Kidney International, Vol. 25 (1984), pp. 534–538

CLINICAL INVESTIGATION

Calcium oxalate kidney stones in patients on continuous ambulatory peritoneal dialysis

ARIE OREN, HARRY HUSDAN, PEI-TAK CHENG, RAMESH KHANNA, ANDREAS PIERRATOS, GEORGE DIGENIS, and DIMITRIOS G. OREOPOULOS

The Metabolic-Renal Laboratory and Department of Medicine, Toronto Western Hospital, the Department of Laboratories, Mt. Sinai Hospital, and the Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Calcium oxalate kidney stones in patients on continuous ambulatory peritoneal dialysis. Kidney stones were passed by ten out of 186 patients with endstage renal disease who were treated with continuous ambulatory peritoneal dialysis (CAPD). Stones from seven patients were examined by x-ray diffraction. In five of them the stones were composed of calcium oxalate monohydrate. The urine calcium oxalate activity product was determined in 44 CAPD patients, eight of whom were stone formers, and compared to that of 120 normal volunteers. In CAPD patients, mean urine ionic-calcium concentration was lower than in normal subjects whereas mean urine ionic-oxalate concentration was significantly higher than in normal subjects. In normal urine samples, the calcium oxalate activity product showed a significant correlation with both the urine ionic-calcium and the ionic-oxalate concentrations. In contrast, in CAPD patients the calcium oxalate activity product correlated with the ionic-calcium concentration but not with ionic-oxalate. Although the urine ionic-calcium concentration is lower in CAPD patients than in normal subjects, it is the relative increase in its concentration which appears to be associated with the increased risk of kidney stone formation in these patients. This relative hypercalciuria seems to follow 1,25(OH)$_2$ vitamin D$_3$ administration.

Calculs rénaux d'oxalate de calcium chez des malades en dialyse péritonéale continue ambulatoire. Des calculs rénaux ont été éliminés par dix de 186 malades avec une néphropathie terminale traitée par dialyse péritonéale continue ambulatoire (CAPD). Les calculs de sept malades ont été examinés par diffraction aux rayons. Dans cinq d'entre eux, les calculs étaient composés d'oxalate de calcium monohydraté. Le produit d'activité urinaire de l'oxalate de calcium à été déterminé chez 44 malades en CAPD, dont huit étaient lithiasiques, et comparés à celui de 120 volontaires normaux. Chez les malades en CAPD, la concentration urinaire moyenne en ions calcium était plus faible que celle de sujets normaux, alors que la concentration moyenne en ion oxalate était significativement plus élevée que chez les normaux. Dans les échantillons urines normales, le produit d'activité de l'oxalate de calcium indiquait une corrélation significative avec les concentrations urinaires d'ions calcium et d'ions oxalate. A l'opposé, chez les malades en CAPD, le produit d'activité de l'oxalate de calcium était corrélé avec la concentration d'ions calcium mais non d'ions oxalate. Bien que la concentration urinaire d'ions calcium soit plus faible chez les malades en CAPD que chez les sujets contrôles, c'est l'augmentation relative de sa concentration qui semble être associée avec l'augmentation de risques de formation calculeuse chez ces malades. Cette relative hypercalciurie semble suivre l'administration de 1,25(OH)$_2$D vitamine D$_3$.

Received for publication March 24, 1983
and in revised form July 26, 1983

The spectrum of disturbances described in renal failure does not appear to include nephrolithiasis. It is well known that kidney stone formation usually ceases when recurrent stone formers develop renal failure [1]. It was thought that the low concentration of urinary calcium found in terminal renal failure makes it highly unlikely that such patients would form kidney stones. In recent years, however, several centers have reported kidney stones in previously nonstone-forming dialysis patients [2–5]. The present study reports the frequency and composition of kidney stones observed in patients with terminal renal failure treated with continuous ambulatory peritoneal dialysis (CAPD) and highlights some of the factors responsible for their formation.

Methods

During 1977 to 1981, 186 patients with endstage renal disease were maintained on the Toronto Western Hospital (TWH) CAPD program [6]. Ten out of these 186 patients developed kidney stones while on CAPD. The stones from seven patients were collected for crystallography and analyzed by x-ray diffraction analysis (XRD), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) [7]. The presence of protein matrix was studied chemically by the Lowry method and inferred by the presence of a very broad band in the x-ray diffraction patterns.

