Fluoride Reabsorption by Nonionic Diffusion in the Distal Nephron of the Dog (43176)

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Abstract. **This study was done to test the hypothesis that fluoride reabsorption is extensive from the distal nephron, the major site for tubular fluid acidification, and to compare the distal nephron handling of fluoride and chloride. Ten stop-flow studies were done in five dogs anesthetized with pentobarbital. Urinary alkalinization was achieved by the intravenous infusion of sodium bicarbonate and acetazolamide or lithium chloride. Acidification was achieved by the infusion of sodium nitrate or sodium sulfate. The results indicate that the extent of fluoride reabsorption from the distal nephron is inversely correlated with urinary pH ($P < 0.001$). When the urine was strongly acidified by the infusion of sodium sulfate, urine to plasma fluoride concentration ratios were less than 1.0, a finding not previously reported from studies of the renal handling of fluoride. The reabsorption of fluoride from the distal nephron was not correlated consistently with that of chloride. The results indicate that the distal nephron is an important site for the reabsorption of fluoride and they provide additional evidence that HF is the permeating moiety.** [P.S.E.B.M. 1991, Vol 196]

The removal of fluoride from plasma and soft tissue occurs by calcified tissue uptake and by renal excretion. The skeletal clearance of fluoride is extremely rapid and exceeds even that of calcium (1). Compared with the other halogens, the renal clearance of fluoride is also unusually high. Whereas the clearances of chloride, iodide, and bromide in healthy adult humans are normally less than 2 ml/min, that of fluoride is 30–40 ml/min, although there may be considerable variation within and among individuals (2, 3).

The mechanism underlying the renal reabsorption of fluoride was first studied by Chen *et al.* (4). Using standard renal clearance methods in dogs, they found a positive correlation between urinary flow rate and fluoride clearance when mannitol or hypertonic saline was used to produce graded levels of diuresis. The results of several other subsequent studies have indicated the same relationship (5, 6). Carlson *et al.* (5) suggested that, because of its relatively large hydrated radius, ionic fluoride was handled by the kidney in the same way as water. However, other findings in the report by Chen *et al.* (4) suggested that the relationship between urinary flow rate and fluoride clearance was not mechanistically linked. When they used sodium sulfate or sodium nitrate as the diuretic agent, the clearance of fluoride did not increase with flow rate.

The latter observation prompted Whitford *et al.* (7) to evaluate further the relationship between urinary flow rate and the renal handling of fluoride. They showed that the two variables could be separated and that the magnitude of the clearance was correlated positively with urinary pH. They proposed that the reabsorption of fluoride occurs by the diffusion of the weak acid HF, which has a pK_a (approximately 3.4) close to that of lactic acid and acetylsalicylic acid. They suggested that the failure of fluoride clearance to increase during a diuresis induced by sulfate or nitrate (4) was due to a simultaneous acidification of the tubular fluid, which would promote the reabsorption of fluoride as HF. They also suggested that when fluoride clearance does correlate with urinary flow rate, the relationship is secondary to a dilutional increase in urinary pH. Since then, several other reports of studies with rats, dogs, and humans have confirmed the pH dependence of the renal handling of fluoride (8–14). Based on these findings and those from studies using other systems (15–23), it appears that many cell membranes and epithelia are virtually impermeable to ionic fluoride and that the migration of fluoride between adjacent

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body fluid compartments of differing pH occurs by the diffusion of HF.

One implication of this hypothesis is that the reabsorption of fluoride from the distal nephron should be demonstrable because it is there that the tubular fluid undergoes its greatest change in pH (24). To test this possibility, the renal stop-flow technique was used in dogs experiencing diuresis induced with a variety of solutes that diminished or enhanced the pH drop that normally occurs within the distal nephron.

Another objective of this study was to examine the relationship between the distal tubular handling of chloride and fluoride. This relationship was of interest because Walser and Rahill (25) reported that the renal clearances of fluoride and chloride were directly related during a strong chloruresis. They suggested that the two halogens might be co-transported, perhaps by a similar mechanism. Insofar as we are aware, this possibility has not received further research attention.

