Journal of Clinical Investigation
Vol. 41, No. 12, 1962

THE EFFECTS OF SALT RESTRICTION ON THE RENAL CONCENTRATING OPERATION IN NORMAL, HYDROPENIC MAN *

By RICHARD M. STEIN,† BARRIE H. LEVITT, MARVIN H. GOLDSTEIN,† JEROME G. PORUSH,† GILBERT M. EISNER,† AND MARVIN F. LEVITT

(From the Section of Renal Diseases, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.)

(Submitted for publication June 18, 1962; accepted July 30, 1962)

In the presence of antidiuretic hormone, the elaboration of a concentrated urine by the absorption of solute-free water depends upon the osmotic gradient established between collecting duct fluid and the hypertonic medullary interstitium (1–3). The quantity of solute deposited within the medulla depends, in large part, upon the rate at which sodium is presented to the ascending limb of the loop of Henle (2, 4, 5).

Considerable evidence indicates that prolonged salt restriction results in a decreased extracellular fluid volume and glomerular filtration rate (GFR) coincident with a sharp reduction in sodium excretion (6–8). It might be anticipated that such changes could affect medullary salt supply and thereby influence the renal concentrating operation. The reported effects of salt restriction on the concentrating operation appear to vary depending upon the species studied. Experiments in the dog have demonstrated that dietary salt restriction reduces maximal urine osmolality (9, 10), whereas similar studies in man (4) and the rat (11) have failed to reveal any such alteration.

The present studies were undertaken in order to elucidate further the effects of prolonged salt restriction on the concentrating operation in normal man under conditions of maximal hydropenia.

METHODS

Three experimental protocols were employed in maximally hydropenic subjects free of cardiovascular or renal disease. In the experiments of Group I, a solute diuresis was established with a hypertonic mannitol infusion in subjects maintained on both high and low salt diets. In those of Group II, subjects prepared as in Group I received intravenous aminophylline during a mannitol diuresis at high levels of solute clearance. In those of Group III, similarly prepared subjects received aminophylline at low levels of solute clearance during a mannitol diuresis.

Maximal hydropenia was established in all subjects by a 16-hour overnight fast. Twelve hours before the study, each subject received 5 U of vasopressin tannate in oil intramuscularly. Urine was collected in 11 female subjects by bladder catheterization, with emptying assured by double air washouts. In five male subjects, urine was obtained by spontaneous voiding. After priming doses of inulin and para-aminohippurate (PAH), an intravenous infusion was administered at a constant rate of 1.0 ml per minute with a Bowman constant infusion pump. This infusion contained aqueous vasopressin in a concentration adequate to deliver 50 mU per kg body weight per hour and sufficient quantities of inulin and PAH to produce satisfactory plasma levels. Urine specimens were collected at approximately 10- to 30-minute intervals. Heparinized blood specimens were obtained at 30- to 60-minute intervals throughout the study. The three experimental protocols of the present studies are described below.

Group I. Six subjects were studied after 7 days of a high salt diet containing at least 250 mEq of sodium per day, and again after 7 days of a low salt diet containing 25 mEq of sodium per day. In addition, three of these subjects were studied on a third occasion after a high salt diet had been reinstituted. One hundred grams of protein per day were included in both diets. After 2 to 4 control urine collections were obtained, a solute diuresis was established by the infusion of a hypertonic (10 per cent) mannitol solution. The infusion was administered at increasing rates until a urine flow of 12 to 25 ml per minute was achieved.

Group II. In six salt-restricted subjects and in four subjects maintained on high salt diets, a hypertonic mannitol solution was infused until urine flow was stabilized at rates greater than 8 ml per minute, ranging from 8 to 20 ml per minute. After this steady state of urine flow was achieved, aminophylline was administered intravenously at the rate of 12.5 to 25 mg per minute for 20

* Supported by Grant A-277 from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.; presented in abstract form at the 54th Annual Meeting, American Society for Clinical Investigation, May, 1962 (see J. clin. Invest. 1962, 41, 1402).

† U. S. Public Health Service Postdoctoral Research Fellow, National Heart Institute, Bethesda, Md.

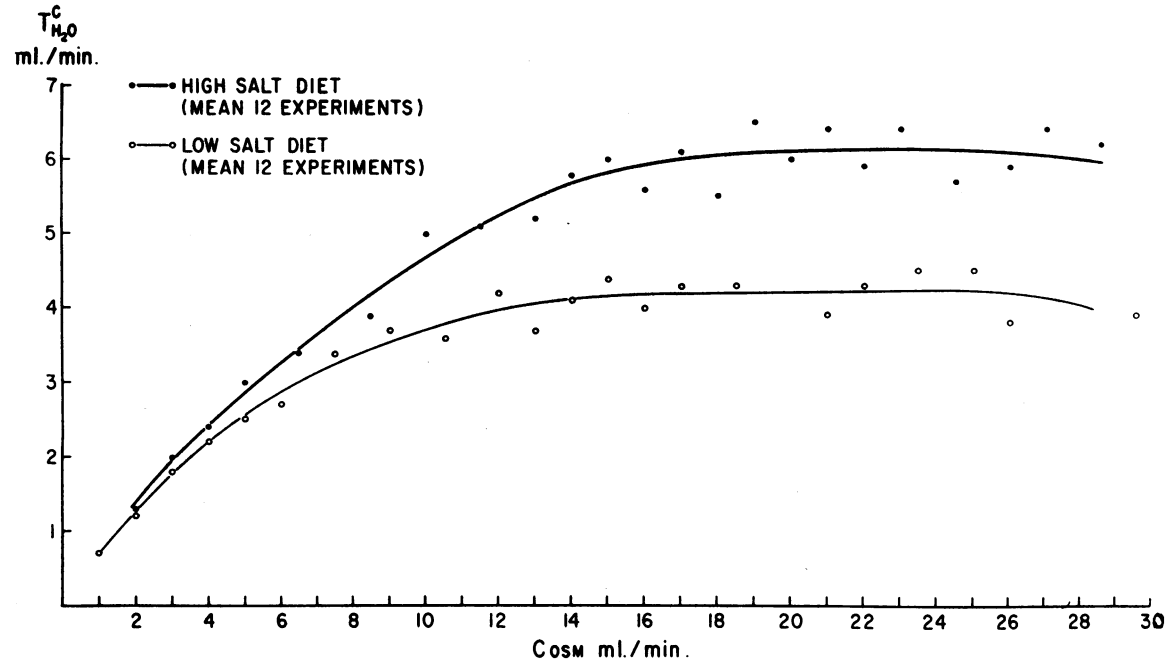

FIG. 1. EFFECT OF HIGH AND LOW SALT DIETS ON FREE WATER REABSORPTION ($T^c_{H_2O}$) AND SOLUTE CLEARANCE (C_{osm}) DURING MANNITOL DIURESIS. All C_{osm} and corresponding $T^c_{H_2O}$ values are grouped about successive 1-ml increments in C_{osm} and represent the mean values for each group.

minutes. Urine collections were continued for the subsequent 45 minutes.