To further elucidate the pathogenesis of this complication, we studied the composition of 24-hr urine samples from 44 of the CAPD patients, including the stone formers, and 120 healthy control subjects.

None of the stone formers had a history of nephrolithiasis prior to dialysis; their initial diseases were: glomerulonephritis (three patients), diabetic nephropathy (three patients), and scleroderma, IgA-nephropathy, malignant hypertension, and medullary cystic disease in one each. They developed stones after being on CAPD from 6 to 9 months. Seven patients had one or two episodes of stones and three as many as four. All stones were passed spontaneously, some of them asymptomatically and some after acute renal colic with hematuria and dysuria with suprapubic discomfort. The episodes of renal colic responded to symptomatic treatment.

The parameters measured were as follows: 24-hr urine for calcium, oxalate, calcium oxalate (CaOx) activity product, as

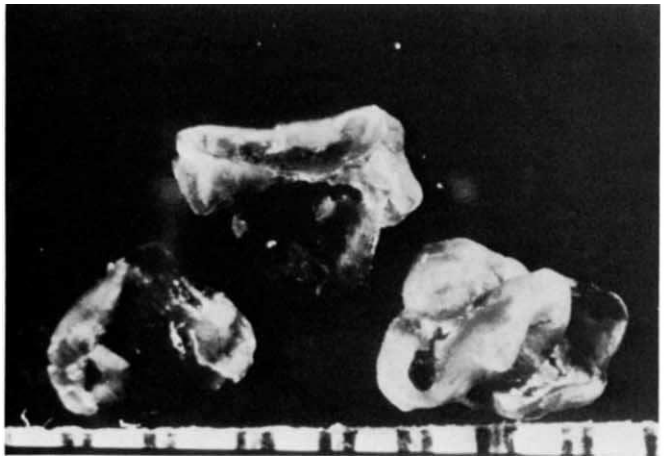

Fig. 1. *General appearance of stones passed by patients on CAPD.*

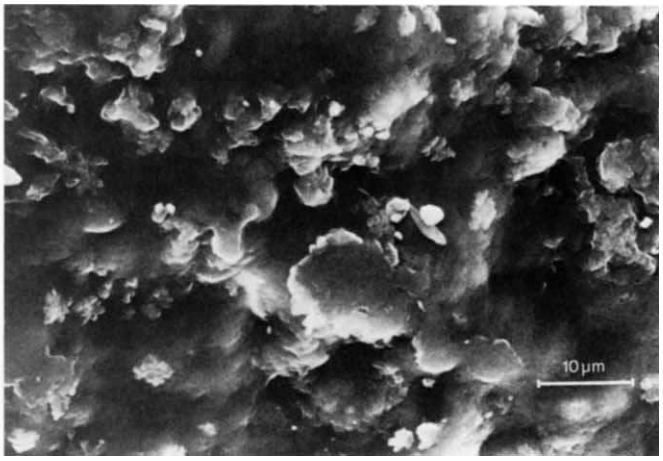

Fig. 2. *Ultrastructure of CaOx stones on scanning electron microscope.* (×1200)

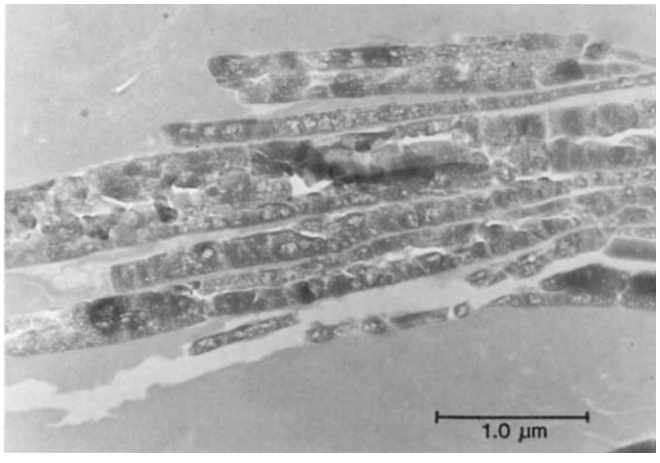

Fig. 3. *The CaOx crystals on transmission electron microscopy.* (×20,000)

well as serum calcium, and PTH measured on the same day. Some of the patients had repeated investigations at 6-month intervals.