Materials and Methods

The stop-flow technique used in this study was essentially the same as that originally described by Malvin *et al.* (26). Five female dogs weighing from 14 to 23 kg were anesthetized with sodium pentobarbital (35 mg/kg iv). Two stop-flow studies were done with each dog so that it served as its own control. Following the insertion of an endotracheal tube, a femoral artery and a jugular vein were cannulated with PE190 polyethylene tubing for blood sampling and fluid administration, respectively. Through a subcostal incision, the right ureter was catheterized with PE240 polyethylene tubing at the level of the renal pelvis. A gravity-drip sustaining infusion (Table I) was then started at 10–12 ml/min followed by a 2.0-ml priming injection, which delivered 0.20 mmol of sodium fluoride, 2.5 μCi of hydroxymethyl ^{14}C-inulin, and 0.10 g of carrier inulin (mol wt, 5000).

When the urinary flow rate reached 8–10 ml/min, which occurred approximately 1 hr after starting the sustaining infusion, urine and blood samples were collected for three 6-min control (free-flow) renal clearance periods. The urine samples were collected under mineral oil. The ureteral catheter was then clamped for 8 min. Six minutes after occluding the catheter, 10 ml of a 3% (w/v) creatinine solution were administered intravenously. The appearance of creatinine in the stop-flow samples indicated the formation of urine that was formed after the release of the ureteral clamp. After the clamp was released, 25–30 1.0-ml stop-flow urine samples were collected. Each sample was immediately covered with mineral oil to minimize the loss of CO_2 and changes in pH. No sample was exposed to the atmosphere for more than 5 sec. Five minutes after the collection of the stop-flow samples, three more 6-min free-flow renal clearance samples were taken.

A second infusate, different in composition, was then started and after approximately 1 hr of infusion, collections for three more free-flow renal clearance periods were made. These were followed by another 8-min period during which the ureteral catheter was clamped. After 6 min of occlusion, the creatinine solution was again administered intravenously. Another 25–30 1.0-ml stop-flow samples were then collected and, finally, samples were collected for three more free-flow clearance periods. Blood collections were made at the midpoint of each free-flow clearance period and at the beginning and end of each stop-flow period.

The sustaining infusates all contained mannitol, 1.0 mmol/liter of sodium fluoride, 0.5 g/liter of alkali-stable inulin, and 5 μCi/liter of hydroxymethyl ^{14}C-inulin. Their other solutes are shown in Table I. The studies were designed to permit the collection of stop-flow data under two conditions in each dog. In Experiment 1, the first infusate contained sodium chloride, which tends to mildly acidify samples from the distal nephron. The second infusate delivered sodium bicarbonate and acetazolamide to alkalinize the urine. In

Table I. Composition of Infusates[a]

Experiment	Infusate	Mannitol (%)	NaCl	$NaHCO_3$	$NaNO_3$	LiCl	Na_2SO_4	Drugs
1	1st	10	145	—	—	—	—	—
	2nd	10	—	145	—	—	—	Acetazolamide[b]
2	1st	6	—	—	150	—	—	—
	2nd	8	—	—	—	100	—	—
3	1st	15	—	—	—	—	—	—
	2nd	5	—	—	—	—	140	—
4	1st	10	150	—	—	—	—	—
	2nd	10	—	—	—	—	150	—
5	1st	10	—	—	—	—	140	—
	2nd	10	—	—	—	—	140	Furosemide[c]

[a] Concentrations, except for mannitol and drugs, are mmol/liter.
[b] Infusate concentration was 6.3 μg/ml.
[c] Infusate concentration was 10 μg/ml. In addition, the second priming injection contained 10.0 mg of furosemide.