Group III. In six salt-restricted subjects, aminophylline was administered during the course of a mannitol diuresis before urine flow rates had reached 3 ml per minute. In separate control studies performed in these salt-restricted subjects, a solute diuresis was produced by the infusion of hypertonic mannitol alone. In two of

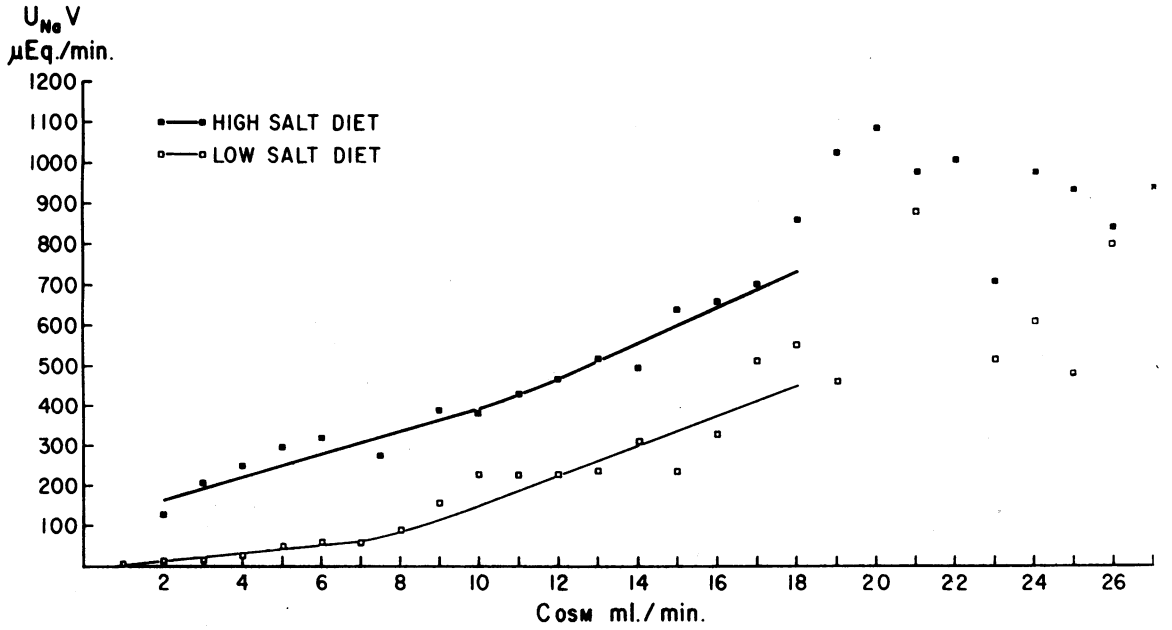

FIG. 2. EFFECT OF HIGH AND LOW SALT DIETS ON SODIUM EXCRETION ($U_{Na}V$) AND SOLUTE CLEARANCE (C_{osm}) DURING MANNITOL DIURESIS. All C_{osm} and corresponding $U_{Na}V$ values are grouped about successive 1-ml increments in C_{osm} and represent the mean values for each group.

these subjects, an additional mannitol diuresis was established 1 week after the institution of a high salt diet. In another group of control studies, five salt-fed subjects received aminophylline during the course of a mannitol diuresis before urine flow rates had reached 3 ml per minute.

All urine and blood specimens were analyzed for osmolality and sodium, potassium, chloride, urea, inulin, and PAH concentrations. Osmolalities were determined with a Fiske osmometer. Other determinations were performed by methods previously described from this laboratory (4). GFR and effective renal plasma flow were measured as the clearances of inulin and PAH, respectively. Solute clearance (C_{osm}) was calculated from the formula $C_{osm} = U_{osm}V/P_{osm}$, where U_{osm} represents urine osmolality, V the rate of urine flow in ml per minute, and P_{osm} plasma osmolality. The rate of free water reabsorption ($T^c_{H_2O}$) was calculated as $T^c_{H_2O} = C_{osm} - V$.

TABLE I

Mannitol diuresis in subjects on high and low salt diets *

Subject	Diet	Urine flow †	U_{max} †	$U_{Na}V$ †	U_{urea}/U_{osm} †	C_{osm} range	$T^c_{H_2O}$ ‡ Mean maximum	C_{inulin} Mean §
		ml/min	*mOsm/kg H_2O*	*μEq/min*		*ml/min*	*ml/min*	*ml/min*
J.D.	High salt I	0.9	1,384	207	0.25	3.6–33.4	7.7	101
	Low salt	0.4	1,380	2	0.40	1.7–25.9	5.4	85
	High salt II	0.7	1,118	80	0.20	2.2–30.7	6.9	101
G.E.	High salt I	0.5	1,128	34	0.36	2.0–31.0	9.0	122
	Low salt	0.6	922	2	0.46	1.7–27.3	4.6	94
	High salt II	0.6	1,140	51	0.30	1.6–30.9	8.8	98
J.P.	High salt I	0.8	1,390	93	0.30	2.4–30.3	6.5	105
	Low salt	0.6	1,123	4	0.39	1.9–24.7	5.1	89
	High salt II	0.9	1,264	185	0.23	3.3–27.0	6.9	101
N.B.	High salt	1.3	1,350	222		3.8–30.7	7.3	92
	Low salt	0.5	1,270	22		1.7–26.4	5.7	78
T.R.	High salt	0.8	812	126		2.1–20.2	6.1	89
	Low salt	0.4	759	6		1.0–17.0	4.6	84
B.L.	High salt	1.1	738	322		2.8–22.0	5.5	94
	Low salt	0.3	743	3		0.9–15.6	3.4	65
G.C.	High salt	1.0	1,037	294		2.9 –20.7	5.7	84
	Low salt	0.4	1,086	34		1.5 –18.2	4.5	84
F.M.	High salt	1.0	827	217		2.8–17.5	4.5	81
	Low salt	0.6	806	3		1.5–15.0	3.5	66
M.G.	High salt	0.9	1,115	210		3.4–22.4	5.9	83
	Low salt	0.6	963	12		1.9–21.2	4.8	94
M.W.	High salt	0.7	790	192		1.9–13.6	4.0‖ (C_{osm} 11.2)	64
	Low salt	0.4	871	8		1.3–11.2	4.0‖	70
J.F.	High salt	1.0	646	175		2.1–13.1	4.4‖ (C_{osm} 12.6)	120
	Low salt	0.9	640	2		1.5–12.6	3.3‖	82
R.L.	High salt	0.6	771	146		1.7–14.0	4.6‖ (C_{osm} 10.9)	73
	Low salt	0.3	821	2		0.8–10.9	2.6‖	111
Mean	High salt	0.88	958	185		2.54	5.88	90.0
	Low salt	0.50	949	8		1.45	4.29	83.5