The CaOx activity product in the urine was calculated with a computer program designed by Robertson, Peacock, and Nordin [8], Robertson [9], and Robertson, Peacock, and Nordin [10] using nine different individually measured constituents in the urine (calcium, magnesium, sodium, potassium, ammonium, phosphate, oxalate, citrate, and sulfate) and pH measurements. With this same program, we also calculated the concentrations of the ionic calcium (Ca^{++}) and oxalate (Ox^{--}) in the urine.

Serum calcium was measured with an atomic absorption spectrophotometer (model AA/120, Varian-Techtron, Springvale, Australia) and corrected for total serum proteins [11]. Urinary oxalate was determined using a colorimetric method [12, 13]. Plasma PTH was measured by a radioimmunoassay which detects both the carboxy and amino terminals of the PTH molecule [14].

Most of these patients took $1,25(OH)_2$ vitamin D_3 by mouth to control renal osteodystrophy [15, 16]. The mean dose per day during the month preceding the investigation was calculated.

The calculated urine CaOx activity product was correlated with the urine ionic calcium and ionic oxalate concentrations in both CAPD patients and control subjects. Urine CaOx activity product in CAPD patients was correlated with their serum Ca, PTH, and dose of $1,25(OH)_2$ vitamin D_3. Urine ionic Ca was also correlated with the daily dose of $1,25(OH)_2$ vitamin D_3. Simple linear regression analysis was used for the above correlations [17].

Results

All the stones collected were very small, that is, less than 3 mm in size (Fig. 1). The stones produced by five of the seven patients contained substantial amounts of Ca oxalate monohydrate (COM), ($Ca\ C_2O_4 \cdot H_2O$) crystals, as demonstrated by x-ray diffraction. The Ca oxalate crystals were mixed with protein matrix in stones of two of these five patients. The amount of matrix in stones of the three other patients was undetectable by XRD, indicating that these stones contained very little organic matrix. Of the remaining two patients, one had stones composed of calcium apatite crystals while the other passed two stones, one of which was composed of calcium oxalate monohydrate and the other of matrix.

Ultrastructural studies showed that the COM stones were composed of numerous small crystals of 1 to 3 μm in size. As can be seen by scanning electron microscopy (Fig. 2), these crystals are exposed to the stone surfaces, in an apparently unorganized manner. However, as shown by transmission electron microscopy (Fig. 3), the crystals are actually stacked up in a fairly orderly manner inside the COM stones.

The mean total 24-hr urinary calcium and oxalate excretions in 44 CAPD patients and 120 normal volunteers are shown in Table 1. Patients on CAPD excreted significantly less calcium, oxalate, and urine volume per 24-hr than do normal control subjects. The urine pH, however, did not differ significantly in these two groups.

Table 2 shows the mean calculated urine ionic calcium and oxalate concentrations in the CAPD patients and normal control subjects. The patients show significantly lower calcium but higher ionic oxalate concentrations than the control subjects.

Figure 4 shows the values of the urine CaOx activity product in the 44 CAPD patients and the 120 normal control subjects. The "formation product" line separates the labile region, where

Table 1. Total Ca and oxalate excretion in 24-hr urine (mean ± SD) in CAPD patients and normal subjects

	CAPD patients (N = 44)	Normal subjects (N = 120)	P value
Calcium, *mmoles/day*	0.2 ± 0.2	4.1 ± 2.1	< 0.0001
Oxalate, *μmoles/day*	120 ± 90	350 ± 150	< 0.0001
Volume, *ml/day*	335 ± 280	1419 ± 618	< 0.0001
pH	6.25 ± 1.1	6.24 ± 0.7	NS