Experiment 2, the major anion in the first infusate was nitrate, which has been reported to acidify the urine (27). Sodium nitrate was replaced by lithium chloride in the second infusate. Lithium has been shown to inhibit distal nephron proton transport (28, 29). In Experiment 3, the first infusate contained only mannitol. Sodium sulfate was added to the second infusate to enhance acidification by the distal nephron. The fourth experiment was similar to the third except that the first infusate included sodium chloride to increase the distal load of sodium. In the fifth experiment, both infusates contained sodium sulfate. Furosemide was given during the second stop-flow study to increase the delivery of solute, especially chloride, to the distal nephron to determine whether chloride competed with fluoride transport. Thus, the compositions of the infusates were chosen to vary tubular fluid pH and the distal delivery of solutes for the purpose of determining how these changes would modify the reabsorption of fluoride.

The pH and PCO_2 values of the urine samples were determined using a Radiometer BMS 3 Mk II system. Plasma and urine samples were analyzed for fluoride with the ion-specific electrode using a modification of the method of Fry and Taves (30), for phosphate (31) and creatinine (32) by spectrophotometry, for chloride by electrometric titration, for potassium by flame photometry using lithium as an internal standard, and for ^{14}C-inulin by liquid scintillation counting using external standards.

The fluoride, chloride, phosphate, and potassium urine to plasma (U/P) concentration ratios were factored by the ^{14}C-inulin U/P ratio of the same sample. The resulting ratio of ratios is the equivalent of a fractional renal clearance (26). For example, a U/P solute:U/P inulin value of 0.80 would indicate that 80% of the filtered amount of solute was excreted and that 20% was reabsorbed.

Stop-flow evidence of phosphate reabsorption was used as a marker for proximal tubular samples (26, 33). Distal nephron samples were identified by elevated U/P ^{14}C-inulin, U/P potassium ratios, and/or sample acidification (24, 26). Statistical evaluations of the data were done using the repeated measure t test or by linear regression analysis as appropriate, and $P < 0.05$ was selected as the indicator for statistical significance.

Results

Plasma fluoride concentrations, which tended to increase gradually in each experiment, were similar among the dogs. They fell within the 74- to 140-μmol/liter range. With the exception of an increase in urinary flow rate (34), renal function is not known to be affected by acutely elevated plasma fluoride levels in this range.

The results of Experiment 3 are plotted in the standard stop-flow format (Fig. 1). The samples from the proximal tubular region had reduced U/P phosphate:U/P ^{14}C-inulin ratios, whereas the samples from the distal nephron showed acidification, potassium secretion, and/or elevated U/P ^{14}C-inulin ratios. Similar results were observed in all of the experiments.

