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Prevention of calcium stones with thiazides

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In 1962, we began a clinical trial designed to assess the efficacy of the thiazide diuretics in the prevention of calcific urinary calculi. During the subsequent 15 years, we have initiated thiazide therapy in 346 patients. We have also conducted a series of investigations designed to clarify the mechanism by which thiazides prevent stone growth.

Hypocalciuric action of thiazides

The initial rationale for the use of thiazides in stone prevention was based on the observation that thiazide diuretic therapy resulted in reduced urinary excretion of calcium, an effect first reported by Lamberg and Kuhlback in 1959 [1] and subsequently confirmed by a number of investigators [2–5]. The hypocalciuric effect usually begins within two to three days of starting the drug [5], is usually maximal within six days, and is nearly always sustained. The magnitude of the reduction in urine calcium excretion is variable, but with the dose of hydrochlorothiazide usually employed by us (50 mg twice daily), the mean reduction in urine calcium excretion is 150 mg/day, and in patients with hypercalciuria the urine calcium has been seen to decrease by as much as 400 mg/day. Occasionally, the decrease is much less pronounced, and in a small percentage of normal subjects and patients, there is little discernible effect. It should be emphasized that this hypocalciuric effect is unique to thiazide diuretics and related drugs, such as chlorthalidone and metolazone, whereas other commonly used diuretics either have no significant effect on calcium excretion (e.g. spironolactone, triamterene), or they produce hypercalciuria (e.g. furosemide, ethacrynic acid).

The mechanism by which thiazides reduce urinary calcium excretion has engaged the attention of a number of investigators but is still not entirely clear. We have found that diazoxide, a member of the thiazide family which lacks a natriuretic effect, does not possess the hypocalciuric action in man, suggesting that the hypocalciuria is related in some way to the natriuresis. At the site in the nephron where chlorothiazide exerts its primary effect (probably the cortical diluting site of the distal nephron), there is a dissociation between sodium transport and calcium transport, and at this site chlorothiazide selectively inhibits sodium reabsorption without a concomitant inhibition of calcium reabsorption [6]. Subsequent studies in dogs have suggested that thiazides might actually enhance distal tubular calcium reabsorption, and they also have demonstrated that the dissociation between sodium and calcium clearance is not dependent upon volume depletion, because the response is rapid and also because the effect is unilateral when the drug is injected into one renal artery [7]. Moreover, this acute effect is not dependent upon the presence of parathyroid hormone since it occurs in parathyroidectomized dogs if sufficient drug is infused to correct for the reduced tubular secretion of chlorothiazide which follows parathyroidectomy [7].

The hypocalciuric response to chronic thiazide administration in man appears to be somewhat more complicated. This response is blocked if volume depletion is prevented by sodium chloride administration [8,9], which suggests that it may be dependent on enhanced sodium reabsorption (and calcium secondarily) by the proximal tubule in response to volume depletion. Moreover, the hypocalciuric response in man appears to be blunted or absent in some hypoparathyroid patients, which has prompted the suggestion that the presence of parathyroid hormone is a prerequisite for thiazide-induced hypocalciuria [9–1]. This conclusion, however, is difficult to reconcile with the reports that thiazides reduce urinary calcium excretion in parathyroidectomized rats [12,13]. Furthermore, we have demonstrated a marked hypocalciuric response to thiazides in the occasional hypoparathyroid patient. Thiazide adminstration does not increase the serum levels of parathyroid hormone [14–16] or the urinary excretion of

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cyclic AMP [11]; in fact, serum PTH levels may decrease in hypercalciuric patients during thiazide administration [15]. It has been postulated that thiazides may potentiate the action of parathyroid hormone by inhibiting phosphodiesterase, an enzyme which accelerates degradation of cyclic AMP [17].