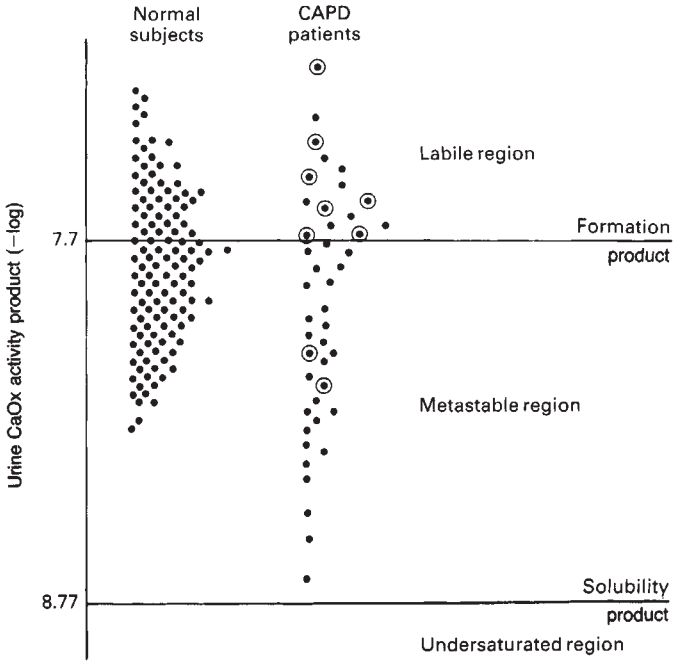

Fig. 4. *Urine CaOx activity products in normal subjects and CAPD patients. Circles* surrounding *closed circles* indicate patients who passed stones.

spontaneous crystallization or precipitation occurs, from the metastable region, where nucleation does not occur under normal circumstances [18]. It is interesting to note that the urine of those CAPD patients forming stones had a product in the labile region. The two stone patients whose CaOx activity product was in the metastable region were the two with calcium apatite and matrix stones.

The correlations between the calcium oxalate activity product and the urinary ionic concentration of calcium and oxalate in normal control subjects and CAPD patients are shown in Figures 5 and 6, respectively. The values of the activity product are expressed as the negative logarithm (to base 10). Thus, the smaller the number, the greater the activity product. In normal control subjects (Fig. 5), large increases in ionic calcium are necessary but small increases in ionic oxalate concentrations are sufficient to raise the activity product. In CAPD patients (Fig. 6) on the other hand, the calcium oxalate activity product increases with increasing ionic calcium concentration but is independent of the ionic oxalate concentration, which is already elevated.

The results of the correlation between urine CaOx activity product and serum calcium, PTH and the daily dose of $1,25(OH)_2$ vitamin D_3 in CAPD patients (Table 3) indicate that the urinary calcium oxalate activity product shows a positive correlation with serum calcium concentration, with the dosage of $1,25(OH)_2$ vitamin D_3 administered, and a negative correlation with plasma PTH. There is also a significant ($P < 0.001$) positive correlation between the dosage of $1,25(OH)_2$ vitamin D_3 and urinary ionic Ca.

Table 2. Calculated urine ionic Ca^{++} and Ox^{--} concentrations (mean ± SD) in CAPD patients and normal subjects

	CAPD patients (N = 44)	Normal subjects (N = 120)	P value
Ca^{++}, *mmoles/liter*	0.48 ± 0.4	1.59 ± 0.9	< 0.0001
Ox^{--}, *mmoles/liter*	0.25 ± 0.1	0.15 ± 0.1	< 0.0001

Discussion

Kidney stone formation in ten of 186 CAPD patients (5.4%) described in this study represents an unusually high incidence of this disorder. To our knowledge, it must be considered a previously unrecognized complication of this type of dialysis treatment. In patients on chronic hemodialysis, the reported incidence of stones varies from 5 to 22% [3, 4, 19].

To our knowledge, development of kidney stones in dialyzed patients was reported first by Oreopoulos and Silverberg [2] in 1974. They described two patients, one on chronic peritoneal and the other on chronic hemodialysis, who developed calcium oxalate stones. Bommer et al [3] confirmed this observation, that is, de novo formation of stones in a large percentage of patients on chronic hemodialysis. These investigators in their initial analysis found that the stones were composed of matrix, but subsequent systematic sectioning of the stones confirmed the presence of oxalate microcrystals [20]. Keiji and Kanichi [5] described nine hemodialysis patients passing calcium oxalate stones, while Carals et al [4] observed kidney stones among 7.5% of 160 patients on chronic hemodialysis. Koga et al [19] using computerized tomography found a high incidence of mineral-containing stones (51.1%). Our findings indicate, that under certain conditions, which seem to be predominant in our patients, the formation of calcium oxalate stones is enhanced, whereas less frequently matrix or calcium apatite stones can occur. Attention therefore was focused on the role of oxalic acid and calcium.

