that osmotic diuresis is the major physiological mechanism regulating the rate of urinary flow in these patients with renal disease. 2. In these patients with renal disease there appears to be a "critical" level of the glomerular filtration

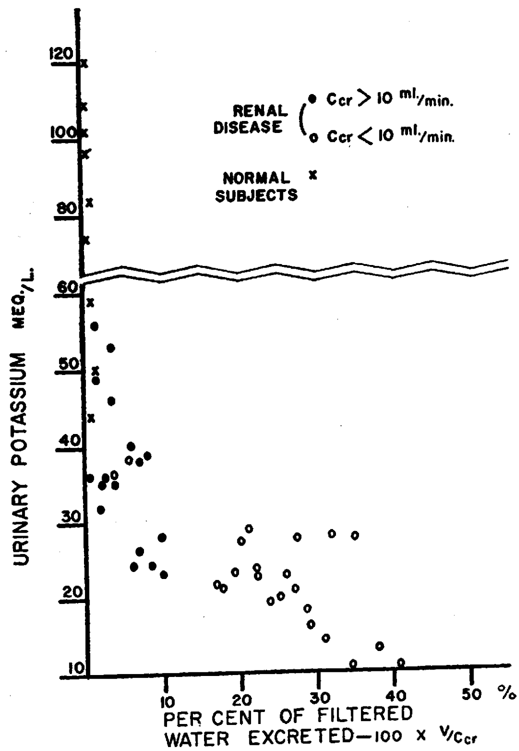


FIG. 7. Relation of urinary concentration of potassium (m.Eq./l) to $\frac{V \times 100}{C_{Cr}}$. A linear relationship between these variables is possibly more apparent for those patients with $C_{Cr}$ less than 10 ml/min. (hollow dots).

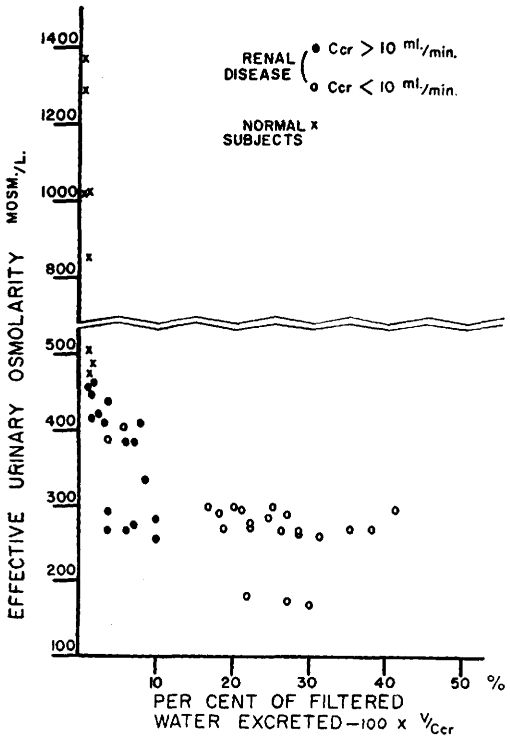


FIG. 8. Relation of effective urinary osmolarity (mOsm/l) to $\frac{V \times 100}{C_{Cr}}$. There is an apparent heterogeneity of populations, depending upon whether $C_{Cr}$ exceeds or is less than 10 ml/min.

rate, approximately 10 ml/min., at which: a) $C_K/C_{Cr}$ exceeds 100%; b) $V/C_{Cr}$ exceeds 15%; c) the antidiuretic response to single intravenous injections of pitressin in physiological dosage (0.57 mU/Kg) is markedly diminished; d) there is an alteration in the relationship between $V/C_{Cr}$ and the urinary concentrations of sodium, potassium and total solute.

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## Effect of Total Body Irradiation on Rabbit Pituitary as Measured by Gonadotropin Response in Chicks.* (21004)

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Certain lines of evidence have suggested that endocrine imbalances occur following total body irradiation. Botkin(1) found in the rat thyroid following irradiation an initial 24-hour upsurge of activity followed by a progressive decline until the 6th day. Response after that time was not reported. Monroe(2) reported an initial increase under the same conditions but that on the 7- and 30-day analyses the response was the same as in the controls. Both investigators used as an index of "activity" the ability of the rat thyroid to incorporate $I^{131}$ into its protein bound fractions. Patt(3) reported a progressive increase in adrenal activity which was measured by an increase in gland weight. Early reports in the literature by Witschi(4) showed that male rats could be sterilized by exposing the scro-

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