* Abbreviations: $U_{Na}V$ = rate of sodium excretion, U_{urea}/U_{osm} = fraction of urine solute composed of urea, C_{osm} = solute clearance rate, $T^c_{H_2O}$ = rate of free water reabsorption, C_{inulin} = inulin clearance rate.

† Measurements obtained before the infusion of mannitol.

‡ The maximal $T^c_{H_2O}$ value derived from the plateau portion of the $T^c_{H_2O}$-C_{osm} curve in each study.

§ Mean clearance of inulin from all collection periods during the mannitol diuresis.

‖ Within the range of C_{osm} attained in these studies, $T^c_{H_2O}$ may not have reached maximal levels. The recorded $T^c_{H_2O}$ values are compared at the C_{osm} noted in parentheses.

RESULTS

1. *Mannitol diuresis in subjects on high and low salt diets.* Maximal $T^c_{H_2O}$ was diminished by dietary salt restriction in 11 of 12 subjects. The mean maximal $T^c_{H_2O}$ in the salt-restricted subjects was 4.3 ml per minute and that in the high salt subjects 5.9 ml per minute. Composite curves from all studies performed on each diet are shown in Figure 1, where $T^c_{H_2O}$ has been plotted against C_{osm}. As C_{osm} increased beyond 4 ml per minute, the difference in $T^c_{H_2O}$ between the two groups became apparent. In subjects on high salt diets, $T^c_{H_2O}$ values increased progressively until C_{osm} approached 17 ml per minute, whereas $T^c_{H_2O}$ in salt-restricted subjects increased more slowly and became stabilized at a C_{osm} of 14 ml per minute. Thereafter, $T^c_{H_2O}$ values in both groups remained maximal over a wide range of C_{osm}, but showed a slight tendency to fall as C_{osm} increased beyond 25 ml per minute.

Despite the difference in $T^c_{H_2O}$, maximal urine

TABLE II

*Aminophylline administered to subjects on a low salt diet at high levels of solute clearance**

Subject	C_{osm}	$T^c_{H_2O}$	$U_{Na}V$	C_{inulin}
	ml/min	*ml/min*	*μEq/min*	*ml/min*
M.W.	11.0 † Aminophylline	4.0	321	77
	14.1	3.9	673	78
	20.7	3.2	1,360	122
J.F.	11.8 † Aminophylline	3.3	248	84
	16.0	3.4	655	94
	26.1	2.4	1,560	116
R.L.	10.5 † Aminophylline	2.6	400	111
	12.6	2.3	815	133
	18.1	1.7	1,570	151
T.R.	16.6 † Aminophylline	4.6	613	87
	22.9	4.9	1,120	103
	30.8	3.8	1,940	108
B.L.	15.4 † Aminophylline	3.4	316	60
	24.5	3.7	749	79
	30.7	2.9	1,330	89
M.G.	21.2 † Aminophylline	4.6	859	96
	24.9	3.7	1,250	104
	30.4	4.4	1,540	129

* Abbreviations as in Table I.
† Mean of 3 collection periods obtained in a steady state before the administration of aminophylline.

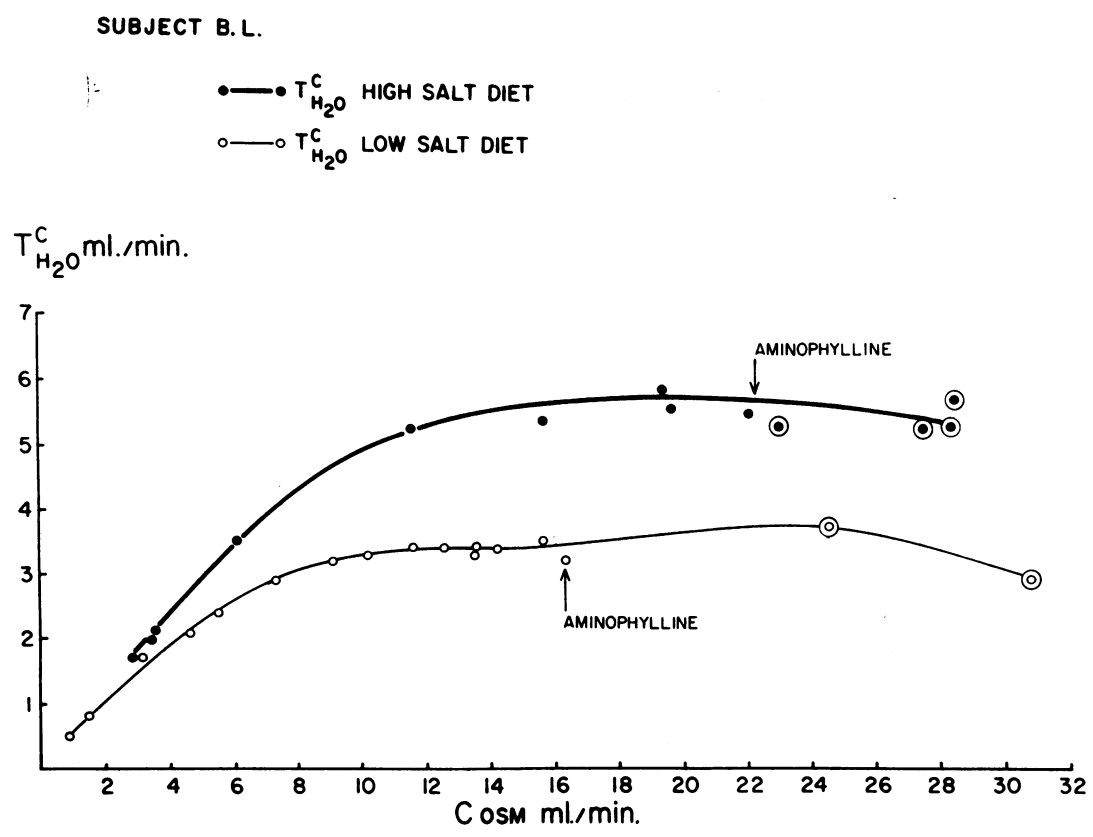

FIG. 3. EFFECTS OF AMINOPHYLLINE SUPERIMPOSED ON A MANNITOL DIURESIS AT HIGH LEVELS OF SOLUTE CLEARANCE. Typical experiments performed in Subject B.L. on high and low salt diets are depicted.

osmolalities were comparable in both groups of subjects, averaging 958 and 949 mOsm per kg on high and low salt diets, respectively. Plasma osmolalities were also comparable. However, control V, C_{osm}, and $T^c_{H_2O}$, before the administration of mannitol, were lower in the salt-restricted subjects.