Oxalic acid is an end product of amino acid and ascorbic acid metabolism, normally excreted in the urine. Plasma oxalate levels are elevated in uremic patients, from two to four times the normal level, depending on the degree of renal failure and the efficiency of dialysis [21, 24, 25]. Calcium oxalate deposition in several organs, such as the heart and the joints, has been reported to be a complication of chronic renal failure [22, 23, 26–29]. Hautmann, Lehmann, and Komor [30], after measuring the ionic calcium and oxalate concentrations in renal tissue samples, suggested that their high concentrations in the human papilla contribute to the formation of the calcium oxalate deposits, which serve as the basis of stone formation.

The fact that increase in urine oxalate concentration increases the risk of calcium oxalate crystal formation has been recognized as one of the main causes of calcium oxalate stones [31]. It has been shown that the degree of urine saturation of calcium oxalate, expressed in terms of its corresponding activity product, is the most important single factor in the pathogenesis of kidney stones [32, 33] and depends on the ionic calcium

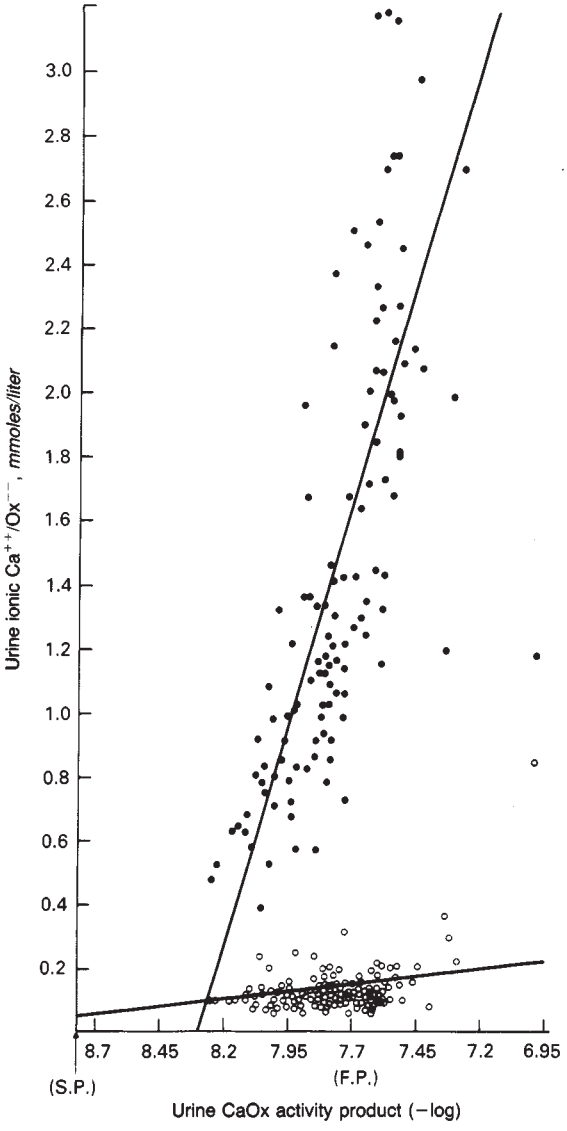

Fig. 5. *Correlation of urine CaOx activity product and urine ionic Ca* (●) [r = 0.64, $P < 0.0001$] *and ionic oxalate* (○) [r = 0.29, $P < 0.001$] *concentration in normal subjects. S.P. and F.P. denote solubility product and formation product, respectively.*

Table 3. Correlation of urine CaOx activity product with serum calcium, plasma PTH, and daily dose of $1,25(OH)_2$ vitamin D_3

	r	*P*
CaOx vs. serum Ca	+0.43	0.002
CaOx vs. plasma PTH	−0.41	0.003
CaOx vs. daily dose of $1,25(OH)_2$ vitamin D_3	+0.54	< 0.004

and oxalate concentrations in the urine [18, 34]. As was shown by Robertson and Nordin [18], the CaOx activity product can be increased in normal subjects either by large increases in urine calcium or small increases in urine oxalate concentrations. Our findings in healthy volunteers confirm this observation.