Other thiazide effects on calcium metabolism

The effect of thiazides on the intestinal absorption of calcium is a matter of considerable importance: it has a bearing on thiazide-induced changes in skeletal function and urine oxalate excretion, and it also has a bearing on the possibility that chronic thiazide therapy might induce metastatic calcification. There appears to be no consistent effect of acute thiazide administration on intestinal calcium absorption. A review of five papers which record thiazide-induced changes in fecal calcium in 34 patients indicates that fecal calcium may be diminished, unchanged, or increased during the initial days of thiazide administration [2, 5, 18–20). There are a number of possible explanations for the divergent results. The first is that there may be a true individual difference in the actue effect of thiazides on intestinal calcium absorption depending upon the nature of the underlying disorder and the state of total body calcium reserves. Another possibility is that the divergent results may be related in part to differences in drug dosages employed by different investigators. A third possibility is that the conflicting results may be a reflection of the methodologic problems associated with conventional calcium balance studies. We have reported some evidence which confirms the initial reduction in fecal calcium excretion observed in the majority of our balance studies [5]. In one of our patients, whose fecal calcium fell by 44% initially during thiazide treatment, radioactive calcium (^{47}Ca) was injected i.v. during the control period and again during the period of drug administration [5]. The recovery of the administered tracer dose in the stools and the calculated endogenous fecal calcium was considerably less in the treatment period than in the control period.

Although the acute effects of thiazides on intestinal calcium absorption appear to be somewhat controversial, there is fairly good evidence, though based on limited studies, that intestinal calcium absorption may decrease during long-term thiazide administration. In two patients with idiopathic hypercalciuria, we repeated calcium balance studies after 10 months' and 38 months' treatment in one patient and after eight and 21 months' treatment in the other. In the first patient, in whom there had been an initial decrease in fecal calcium in response to thiazide administration, fecal calcium excretion had risen to the pretreatment level eight months later, despite a slightly reduced calcium intake; but after 38 months, fecal calcium exceeded pretreatment values by 238 mg/day (Fig. 1). In the second patient, in whom there had been no significant initial effect of thiazides on fecal calcium excretion, fecal calcium excretion had increased by 51 mg/day after 21 months but not after eight months' therapy, and calcium balance was no longer positive at the time of the last study [5]. A similar sequence of events has been observed in one of three osteoporotic patients during long-term thiazide administration [20]. Ehrig, Harrison, and Wilson [21], using a double isotopic technique, have studied intestinal calcium absorption during long-term thiazide in 22 patients with recurrent calcium stones. After three to 16 months' therapy, calcium absorption was significantly decreased in 10 patients and unchanged in 12. However, in six of the 12 patients in whom calcium absorption was unchanged, the repeat studies were done after only four months' treatment, and it is quite possible that changes would have been observed in these patients as well if the studies had been carried on for longer periods of time. These studies should be extended to more patients, with various forms of calcium urolithiasis, including absorptive and renal hypercalciurias. It would be of some interest to determine if the reduction in intestinal calcium absorption during thiazide therapy is generalized, or if it is characteristic of only certain forms of calcium urolithiasis.

We have also investigated the effects of thiazides on bone turnover in patients with stone disease and osteoporosis, using calcium kinetic techniques. In

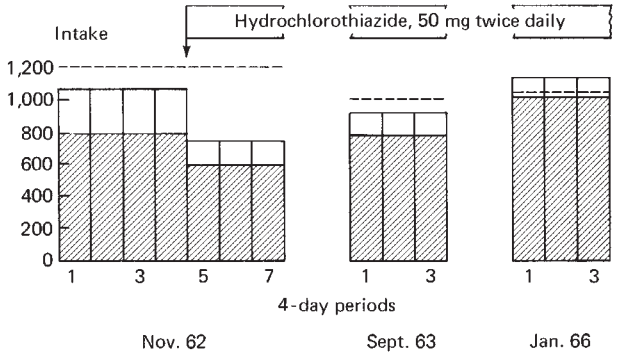

Fig. 1. *Calcium balance studies in a patient (male) with recurrent calcium stones prior to and during thiazide therapy.* In January, 1966, after 38 months on treatment, fecal calcium *(open bars)* exceeded pretreatment values by 238 mg per day. The values for urinary *(solid bars)* and fecal *(open bars)* calcium excretion are the mean values for the entire 16 days' pretreatment period and for the entire 12 days of each of the three different treatment periods. Each calcium balance study was preceeded by an eight-day equilibrium period on the constant diet.

these studies, the patients with stone disease demonstrated an initial decrease in bone resorption which was followed some months later by reduced bone formation, so that eventually the entire process of bone turnover appeared to be significantly diminished; the three osteoporotic patients demonstrated similar results [20]. This appears to be another example of the close coupling of bone formation and bone resorption [22], a finding which had been demonstrated previously with other agents that suppress bone resorption [23, 24]. Thus, there appears to be strong evidence that although significant amounts of calcium may be retained by the body during the initial periods of thiazide administration, there is eventually a return to a state of zero calcium balance.