Control rates of sodium excretion in the salt-restricted subjects averaged 8 μEq per minute, compared to 185 μEq per minute in the group maintained on a high salt diet. A composite curve relating sodium excretion to C_{osm} for all subjects on both dietary regimens is presented in Figure 2. As C_{osm} rose from control levels to 7 to 11 ml per minute, the rate of sodium excretion in both groups of subjects increased only modestly, but thereafter rose at a more rapid rate. In the salt-restricted subjects, sodium excretion remained lower at every level of C_{osm}. At high levels of solute clearance, however, sodium excretion in the salt-restricted group exceeded the control rates of excretion noted in the subjects on a high salt diet. No significant differences in plasma sodium concentrations were noted in the subjects maintained on the two diets.

In the control collection periods, before the infusion of mannitol, the fraction of urine solute composed of urea (U_{urea}/U_{osm}) was consistently higher in the salt restricted subjects (Table I). Because of the lower control rates of urine flow in these subjects, rates of urea excretion ($U_{urea}V$) were similar in both dietary groups. During the ensuing mannitol diuresis, urine urea concentrations fell markedly and the difference noted between the two groups at control rates of urine flow tended to disappear.

GFR in subjects fed a low salt diet averaged 7 per cent less than that noted in salt-fed subjects

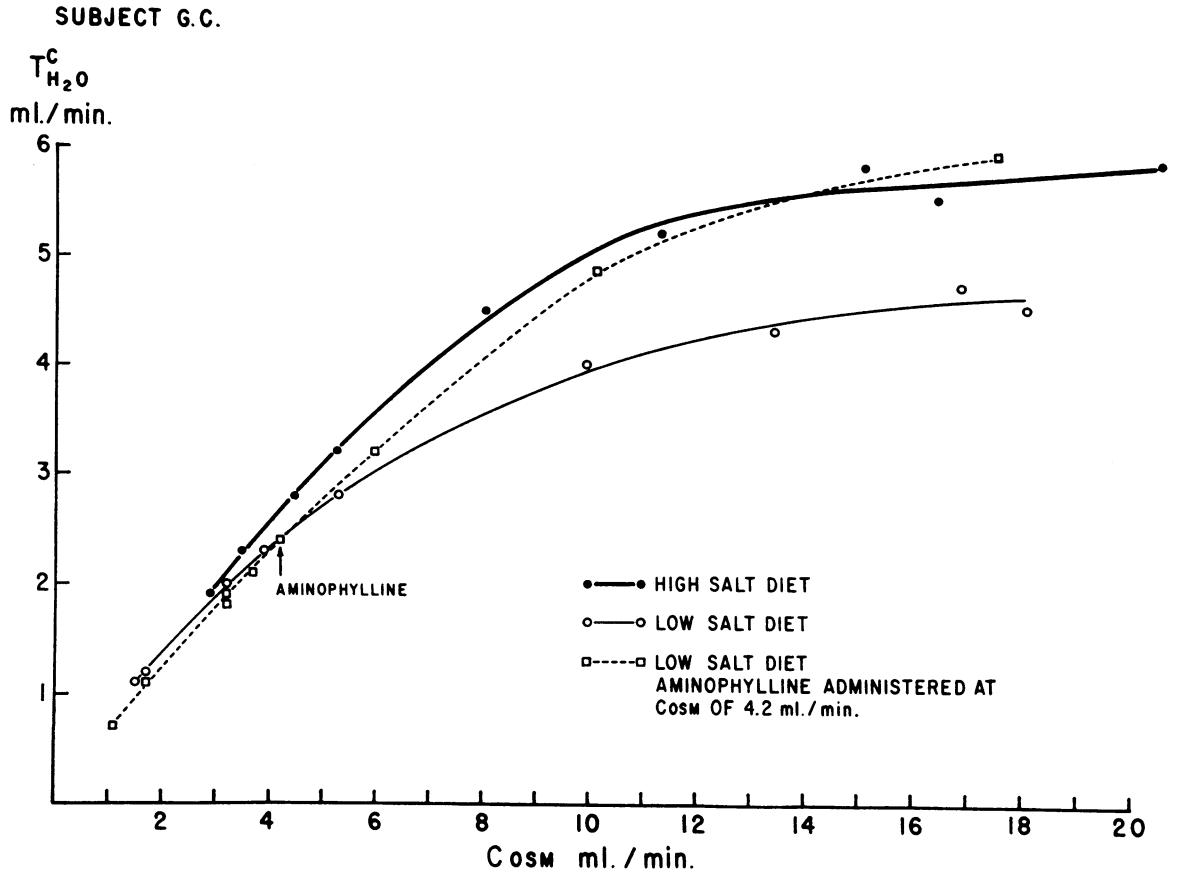

FIG. 4. EFFECTS OF AMINOPHYLLINE ADMINISTERED AT LOW LEVELS OF SOLUTE CLEARANCE DURING A MANNITOL DIURESIS TO A SALT-RESTRICTED SUBJECT. Control $T^c_{H_2O}$–C_{osm} curves obtained in this subject on high and low salt diets after infusions of mannitol alone are also presented.

(Table I). Three subjects, however, demonstrated little or no change in GFR and in two others it was somewhat higher after salt depletion.

Control rates of potassium excretion were variable, but somewhat lower in the salt-restricted subjects. As C_{osm} rose to 8 to 10 ml per minute, the rate of excretion increased in both groups, but thereafter tended to become stable.