In this study, to our knowledge, we have shown for the first time that in CAPD patients there is a significant correlation between the levels of urinary CaOx activity product and urine

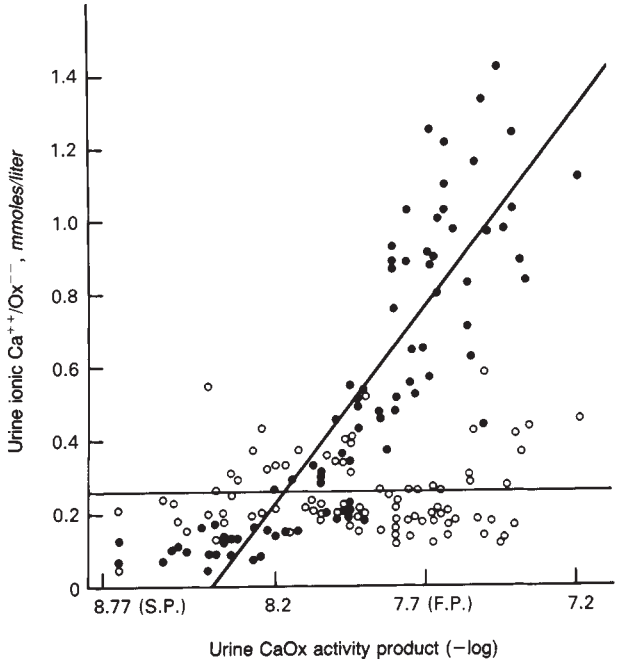

Fig. 6. *Correlation of urine CaOx activity product and urine ionic Ca* (●) [r = 0.84, $P < 0.0001$] *and ionic oxalate* (○) [r = 0.02, $P = 0.4$] *concentrations in patients on CAPD. S.P. and F.P. denote solubility product and formation product, respectively.*

calcium concentrations *only*, but not with oxalate concentrations. Thus, unlike normal people, CAPD patients show consistently high urine-oxalate concentrations and have urinary CaOx activity products which are more sensitive to changes in urine calcium than are normal subjects but are independent of changes in urine oxalate.

The fact that some of our normal control subjects have CaOx activity product values greater than the formation product is consistent with the theory that the kidney stone formation depends not only on the activity of CaOx but also on the level of urinary inhibitors of crystallization [35]. As has been shown previously, patients with renal failure have significantly lower values of inhibitors of calcification in urine, than do normal subjects [36]. It may be speculated that, in view of the consistently high urine oxalate concentrations and decreased urinary inhibitors of calcification in uremia, a relative increase in urine calcium concentration is a major cause of kidney stone formation in our dialysis patients.

The positive correlation between urinary CaOx activity product and serum calcium and between urinary CaOx activity product and urine calcium, was to be expected. However, the surprising negative correlation found between the urinary CaOx activity product and plasma PTH level suggests that some other factor might be responsible for the elevation of serum calcium found in these patients. The highly significant correlation between the dosage of $1,25(OH)_2$ vitamin D_3 and urinary ionic Ca and CaOx activity product levels supports the hypothesis that treatment with $1,25(OH)_2$ vitamin D_3 played an important role in the pathogenesis of kidney stones in our patients.

In conclusion, our CAPD patients demonstrated an increase in urine calcium in response to treatment with $1,25(OH)_2$ vitamin D_3. In the presence of a consistently high urine-oxalate concentration, a relative increase in urine calcium is responsi-

ble for the rise in urinary calcium-oxalate activity product and stone formation in some of these patients. The probability of this adverse effect of $1,25(OH)_2$ vitamin D_3 should be considered when this drug is administered to dialysis patients who pass urine.