The effect of thiazides on urinary hydroxyproline excretion, an index of bone resorption, provide further confirmatory evidence for the general conclusion arrived at above. We have consistently observed a one-third reduction in urinary hydroxyproline excretion during thiazide therapy [25]. The urinary excretion of hydroxyproline also decreases during thiazide administration in the rat [26]. In rats pretreated with ^{45}Ca, the concentration, and the specific activity of ^{45}Ca in the bones are significantly higher in the thiazide-treated animals than in controls, suggesting that the breakdown of bone mineral and bone matrix is reduced during thiazide administration. [26].

There is some confusion in the literature concerning the effects of thiazides on serum calcium concentrations. During the first few days of thiazide administration, there is frequently a slight rise in total serum calcium concentrations to the upper limit of the normal range or even to levels slightly above the normal range [5]. This is due to hemo-concentration (with a resultant rise in the protein-bound fraction of the blood calcium) which can be demonstrated if the ultrafiltrable (non-protein-bound) fraction of the serum calcium is measured simultaneously (Fig. 2). For the past eight years, we have measured the calcium concentrations in the serum ultrafiltrate, in addition to total blood calcium concentrations, in our thiazide-treated patients at yearly intervals. Although a rise of the serum ultrafiltrable calcium concentration within the normal range is sometimes observed, elevations above the normal range have been found in only six patients, and this change may not become evident until a year or more has elapsed. The degree of hypercalcemia is usually slight and is thought to represent an unmasking of normocalcemic hyperparathyroidism by thiazides. Three of the six patients underwent parathyroidectomy which corrected the hypercalcemia. Single parathyroid adenomas were removed in two patients; in the third, all four parathyroid glands appeared grossly normal at the time of surgery, and two glands and a portion of a third which were removed appeared histologically normal. The remaining three patients who developed hypercalcemia during thiazide therapy have shown no progression of their stone disease and appear to be suffering no ill effects from their mild hypercalcemia.

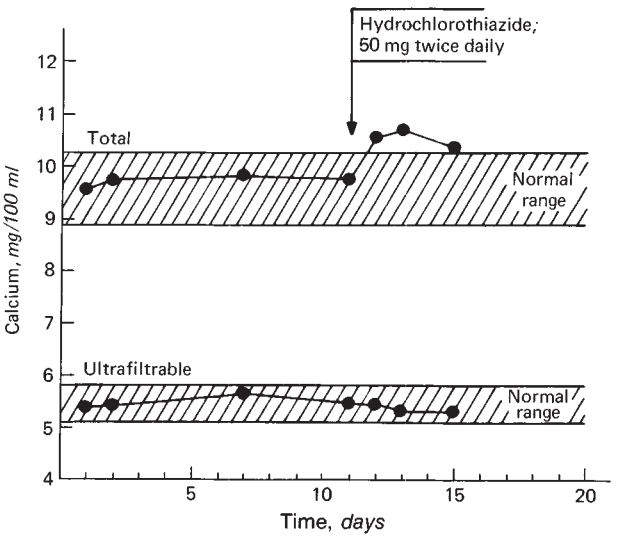

Fig. 2. *Total and ultrafiltrable serum calcium values prior to and during thiazide therapy in a patient having idiopathic hypercalciuria.* There is a temporary rise in total serum calcium values above the normal range during the first few days of thiazide therapy due to hemoconcentration, but there is no significant change in ultrafiltrable calcium values.