II. *The administration of aminophylline at high levels of solute clearance.* In six salt-restricted subjects, aminophylline was administered after the mannitol diuresis became stabilized at a C_{osm} averaging 14 ml per minute, with a range from 11 to 21 ml per minute. An abrupt increase in GFR averaging 38 per cent, with a range from 24 to 58 per cent, was noted. With the increment in GFR, C_{osm} rose an average of 12 ml per minute, with a range from 8 to 15 ml per minute. Although the calculated increment in filtered sodium

TABLE III

*Aminophylline administered to subjects on a high salt diet at high levels of solute clearance**

Subject	C_{osm}	$T^c_{H_2O}$	$U_{Na}V$	C_{inulin}
	ml/min	*ml/min*	*μEq/min*	*ml/min*
M.W.	13.2 †	4.5	654	72
	Aminophylline			
	19.7	4.9	1,090	84
	25.8	4.9	2,040	89
J.F.	12.8 †	4.3	485	122
	Aminophylline			
	14.8	4.6	755	143
	24.6	4.6	1,960	174
T.R.	19.4 †	6.3	897	88
	Aminophylline			
	26.9	7.0	1,490	104
	36.9	6.5	2,520	121
B.L.	21.0 †	5.6	1,760	97
	Aminophylline			
	22.9	5.2	1,990	99
	27.4	5.2	2,490	109
	28.3	5.2	2,560	113

* Abbreviations as in Table I.
† Mean of 3 collection periods obtained in a steady state prior to the administration of aminophylline.

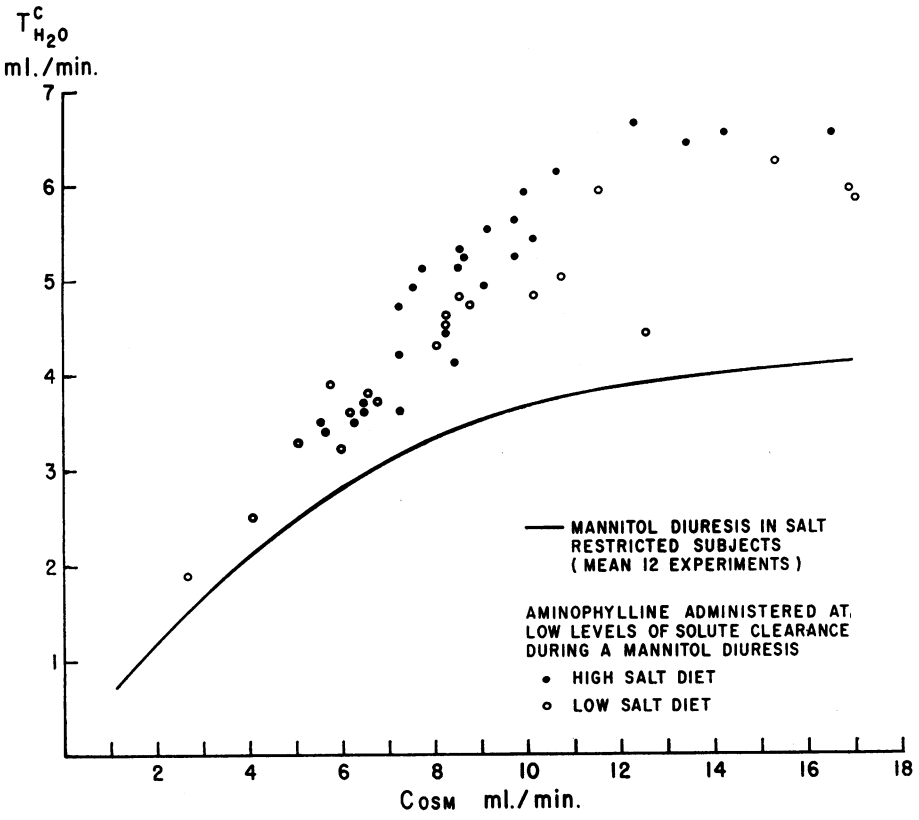

FIG. 5. $T^c_{H_2O}$ VALUES OBTAINED AFTER AMINOPHYLLINE ADMINISTRATION AT LOW LEVELS OF SOLUTE CLEARANCE DURING A MANNITOL DIURESIS IN SUBJECTS ON HIGH AND LOW SALT DIETS. The mean $T^c_{H_2O}$–C_{osm} curve obtained after infusions of mannitol alone in salt-restricted subjects is also depicted.

load averaged 4,800 μEq per minute, mean sodium excretion increased only 1,100 μEq per minute. Despite the increments in GFR, filtered sodium, and solute and water excretion induced by aminophylline, no measurable increase was recorded in $T^c_{H_2O}$ (Table II, Figure 3). In five of these subjects, $T^c_{H_2O}$ fell somewhat as C_{osm} exceeded 20 to 25 ml per minute.

In four subjects studied on high salt diets, aminophylline was administered when C_{osm} became stabilized at a rate greater than 13 ml per minute, ranging from 13 to 21 ml per minute. Under these conditions, as in the salt-restricted subjects, no significant rise in $T^c_{H_2O}$ was observed (Table III, Figure 3). However, the slight fall in $T^c_{H_2O}$ noted in the salt-free subjects at higher levels of C_{osm} was less evident.

III. *The administration of aminophylline at low levels of solute clearance to subjects maintained on both high and low salt diets.* During a mannitol diuresis in salt-restricted subjects, the administration of aminophylline at low levels of C_{osm} resulted in an abrupt increase in GFR averaging 42 per cent. During the period of the sustained increase in GFR, the rise in C_{osm} was associated with $T^c_{H_2O}$ levels appreciably higher than those noted in the same subjects when the diuresis was produced solely by mannitol (Figures 4, 5). In both salt-restricted and salt-fed subjects, the administration of aminophylline resulted in $T^c_{H_2O}$–C_{osm} curves that were very similar (Figure 5).

DISCUSSION

These data indicate that dietary salt restriction diminished the maximal $T^c_{H_2O}$ in man. This concentrating defect was corrected by the administration of aminophylline at a low C_{osm}.

Goldsmith and co-workers (10), studying the effect of salt restriction on the concentrating operation in the dog, have also noted a decrease in maximal $T^c_{H_2O}$. Several of their findings, however, differ from those reported here in man. First, rates of sodium excretion at varying levels of C_{osm} were similar in dogs maintained on high and low salt diets. In addition, dogs maintained on a salt-poor diet showed a decrease in maximal U_{osm} and excreted hypotonic urine at urine flow rates of approximately 9 ml per minute. These workers postulated that salt restriction reduced tubular permeability to water so that distal tubular fluid failed to reattain isotonicity despite the presence of antidiuretic hormone (10). When GFR was increased in the salt-depleted dog by the prolonged administration of glucocorticoids, the concentrating defects were corrected. It was suggested that an increase in GFR in the dog might indirectly enhance distal tubular permeability to water (10).