Acknowledgments

Portions of this work were supported by the Ontario Branch of the Canadian Kidney Foundation and the National Institutes of Health grant AM82213. The authors thank the staff of the Metabolic-Renal Laboratory, especially Mrs. L. Grass, Ms. N. Lagdamen, and Mr. R. Vogl for technical assistance, Ms. R. Muhlbacher for collection of data, Dr. J. O. Godden for editing the final manuscript, and Mrs. K. Polegato and F. Razack for secretarial assistance.

Reprint requests to Dr. D. G. Oreopoulos, Division of Nephrology, Suite 525, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada

References

1. HOWARD JE: "Boiler crud" in urinary pipes *(editorial). N Engl J Med* 286:485–486, 1972
2. OREOPOULOS DG, SILVERBERG S: Calcium oxalate urinary-tract stones in patients on maintenance dialysis. *N Engl J Med* 290:1438–1439, 1974
3. BOMMER J, RITZ E, TSCHOPE W, WALDHERR R, GEBHARDT M: Urinary matrix calculi consisting of microfibrillar protein in patients on maintenance hemodialysis. *Kidney Int* 16:722–728, 1979
4. CARALS A, LLOVERAS J, ANDREV J, BRULLES A, MASRAMON J, LLORACH M, VIDAL MT, FERNANDEZ CONDE M, AUBIA J: Urinary calculi in chronic dialysis patients *(letter). Lancet* 2:1024–1025, 1979
5. KEIJI O, KANICHI E: Ureteric colic in patients on hemodialysis *(abstract)*, in *Tenth Ann Clin Dial Transpl Forum*, Washington D.C., National Kidney Foundation in Association with the American Society of Nephrology, 1980, p 48
6. OREOPOULOS DG, KHANNA R, WILLIAMS P, VAS SI: Continuous ambulatory peritoneal dialysis. *Nephron* 30:293–303, 1982
7. CHENG PT, PRITZKER KPH, TAUSCH J, PITTAWAY A, MILLARD J: Analytical scanning electron microscopy and X-ray microdiffractiometry of renal calculi using etched plastic sections. *Scanning Electron Microsc* III:163–168, 1981
8. ROBERTSON WG, PEACOCK M, NORDIN BEC: Activity products in stone-forming and nonstone-forming urine. *Clin Sci* 34:579–594, 1968
9. ROBERTSON WG: Measurement of ionized calcium in biological fluids. *Clin Chim Acta* 24:149–157, 1969
10. ROBERTSON WG, PEACOCK M, NORDIN BEC: Measurement of activity products in urine from stone-formers and normal subjects, in *Urolithiasis: Physical Aspects*, edited by FINLAYSON B, Washington, D.C., National Academy of Sciences, 1972, pp 79–95
11. HUSDAN H, RAPOPORT A, LOCKE S: Influence of posture on the serum concentration of calcium. *Metabolism* 22:787–797, 1973
12. HODGKINSON A, WILLIAMS A: An improved colorimetric procedure for urine oxalate. *Clin Chim Acta* 36:127–132, 1972
13. HUSDAN H, LEUNG M, OREOPOULOS D, RAPOPORT A: Modified method for urinary oxalate *(letter). Clin Chem* 22:1538, 1976
14. MURRAY TM, KENTMANN HT: The immunochemical specificity of antisera to bovine parathyroid hormone: An approach to region-specific radioimmuno-assay. *J Endocrinol* 56:493–501, 1973
15. MALLUCHE HH, GOLDSTEIN DA, MASSRY SG: Management of renal osteodystrophy with $1,25(OH)_2D_3$. II. Effects on histopathology of bone: Evidence for healing of osteomalacia. *Miner Electrolyte Metabol* 2:48–55, 1979
16. VELENTZAS C, OREOPOULOS DG, PIERRATOS A, MEEMA HE, RABINOVICH S, MEINDOCK H, HUSDAN H, MURRAY TM, OGILVIE R, KATIRTZOGLOU A: Treatment of renal osteodystrophy with 1,25-dihydroxycholecalciferol. *Can Med Assoc J* 124:577–583, 1981