Our experience with respect to thiazide-induced changes in serum calcium concentrations is comparable to that of Jorgensen, Transbol, and Binder, who noted a similar increase in total serum calcium concentrations during the first five days of thiazide administration but were unable to demonstrate any significant thiazide-induced increase in the serum concentrations of ultrafiltrable or ionized calcium in 10 normocalcemic stone patients and 10 hypercalcemic patients with hyperparathyroidism [27]. Duarte et al reported one patient whose total serum calcium concentration rose from 10 to 12.4 mg/100 ml on the ninth day of thiazide treatment and then fell to normal by the 14th day; however, serum ultrafiltrable calcium remained at control levels throughout the entire period [28]. Stote et al found that both total and ionized calcium concentrations were significantly increased during administration of hydrochlorothiazide and for at least two weeks after withdrawal of the drug [16]. The maximum mean serum ionized calcium concentration reported in

their study, however, was 4.05 mg/100 ml (an increase of 0.42 mg/100 ml above control levels), which occurred on the 17th day of drug administration; this value probably lies within the normal range, although the authors did not provide this information in their paper.

Although the danger of thiazides inducing significant hypercalcemia is remote in the patient with normal calcium metabolism, this may not be so if the patient has a disease associated with increased bone resorption, such as malignancy, primary hyperparathyroidism, sarcoidosis, immobilization, Paget's disease, etc. In such instances, thiazides may induce hypercalcemia or aggravate pre-existing hypercalcemia and should be used with extreme caution [29].

Thiazides have been reported to cause parathyroid enlargement and hyperplasia in the dog [30], but the doses used in these experiments were much greater on a weight-to-weight basis than those given to humans. Parathyroid hyperplasia, however, did not occur during chronic thiazide administration in rats [31], and there is no good evidence that thiazides induce parathyroid hyperactivity or increased sensitivity to parathyroid hormone in man. As previously mentioned, there is no evidence of increased parathyroid hormone secretion during thiazide administration to humans [14–16] and serum PTH levels may, in fact, diminish in hypercalciuric patients during thiazide administration [15]. Moreover, our observations previously referred to, of diminished urine hydroxyproline excretion and decreased bone turnover during thiazide administration, are incompatible with increased production of parathyroid hormone or increased skeletal sensitivity to it. It is acknowledged, however, that the effects on bone were assessed principally from kinetic analysis but not by a direct histological examination of bone or by a quantitative measurement of bone mineral content.

Effect of thiazides on other urinary constituents

Although the hypocalciuric action of thiazides prompted its initial use for stone prevention, it now appears likely that there are other thiazide-induced changes in the composition of urine which are of equal or greater significance with regard to stone prevention. Perhaps the best known of these effects is the 20 to 30% increase in urinary magnesium excretion which is evident during the initial period of thiazide administration. The magnesium ion is known to block the calcification of organic matrix *in vitro* [32] and to enhance the solubility of calcium oxalate *in vitro* [33]. There are, however, conflicting data as to the duration of the increased urinary magnesium excretion. We found that this effect was still evident in two of our patients who were studied on the same diet, 10 months and 22 months after thiazide therapy was begun [5]. Moreover, in a group of our patients having stone disease, studied under *ad lib* dietary conditions, urine magnesium excretion still exceeded pretreatment levels after two years' thiazide therapy [34]. Others have reported that increased urine magnesium is no longer evident after five days [35] or after one month [36]. We believe, however, that at least in some patients, increased loss of magnesium in the urine probably persists for many years, because we have observed that serum magnesium levels may gradually decline for as long as seven years after thiazide therapy is started.

A less well known thiazide effect is a marked increase of approximately 50% in urinary zinc excretion [37, 38] which is sustained during long-term thiazide therapy [39]. Zinc is a potent inhibitor of calcification *in vitro;* calcification of rachitic rat cartilage is partially inhibited when physiologic concentrations of zinc (0.1 mM) are added to the incubating medium in the absence of magnesium, but calcification is completely blocked when a minute amount of magnesium, insufficient by itself to affect the system, is added [40]. If the calcification of rachitic rat cartilage bears any relationship to the formation of calcific renal calculi, which also consist of calcium salts deposited in an organic matrix, this effect may contribute to the efficacy of thiazides in preventing calcium stone. If, on the other hand, stone formation is largely a matter of precipitation of crystalloids from supersaturated solutions and matrix is purely incidental, the significance of these findings is less certain. Zinc has been shown to have little if any inhibitory effect on the crystallization of calcium oxalate from a supersaturated solution [41]; however, the concentration of zinc used in these experiments (0.005 mM) was at the extreme lower limit of the range found to be effective in retarding calcification of rachitic rat cartilage, and the possibility of a synergistic effect of the magnesium ion was not explored. At the moment, therefore, the significance of the increased urinary zinc excretion remains uncertain.