In addition to the species differences between man and dog noted above, evidence is available to suggest that in the normal hydropenic dog (12), in contrast to the rat (3) and probably to man, distal tubular fluid may fail to reattain isotonicity at a relatively low C_{osm}. During a solute diuresis in the normal dog, $T^c_{H_2O}$ often fails to rise as C_{osm} increases from 4 to 10 ml per minute, and U_{osm} tends to fall towards or below isotonicity as C_{osm} approaches 15 ml per minute (12–14). In both normal and salt-restricted man, however, $T^c_{H_2O}$ rises progressively as C_{osm} approaches 15 ml per minute and remains relatively stable at this maximal plateau as C_{osm} increases from 15 to 25 ml per minute (Figure 1). Thereafter, as C_{osm} continues to rise, $T^c_{H_2O}$ may fall below peak levels (15). In addition, studies with chlorothiazide also unmask a species difference in the capacity for distal tubular fluid to reattain isotonicity. When this drug was administered to the dog after maximal $T^c_{H_2O}$ levels had been achieved, the resulting block in late distal salt absorption was associated with a sharp increase in $T^c_{H_2O}$ (14). The administration of chlorothiazide in man at levels of C_{osm} between 11 and 20 ml per minute produced no increase in $T^c_{H_2O}$ (16, 17). When distal tubular fluid fails to reattain isotonicity, a block in late distal salt absorption would be expected to raise the tonicity of the fluid entering the collecting duct towards isotonicity and increase the measured $T^c_{H_2O}$.

The proposal that a low salt diet reduces distal tubular permeability to water (10) is difficult to reconcile with the findings reported here in man. As mentioned above, it seems unlikely that distal tubular fluid fails to reattain isotonicity in hydropenic man, particularly at modest levels of C_{osm}. Moreover, when aminophylline was administered to salt-restricted man at a low C_{osm}, the $T^c_{H_2O}$ defect was corrected (Figures 4, 5). The administration of this agent at a high C_{osm}, where the consequences of persistent distal tubular fluid hypo-

tonicity would be more manifest, failed to overcome the $T^c_{H_2O}$ defect (Table II, Figure 3). If aminophylline were capable of increasing tubular permeability to water, the effects of its administration on $T^c_{H_2O}$ would be most pronounced at a high C_{osm}. The capacity for aminophylline to correct the $T^c_{H_2O}$ defect does not appear, therefore, to be mediated through any influence on tubular permeability to water. Consequently, it is difficult to implicate diminished distal tubular permeability as the factor limiting $T^c_{H_2O}$ in salt-depleted man.

The difference in $T^c_{H_2O}$ in the two groups of subjects may be explained by the hypothesis that $T^c_{H_2O}$ is limited by a maximal rate of sodium transport at the ascending limb. In this view, it would follow that salt depletion depresses this tubular maximum. This hypothesis would require that sodium transport at the ascending limb be decreased while total sodium reabsorption is enhanced throughout the renal tubule. Moreover, these studies would imply that aminophylline could restore a normal tubular maximum for sodium only when administered at a low C_{osm}. Furthermore, in both groups of subjects, when the filtered sodium load was abruptly increased by aminophylline administration at a high C_{osm}, only a modest fraction of this additional load appeared in the urine. It is unlikely that at such a high C_{osm} all of the increase in sodium reabsorption took place within the proximal tubule. It is therefore apparent that total sodium transport in the distal tubule, if not specifically at the ascending limb, could be augmented even at a high C_{osm}. In addition, micropuncture analyses have failed to demonstrate a tubular maximum for sodium at the ascending limb during a salt or mannitol diuresis (3, 18). Admittedly, the possibility of a maximal rate for sodium transport at the ascending limb cannot be excluded; the data presented here, however, do not support the hypothesis that prior salt restriction depresses the capacity for sodium transport at this site.

An alternative that might explain the difference in $T^c_{H_2O}$ in the two groups of subjects would assume that salt depletion reduces the rate of delivery of sodium to the ascending limb. Consistent with this hypothesis is the observation that salt excretion was sharply reduced per unit of C_{osm} in the salt-free group, particularly at lower levels of C_{osm} (Figure 2). This finding indicates that the capacity for tubular salt absorption against the osmotic gradient established by the non-absorbed solute was augmented by previous salt restriction. It is likely that this enhanced salt absorption occurred, in part, within the proximal tubule. Such a change in proximal tubular function would diminish the percentage of absorbable solute (salt) per unit of mannitol presented to the ascending limb. In support of this hypothesis, when the quantity of salt delivered to the ascending limb during a mannitol diuresis was increased by the administration of aminophylline,[1] at a low C_{osm}, the $T^c_{H_2O}$ defect was corrected (Table IV, Figures 4, 5).

The precise cause of the enhanced tubular salt reabsorption noted after salt restriction remains to be established. It might result in part from the modest and variable reduction in GFR produced by salt depletion.

The observation that maximal urine osmolalities were comparable in both groups of subjects does not invalidate the assumption that salt restriction diminishes medullary salt supply and content. Control V and $T^c_{H_2O}$ before the infusion of mannitol were lower in the salt-restricted subjects (Table I, Figure 1). In this fasting state, the quantity of fluid presented to the collecting duct and coursing through the medulla was diminished after salt depletion. It appears reasonable that a smaller quantity of medullary solute might achieve comparable medullary (and urinary) concentrations if a reduced quantity of water dilutes the medulla. In fact, when urine concentration was plotted against V, salt-free subjects demonstrated a consistently lower U_{osm} at each V (Figure 6).

Another factor that may obscure a difference in maximal U_{osm} between both groups is the relatively greater role of urea in defining U_{osm} at a low V (22, 23). The enhanced tubular salt and water reabsorption in salt-restricted subjects caused the fraction of urine solute composed of urea to rise

[1] Available data suggest that the administration of aminophylline sharply increases salt supply at the ascending limb (19, 20). To what extent this change may be a consequence of an increase in GFR or an inhibition of proximal salt absorption is not clear (21). The effect of this agent during a mannitol diuresis would therefore increase the percentage of absorbable solute (salt) presented to the ascending limb, compared to the percentage delivered by a comparable mannitol diuresis alone.

above that noted in the salt-fed subjects (Table I). In the hydropenic state, urea is highly diffusible, so that an increase in urine urea concentration will be reflected in an increased medullary concentration (24). This factor may tend to obscure the reduction in U_{osm} imposed by the decreased medullary salt content. As the solute diuresis supervenes, the fraction of medullary solute composed of urea diminishes (5) and the influence of the decreased medullary salt content becomes manifest.