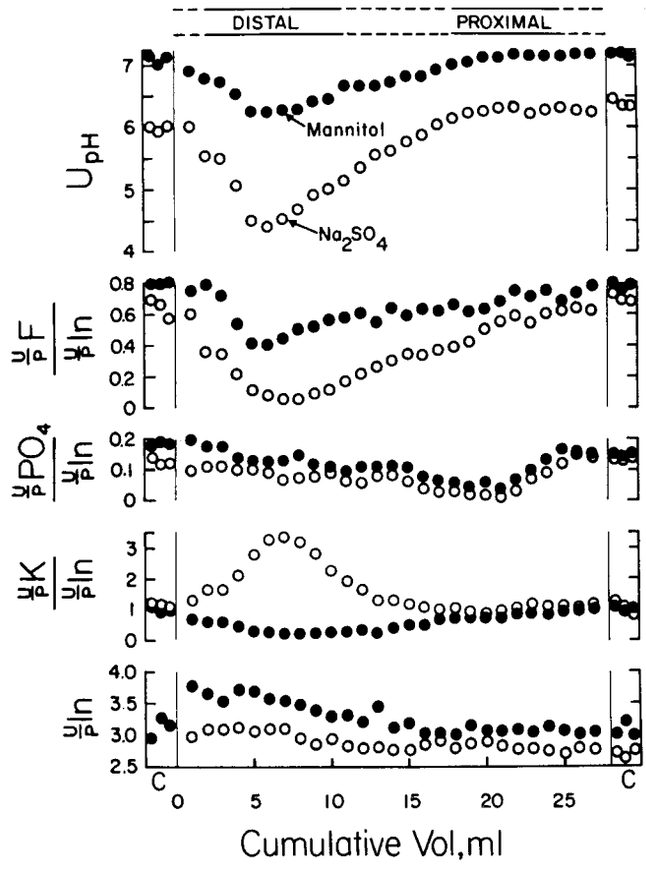

Figure 1. Results of the two renal stop-flow studies of Experiment 3. The infusion of Na_2SO_4 resulted in reduced pH values and U/P fluoride:U/P inulin ratios, especially in the samples from the distal nephron.

In each of the two stop-flow studies of Experiment 3, there was a close relationship between the sample pH values and the U/P fluoride:U/P ^{14}C-inulin ratios (Fig. 1). During the infusion of 15% mannitol, the pH values of the free-flow urine samples ranged from 7.02 to 7.15 and the corresponding U/P fluoride:U/P ^{14}C-inulin ratios were slightly above 0.80. The pH values of the distal nephron samples fell to 6.24, at which time the U/P fluoride:U/P ^{14}C-inulin ratio reached its lowest value of 0.41. During the subsequent infusion of Na_2SO_4, the free-flow pH values ranged from 5.95 to 6.49 and the corresponding U/P fluoride:U/P ^{14}C-inulin ratios ranged from 0.59 to 0.73. The pH values of several of the stop-flow samples from the distal nephron were markedly acidified (pH < 4.6). The associated U/P fluoride:U/P ^{14}C-inulin ratios of these samples ranged from 0.05 to 0.12.

As shown in Table II, a close correspondence between the distal nephron pH values and the U/P fluoride:U/P ^{14}C-inulin ratios occurred in all of the exper-

Table II. pH and U/P Fluoride:U/P ^{14}C-Inulin Values of Distal Nephron Samples, Which were Maximally Acidified

Experiment	Infusate solute[a]	pH	U/P fluoride: ^{14}C-inulin
1	NaCl	6.75[b] ± 0.05[c]	0.49[b] ± 0.01
	$NaHCO_3$, acetazolamide	7.39 ± 0.03	0.61 ± 0.02
2	$NaNO_3$	6.24[b] ± 0.10	0.44[b] ± 0.03
	LiCl	6.60 ± 0.05	0.70 ± 0.03
3	Mannitol only	6.38[b] ± 0.09	0.51[b] ± 0.05
	Na_2SO_4	4.78 ± 0.17	0.15 ± 0.05
4	NaCl	6.44[b] ± 0.08	0.37[b] ± 0.03
	Na_2SO_4	5.22 ± 0.10	0.14 ± 0.02
5	Na_2SO_4	5.91 ± 0.04	0.46[b] ± 0.02
	Na_2SO_4, furosemide	5.99 ± 0.02	0.38 ± 0.01

[a] All infusates contained mannitol (Table I).
[b] Mean values in each experiment differ with statistical significance ($P < 0.05$).
[c] Data expressed as mean ± SE. Each data set represents findings from six to eight distal tubular samples.

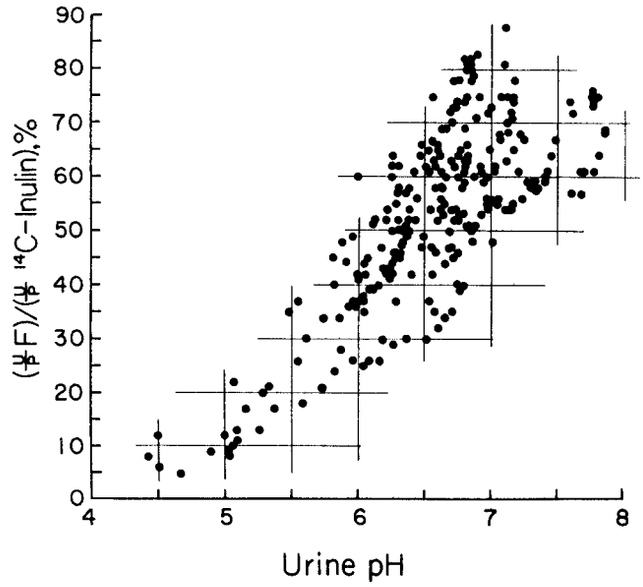

Figure 2. Overall relationship between pH and U/P fluoride:U/P inulin ratios ($r = 0.796$; $P < 0.001$). The data are from all of the stop-flow samples in Experiments 1–5.