17. COLTON T: Statistics in medicine. Boston, Little, Brown and Company, 1974, pp 191–204
18. ROBERTSON WG, NORDIN BEC: Activity products in urine, in *Renal stone research symposium*, edited by HODGKINSON A, NORDIN BEC, London, J. & A. Churchill Ltd., 1968, pp 221–232
19. KOGA N, NOMURA G, YAMAGATA Y, KOGA T: Ureteric pain in patients with chronic renal failure on hemodialysis. *Nephron* 31:55–58, 1982
20. BOMMER J, RITZ E, WALDHERR R, TSCHOPPE W: Nephrolithiasis in dialysed patients—evidence for a peculiar type of matrix stones with Ca-Oxalate inclusions, in *Urolithiasis Clinical and Basic Research*, edited by SMITH LH, ROBERTSON WG, FINLAYSON B, New York, Plenum Press, 1981, pp 703–706
21. BALCKE P, SCHMIDT P, ZAZGORNIK J, KOPSA H, DEUTSCH E: Secondary oxalosis in chronic renal insufficiency *(letter). N Engl J Med* 303:944, 1980
22. OP DE HOEK CT, DIDERICH PP, GRATAMA S, WEISJ-VON HOFWEGEN EJ: Oxalosis in chronic renal failure. *Proc Eur Dial Transplant Assoc* 17:730–735, 1980
23. BALCKE P, SCHMIDT P, ZAZGORNIK J, KOPSA H, DEUTSCH E: Secondary hyperoxalemia in chronic renal failure. *Int J Artif Organs* 5:141–143, 1982
24. ZAREMBSKI PM, HODGKINSON A, PEARSON FM: Elevation of the concentration of plasma oxalic acid in renal failure. *Nature* 212:511–512, 1966
25. STONE WJ, FERGUSON MC: Plasma oxalate levels in chronic renal failure *(abstract). Kidney Int* 12:535, 1977
26. SALYER WR, HUTCHINS GM: Cardiac lesions in secondary oxalosis. *Arch Int Med* 134:250–252, 1974
27. HOFFMAN GS, SCHUMACHER HR, PAUL H: Calcium oxalate microcrystalline-associated arthritis in end-stage renal disease. *Ann Intern Med* 97:36–42, 1982
28. SALYER WL, KEREN D: Oxalosis as a complication of chronic renal failure. *Kidney Int* 4:61–66, 1973
29. FAYEMI AO, ALI M, BRAUN EV: Oxaloxis in hemodialysis patients. A pathologic study of 80 patients. *Arch Pathol Lab Med* 103:58–62, 1979
30. HAUTMANN R, LEHMANN A, KOMOR S: Calcium and oxalate concentrations in human renal tissue: The key to the pathogenesis of stone formation? *J Urol* 123:317–319, 1980
31. ROBERTSON WG, PEACOCK M, HEYBURN PJ, MARSHALL DH, CLARK PB: Risk factors in calcium stone disease of the urinary tract. *Br J Urol* 50:449–454, 1978
32. MARSHALL RW, COCHRAN M, ROBERTSON WG, HODGKINSON A, NORDIN EC: The relation between the concentration of calcium salts in the urine and renal stone composition in patients with calcium-containing renal stones. *Clin Sci* 43:433–441, 1972
33. FINLAYSON B: Symposium on renal lithiasis: Renal lithiasis in review. *Urol Clin North Am* 1:181–212, 1974
34. MARSHALL RW, ROBERTSON WG: Nomograms for the estimation of the saturation of urine with calcium oxalate, calcium phosphate, magnesium ammonium phosphate, uric acid, sodium acid urate, ammonium acid rate and cystine. *Clin Chim Acta* 72:253–260, 1976
35. ROBERTSON WG, PEACOCK M, MARSHALL RW, MARSHALL DH, NORDIN BEC: Saturation-inhibition index as a measure of the risk of calcium oxalate stone formation in the urinary tract. *N Engl J Med* 294:249–252, 1976
36. OREOPOULOS DG, WALKER D, AKRIOTIS DJ, RONCARI DAK, HUSDAN H, SYMVOULIDIS A, DEVEBER GA, RAPOPORT A, REID DBW: Excretion of inhibitors of calcification in urine. Part II. Findings in patients with chronic renal failure. *Can Med Assoc J* 112:827–831, 1975