It has been proposed that salt restriction reduces sodium supply, but not the capacity for transport at the ascending limb. At a high C_{osm}, however, particularly after the administration of aminophylline, salt-restricted subjects demonstrate an appreciable increase in sodium excretion (Tables II, III, Figure 2). At such a high C_{osm}, it appears that sodium supply at the ascending limb is no longer limited. Therefore, a proposal must be sought to explain the failure of this increasing sodium supply to be incorporated within the medulla.

On the basis of direct studies, it has been concluded that a progressive increase in effective medullary blood flow develops during the course of a solute diuresis (25). This proposal is supported by the observation that medullary solute content is reduced under these conditions (26). Such a change in medullary hemodynamics, when sufficient in magnitude, might prevent further retention of medullary solute and limit $T^c_{H_2O}$ despite increasing sodium transport at the ascending limb. If it is assumed that a comparable increase in medullary blood flow develops in salt-depleted subjects during a solute diuresis, this hyperemia

TABLE IV

Aminophylline administered to subjects on a low salt diet at low levels of solute clearance *

Subject	Aminophylline plus mannitol			Mannitol	
	C_{osm}	$T^c_{H_2O}$	C_{inulin}	$T^c_{H_2O}$†	C_{inulin}
	ml/min	*ml/min*	*ml/min*	*ml/min*	*ml/min*
C.R.	5.5	3.0	93	2.5	
		Aminophylline			
	8.3	4.5	128	3.2	94
	8.8	4.7	129	3.4	
	15.4	6.2	144	4.6	
	17.1	5.8	131		
E.M.	5.1	2.4	54	2.4	
		Aminophylline			
	6.8	3.2	81	2.8	55
	12.6	4.4	81	3.5	
D.H.	5.4	3.1	94	2.8	
		Aminophylline			
	6.2	3.6	117	3.0	89
	8.6	4.8	121	3.6	
	11.6	5.9	124	4.2	
P.R.	5.1	3.1	79	2.8	
		Aminophylline			
	6.6	3.8	87	3.3	72
	8.1	4.3	92	3.7	
	10.8	5.0	93	4.1	
F.M.	4.8	2.5	68	2.4	
		Aminophylline			66
	8.3	4.1	96	3.2	
G.C.	4.2	2.4	99	2.4	
		Aminophylline			
	6.0	3.2	109	3.0	84
	10.2	4.8	130	4.0	
	17.0	5.9	154	4.5	

* Abbreviations as in Table I.

† $T^c_{H_2O}$ value obtained from the $T^c_{H_2O}/C_{osm}$ curve produced by mannitol alone at that C_{osm} recorded in the aminophylline plus mannitol study.

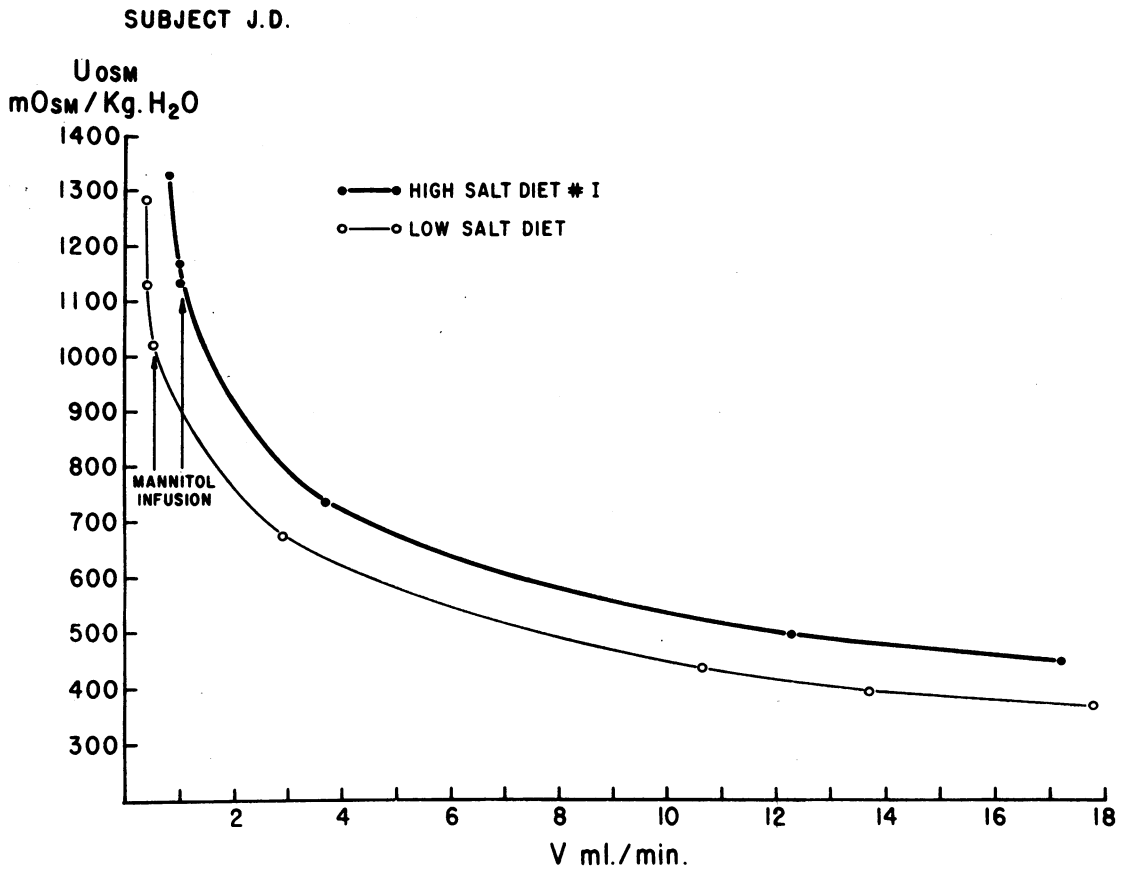

FIG. 6. RELATIONSHIP BETWEEN URINE OSMOLALITY (U_{osm}) AND RATE OF URINE FLOW (V) IN A SUBJECT ON HIGH AND LOW SALT DIETS.

might reach critical levels while sodium supply at the ascending limb is still relatively diminished. Thereafter, any further increase in sodium supply or transport at the ascending limb might not increase the quantity of solute retained within the medulla, nor increase the calculated $T^c_{H_2O}$.