iments. The data in Table II were derived from six to eight sequential distal nephron samples that showed maximal acidification in each of the 10 stop-flow studies. As determined by repeated measures (paired) t test analysis, the differences between the mean values of all of the pH and U/P fluoride:U/P ^{14}C-inulin data pairs were significantly different ($P < 0.001$), with the exception of the pH data in Experiment 5. When the data from all of the individual distal nephron samples used to obtain the data in Table II were analyzed by linear regression, the relationship was described by $y = 0.21x - 0.90$, where urinary pH is x ($n = 64$; $r = 0.892$; $P < 0.001$). Thus, the distal nephron fractional excretion of fluoride increased by approximately 20% with each unit increase in pH.

In Experiment 5, the infusates for the first and second stop-flow studies contained mannitol and Na_2SO_4. They differed in that furosemide was added to the second infusate for the purpose of increasing solute excretion rates. The chloruretic effect of the drug was profound; the fractional excretion of chloride in the free-flow samples and in the proximal tubular samples approached 0.50. The U/P fluoride:U/P ^{14}C-inulin ratios were significantly lower during the administration of furosemide, although the absolute difference was relatively small (0.46 vs 0.38; Table II).

Figure 2 shows the relationship between the urinary pH values and the fractional fluoride excretion data of all of the proximal and distal stop-flow samples in the 10 studies. Linear regression analysis of these data indicated that the relationship was described by $y = 0.21x - .88$, where urinary pH is x ($n = 262$; $r = 0.796$; $P < 0.001$).

Table III shows the results of linear regression analyses of the relationships between the distal nephron fractional excretions of chloride and fluoride in the five dogs. The samples that were so analyzed were the same ones that were used to generate the data of Table II. The slopes ranged from −0.546 in Experiment 5 to 8.734 in Experiment 3. The relationships between the fractional excretions of chloride and fluoride were statistically significant only in these two dogs, but the slopes were opposite in sign. When the data from all of the dogs were combined and analyzed by linear regression, the correlation was not significant. Furthermore, the relationship between urinary pH and the fractional excretion of chloride was not significant ($y = 0.12x - 0.036$; $r = 0.202$; $n = 64$).

Discussion

At the time of its introduction, the renal stop-flow technique represented an important new tool for the localization of the tubular handling of both solutes and water. However, investigators who were among the first to use the technique recognized several of its limiting features (24). These features include variations in the length of nephrons, mixing due to passage through the renal pelvis, the possible movement of tubular fluid during occlusion due to continuing water reabsorption in the distal nephron, and the fact that proximal tubular samples must pass through the distal nephron before their collection. Unless the transport of a solute is extensive and confined largely to the proximal tubule, the latter point is the major reason why the stop-flow technique is more appropriately used to study distal nephron transport.

Table III. Linear Regression Analysis of the Relationship between the Fractional Excretions of Chloride and Fluoride in Distal Nephron Samples

Experiment	Slope	Intercept	Correlation coefficient	*P*
1	1.753	0.496	0.524	>0.05
2	1.609	0.489	0.263	>0.05
3	8.734	0.159	0.889	<0.01
4	1.395	0.222	0.245	>0.05
5	−0.546	0.465	−0.795	<0.01
All	0.891	0.377	0.219	>0.05

Despite these limitations, a considerable amount of important information has been gained with the stop-flow technique. Malvin *et al.* (26) demonstrated that the distal nephron is an important site for the reabsorption of sodium and that the proximal tubule is the site from which glucose and phosphate are reabsorbed and into which para-aminohippuric acid is secreted. At about the same time, Pitts *et al.* (24) confirmed some of these results and, in addition, demonstrated that the distal nephron is where the urine is acidified and where potassium and ammonia are secreted. Our results confirm the utility of the method for localizing solute transport along the nephron, especially the distal nephron.

The urinary pH and U/P fluoride:U/P ^{14}C-inulin data were closely related both in the distal nephron samples (Table II) and in those from the entire nephron (Fig. 2). This was especially evident in the samples from the distal nephron, in which the minimum values for pH and the fractional excretions of fluoride occurred in the same samples. When $NaHCO_3$ and acetazolamide were administered in Experiment 1, the pH values remained well above 7.0, and the fractional fluoride excretions generally exceeded 60% both in the distal (Table II) and proximal tubular samples. When sodium chloride was administered to the same dog, the pH values were approximately 0.6 unit lower, and the fractional fluoride excretions were reduced. Qualitatively similar results were seen in Experiment 2 when lithium chloride was given to alkalinize and sodium nitrate was given to acidify the urine. Relatively acidic distal nephron samples were produced by the administration of sodium sulfate in Experiments 3–5, especially Experiment 3. In these experiments, the reabsorption of fluoride was greater than that associated with any of the other infusates.

The ability of high concentrations of fluoride to inhibit a wide variety of enzyme systems is well established. If fluoride were able to inhibit proton-ATPase, such an inhibition could have affected the results of the present study. The literature appears to contain no data to indicate the effect of fluoride on the activity of this enzyme. However, Tobin *et al.* (35) found that millimolar concentrations of fluoride (which are lethal) inhibited rat kidney ($Na^+ + K^+$)ATPase *in vitro*, but that 12.7 mg of fluoride/kg/day given by subcutaneous injection to rats for 2 to 3 days had no effect on this enzyme nor on Mg^{2+} ATPase. The latter dose is close to the 24-hr LD_{50} and would have resulted in peak plasma fluoride levels of about 800–1000 μmol/liter, values much higher than those observed in the present study. Therefore, it may be concluded with reasonable confidence that enzyme inhibition was not a significant variable in the present study.

The literature indicates that, unlike chloride, iodide, or bromide, whose urinary concentrations under normal conditions are not markedly different from those of plasma in normal adult dogs or humans, the U/P ratio for fluoride is usually in the 30–50 range. Even in the presence of a strong diuresis, which results in relatively low U/P fluoride ratios, fluoride concentrations of bladder urine still remain well above those of plasma (10).

In the present studies that involved the infusion of sodium sulfate, however, many of the stop-flow samples had urinary fluoride levels that were lower than those of plasma. During the infusion of Na_2SO_4 in Experiment 3, the U/P fluoride concentration ratios (not factored by U/P ^{14}C-inulin) of distal nephron Samples 5–10 ranged from 0.17 to 0.30, and they did not reach unity until Sample 16. This can be seen by multiplying the U/P fluoride:U/P inulin ratios by the U/P inulin ratios shown in Figure 1. During the infusion of Na_2SO_4 in Experiment 4, the U/P fluoride ratios of Samples 4–17 were less than unity. During the infusion of sodium sulfate and furosemide in Experiment 5, the U/P fluoride ratios of Samples 2–24 were also less than unity. Thus, the administration of this agent was associated with markedly reduced U/P fluoride ratios that were often less than 1.0, a finding not previously reported from studies of the renal handling of fluoride under any conditions. It may be concluded, therefore, that when the tubular fluid pH is sufficiently low and enough time is allowed, the tubular reabsorption of fluoride can approach completion.