The cause of this alleged increase in medullary blood flow is unknown. It is likely that the rate of outflow of blood from the medulla might be enhanced by the diffusion of solute-free water into the medullary interstitium from the collecting duct ($T^c_{H_2O}$). Inasmuch as $T^c_{H_2O}$ was lower in salt-restricted subjects, the proposal that a progressive and comparable increase in medullary blood flow occurs in both groups of subjects implies that factors in addition to back-diffusion of water at the collecting duct may provoke this change in medullary hemodynamics.

The hypothesis that salt restriction reduces medullary salt content is consistent with the observation that in salt-depleted subjects, $T^c_{H_2O}$ levels reach a plateau at a lower C_{osm} and reveal a greater tendency to fall from peak levels (Tables II, III, Figure 1). A medulla containing less solute would be more likely to be vulnerable to any factor which dissipates medullary solute content and thus limits $T^c_{H_2O}$. Whether progressive medullary hyperemia represents the responsible factor, as alleged, remains to be established.

SUMMARY

1. Data have been presented demonstrating that salt restriction in man diminishes the maximal rate of free water reabsorption ($T^c_{H_2O}$) without changing maximal urine osmolality.

2. Aminophylline was capable of correcting the $T^c_{H_2O}$ defect only when administered at low levels of solute clearance.

3. These findings are best explained by the hypothesis that reduced $T^c_{H_2O}$ in salt-depleted man

results from a reduced medullary salt content secondary to a reduced rate of sodium delivery to the ascending limb at every level of solute clearance.

REFERENCES

1. Wirz, H., Hargitay, B., and Kuhn, W. Lokalisation des Konzentrierungsprozesses in der Niere durch direkte Kryoscopie. Helv. physiol. pharmacol. Acta 1951, **9**, 196.
2. Berliner, R. W., Levinsky, N. G., Davidson, D. G., and Eden, M. Dilution and concentration of the urine and the action of antidiuretic hormone. Amer. J. Med. 1958, **24**, 730.
3. Gottschalk, C. W., and Mylle, M. Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. Amer. J. Physiol. 1959, **196**, 927.
4. Levitt, M. F., Levy, M. S., and Polimeros, D. The effect of a fall in filtration rate on solute and water excretion in hydropenic man. J. clin. Invest. 1959, **38**, 463.
5. Levinsky, N. G., Davidson, D. G., and Berliner, R. W. Effects of reduced glomerular filtration on urine concentration in the presence of antidiuretic hormone. J. clin. Invest. 1959, **38**, 730.
6. McCance, R. A. The effect of salt deficiency in man on the volume of the extracellular fluids, and on the composition of sweat, saliva, gastric juice and cerebrospinal fluid. J. Physiol. 1938, **92**, 208.
7. McCance, R. A., and Widdowson, E. M. The secretion of urine in man during experimental salt deficiency. J. Physiol. 1937, **91**, 222.
8. Black, D. A. K., Platt, R., and Stanbury, S. W. Regulation of sodium excretion in normal and salt-depleted subjects. Clin. Sci. 1950, **9**, 205.
9. Levinsky, N. G., Davidson, D. G., and Berliner, R. W. Changes in urine concentration during prolonged administration of vasopressin and water. Amer. J. Physiol. 1959, **196**, 451.
10. Goldsmith, C., Beasley, H. K., Whalley, P. J., Rector, F. C., Jr., and Seldin, D. W. The effect of salt deprivation on the urinary concentrating mechanism in the dog. J. clin. Invest. 1961, **40**, 2043.
11. Baker, G. P., Levitin, H., and Epstein, F. H. Sodium depletion and renal conservation of water. J. clin. Invest. 1961, **40**, 867.
12. Goodman, B., Cohen, J. A., Kahn, M. H., and Levitt, M. F. Effect of acutely induced hyponatruria on the concentrating mechanism of normal dogs. Clin. Res. 1962, **10**, 248.
13. Giebisch, G., and Lozano, R. The effects of adrenal steroids and potassium depletion on the elaboration of an osmotically concentrated urine. J. clin. Invest. 1959, **38**, 843.
14. Earley, L. E., Kahn, M., and Orloff, J. The effects of infusions of chlorothiazide on urinary dilution and concentration in the dog. J. clin. Invest. 1961, **40**, 857.
15. Eisner, G. M., Porush, J. G., Goldstein, M. H., and Levitt, M. F. An appraisal of free water reabsorption ($T^c_{H_2O}$) in man. J. Mt Sinai Hosp. 1962, **29**, 38.
16. Heinemann, H. O., Demartini, F. E., and Laragh, J. H. The effect of chlorothiazide on renal excretion of electrolytes and free water. Amer. J. Med. 1959, **26**, 853.
17. Goldstein, M. H., Stein, R. M., and Levitt, M. F. Unpublished observations.
18. Giebisch, G., Klose, R. M., and Windhager, E. H. Personal communication.
19. Kleeman, C. R., Maxwell, M. H., and Rockney, R. E. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. I. The role of altered glomerular filtration rate and solute excretion. J. clin. Invest. 1958, **37**, 1799.
20. Goldstein, M. H., Levitt, M. F., Hauser, A. D., and Polimeros, D. Effect of meralluride on solute and water excretion in hydrated man: comments on site of action. J. clin. Invest. 1961, **40**, 731.
21. Davis, J. O., and Shock, N. W. The effect of theophylline ethylenediamine on renal function in control subjects and in patients with congestive heart failure. J. clin. Invest. 1949, **28**, 1459.
22. Levinsky, N. G., and Berliner, R. W. The role of urea in the urine concentrating mechanism. J. clin. Invest. 1959, **38**, 741.
23. Jaenike, J. R. Urea enhancement of water reabsorption in the renal medulla. Amer. J. Physiol. 1960, **199**, 1205.
24. Jaenike, J. R. The influence of vasopressin on the permeability of the mammalian collecting duct to urea. J. clin. Invest. 1961, **40**, 144.
25. Thurau, K., Deetjen, P., and Kramer, K. Hämodynamik des Nierenmarks. II. Wechselbeziehung zwischen vasculärem und tubulärem Gegenstromsystem bei arteriellen Drucksteigerungen, Wasserdiurese und osmotischer Diurese. Pflügers Arch. ges. Physiol. 1960, **270**, 270.
26. Malvin, R. L., and Wilde, W. S. Washout of renal countercurrent Na gradient by osmotic diuresis. Amer. J. Physiol. 1959, **197**, 177.