In 1966, Walser and Rahill (25) reported that the renal clearance of fluoride was related to urinary flow rate when chloride excretion was low but that the clearances of the two halogens varied in the same direction during a strong chloruresis. They inferred that, under the latter condition, the two halogens might be co-transported, perhaps by a similar mechanism, from the proximal tubule. However, a consistent relationship between the renal handling of chloride and fluoride was not evident in the present study (Table III). The U/P fluoride:U/P ^{14}C-inulin ratios in Experiment 5 were generally depressed during the profound chloruresis induced by furosemide rather than elevated, which would have been expected if chloride transport

competed with fluoride transport. Furthermore, Rouch (14) recently reported that fluoride flux from the cortical collecting duct of the rabbit was not affected by DIDS. Similarly, Whitford *et al.* (36) found that, whereas DIDS inhibited strongly the efflux of ^{36}Cl from red blood cells, it had little effect on the efflux of fluoride. These findings do not support the idea that the reabsorption of chloride and fluoride share a common mechanism.

The possibility that fluoride reabsorption may be related in some way to chloride transport in the proximal tubule is not precluded by the present findings. Because proximal tubular samples can be further modified during transit through the more distal portions of the nephron, the stop flow technique is often unable to detect proximal events unless the extent of transport is massive. The present results do, however, indicate that the distal nephron is an important site for the reabsorption of fluoride and they offer additional evidence to support the pH dependence of the renal handling of fluoride and the hypothesis that the permeating moiety is undissociated HF.

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1. Costeas A, Woodward HQ, Laughlin JS. Comparative kinetics of calcium and fluoride in bone. Radiat Res **46**:317–333, 1971.
2. Shiffl H, Binswanger U. Renal handling of fluoride in healthy man. Renal Physiol **5**:192–195, 1982.
3. Waterhouse C, Taves DR, Munzer A. Serum inorganic fluoride changes related to previous fluoride intake, renal function and bone resorption. Clin Sci **58**:145–152, 1980.
4. Chen PS Jr, Smith FA, Gardner DE, O'Brien JA, Hodge HC. Renal clearance of fluoride. Proc Soc Exp Biol Med **92**:879–883, 1956.
5. Carlson CH, Armstrong WD, Singer L, Hinshaw LB. Renal excretion of radiofluoride in the dog. Am J Physiol **198**:829–832, 1960.
6. Ekstrand J, Ehrenbo M, Boreus LO. Fluoride bioavailability after intravenous and oral administration: Importance of renal clearance and urine flow. Clin Pharmacol Ther **23**:329–338, 1978.
7. Whitford GM, Pashley DH, Stringer GI. Fluoride renal clearance: A pH-dependent event. Am J Physiol **230**:527–532, 1976.
8. Whitford GM, Pashley DH. The effect of body fluid pH on fluoride distribution, toxicity and renal clearance. In: Johansen E, Taves DR, Olsen TO, Eds. Continuing Evaluation of the Use of Fluorides, AAAS Selected Symposium 11. Boulder, CO: Westview Press, pp187–221, 1979.
9. Ekstrand J, Ehrenbo M, Whitford GM, Jarnberg PO. Fluoride pharmacokinetics during acid-base changes in man. Eur J Clin Pharmacol **18**: 189–194, 1980.
10. Jarnberg PO, Ekstrand J, Ehrenbo M. Renal excretion of fluoride during water diuresis and induced urinary pH changes in man. Toxicol Lett **18**:141–146, 1983.
11. Jarnberg PO, Ekstrand J, Irestedt L. Renal fluoride excretion and plasma fluoride levels during and after enflurane anesthesia are dependent on urinary pH. Anesthesiology **54**:48–52, 1981.
12. Jarnberg PO, Ekstrand J, Irestedt L, Santesson J. Renal fluoride excretion during and after enflurane anaesthesia: Dependency on spontaneous urinary pH variations. Acta Anesth Scand **24**:129–134, 1980.
13. Ekstrand J, Spak CJ, Ehrenbo M. Renal clearance of fluoride in a steady-state condition in man: Influence of urinary flow and pH changes by diet. Acta Pharmacol Toxicol **50**:321–325, 1982.
14. Rouch AJ. Characteristics of fluoride flux and the absence of a vasopressin-like effect by fluoride in the isolated perfused rabbit cortical collecting duct. PhD thesis, Department of Physiology and Endocrinology, Medical College of Georgia, 1989.
15. Whitford GM, Pashley DH, Reynolds KE. Fluoride absorption from the rat urinary bladder: A pH-dependent event. Am J Physiol **232**:F10–F15, 1977.
16. Whitford GM, Pashley DH. Fluoride absorption: The influence of gastric acidity. Calcif Tissue Int **36**:302–307, 1984.
17. Whitford GM, Callan RS, Wang HS. Fluoride absorption through the hamster cheek pouch: A pH-dependent event. J Appl Toxicol **2**:303–306, 1982.
18. Whitford GM. Physiologic determinants of plasma fluoride concentrations. In: Shupe JL, Peterson HB, Leone NC, Eds. Fluorides: Effects on Vegetation, Animals and Man. Salt Lake City, UT: Paragon Press, pp167–182, 1983.
19. Whitford GM. The Metabolism and Toxicity of Fluoride. Basel: Karger, pp87–90, 1989.
20. Eisenberg AD, Marquis RE. Uptake of fluoride by cells of *Streptococcus mutans* in dense suspension. J Dent Res **59**:1187–1191, 1980.
21. Eisenberg AD, Marquis RE. Enhanced transmembrane proton conductance in *Streptococcus mutants* GS-5 due to ionophores and fluoride. Antimicrob Agents Chemother **19**:807–812, 1981.
22. Whitford GM, Schuster GS, Pashley DH, Venkateswarlu, P. Fluoride uptake by *Streptococcus mutans* 6715. Infect Immun **18**:680–687, 1977.
23. Gutknecht J, Walter A. Hydrofluoric and nitric acid transport through lipid bilayer membranes. Biochim Biophys Acta **644**:153–156, 1981.
24. Pitts RF, Gurd RS, Kessler RH, Hierholzer K. Localization of acidification of urine, potassium and ammonia secretion and phosphate reabsorption in the nephron of the dog. Am J Physiol **194**:125–134, 1958.
25. Walser M, Rahill WJ. Renal tubular transport of fluoride compared with chloride. Am J Physiol **210**:1290–1292, 1966.
26. Malvin RL, Wilde WS, Sullivan LP. Localization of nephron transport by stop flow analysis. Am J Physiol **194**:135–142, 1958.
27. Rector FC Jr, Renal secretion of hydrogen. In: Rouiller C, Muller AF, Eds. The Kidney: Morphology, Biochemistry and Physiology. New York: Academic Press, Vol **III**: p235, 1971.
28. Arruda JAL, Roseman MK, Sehy JT, Nascimento A, Batlle D, Kurtzman NA. Effect of lithium administration on distal nephron function. Min Electrolyte Metab **4**:81–88, 1980.
29. Homer LD, Solomon S. Stop-flow studies on renal handling of lithium in the dog. Am J Physiol **203**:897–900, 1962.
30. Fry BW, Taves DR. Serum fluoride analysis with the fluoride electrode. J Lab Clin Med **75**:1020–1025, 1970.
31. Chen PS Jr, Toribara TY, Warner H. Microdetermination of phosphorus. Anal Chem **28**:1756–1758, 1956.
32. Yatzidis H. New method for direct determination of "true" creatinine. Clin Chem **20**:1131–1134, 1974.
33. Knox FG, Lechene C. Distal site of action of parathyroid hormone on phosphate reabsorption. Am J Physiol **229**:1556–1560, 1975.
34. Whitford GM, Taves DR. Fluoride-induced diuresis: Renal tissue solute concentrations, functional, hemodynamic and histologic correlates in the rat. Anesthesiology **39**:416–427, 1973.
35. Tobin T, Akera T, Dworin JZ, Brody TM. Fluoride nephropathy: Lack of direct involvement of renal ATPase. Can J Physiol Pharmacol **52**:489–495, 1974.
36. Whitford GM, Allison, NB, Pearson, DE. RBC fluoride conductance in the presence of anion transport inhibition [Abstract 400]. J Dent Res **64**:219, 1985.