The effect of thiazides on urine oxalate excretion may prove to be of great importance in stone prevention. In 1971 it was reported that a marked decrease in urine oxalate excretion occurred with the administration of 50 mg of hydrochlorothiazide daily [42]. In 1973, we reported that we did not find urine oxalate changes of a similar magnitude, although we did observe a small but significant reduction in urine oxalate excretion in 39 thiazide-treated patients [43].

Others, however, reported no significant effect of thiazides on urine oxalate excretion [44] (ROSE, personal communication).

Recent observations reported from our laboratory confirm that there is a significant reduction in urine oxalate during chronic thiazide therapy, and they also shed some light on the divergent results reported by different workers [45]. We have measured urine oxalate before and during hydrochlorothiazide therapy in 54 patients with recurrent calcium stones. Although no significant reduction in urine oxalate excretion occurred during the first year of treatment, a significant reduction in urine oxalate excretion was observed in 36 of 47 patients treated for more than 12 months (Fig. 3). In the latter group, urine oxalate excretion during therapy was 15 ± 1.8 mg/24 hr (mean ± SEM) as compared to pretreatment values of 32 ± 3.3 mg/24 hr (Fig. 4).

The striking similarity in the time patterns noted for the thiazide-induced reduction of urine oxalate excretion and of intestinal calcium absorption leads us to believe the two changes are related. This possibility is strengthened by the demonstration that the absorption of dietary oxalate bears an inverse relationship to the amount of free calcium in the intestinal lumen [46]. It seems likely, therefore, that during long-term thiazide therapy more dietary oxalate is precipitated as insoluble calcium oxalate in the intestinal lumen because of reduced intestinal calcium absorption, and thus less oxalate is excreted in the urine. The magnitude of the reduction in oxalate excretion which we have observed is potentially of great clinical significance since relatively small changes in urinary oxalate concentrations may have a marked effect upon the calcium oxalate activity product of urine, whereas changes in urine calcium concentration are believed to be of much less importance in this regard [47].

Thiazide administration frequently results in slight or modest reduction in urine citrate excretion [48], an effect which is possibly secondary to potassium depletion [49]. This is the only thiazide-induced effect which we have observed which could theoretically aggravate stone formation. In view of the efficacy of thiazides in stone prevention, it is obviously of little importance.

Although some patients treated with thiazides have noted increased thirst and fluid intake, 24-hr urine volumes during treatment for the group as a whole do not differ significantly from control values [34]. A temporary increase in urinary inorganic phosphate excretion is characteristic of the initial period of thiazide administration, but control levels are achieved by the 9th day [48]. The urinary excretion of pyrophosphate, which has been shown to vary directly with orthophosphate excretion [50], also undergoes a temporary increase during the initial period of thiazide administration, but control

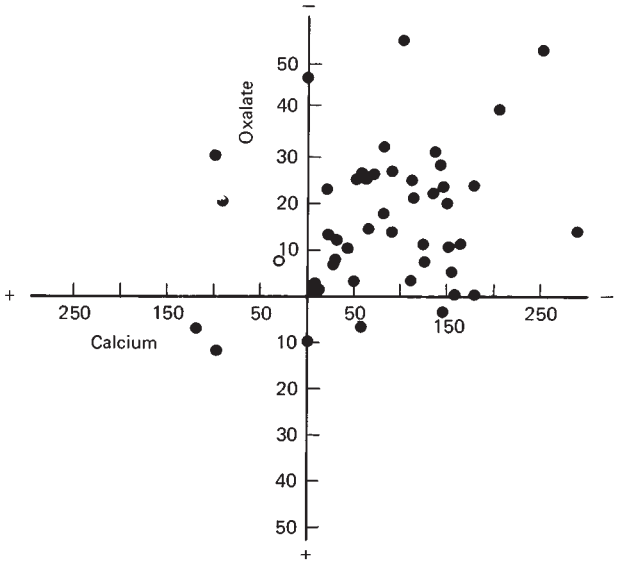

Fig. 3. *Urinary oxalate and calcium excretion in 51 patients having stone disease who had been taking thiazides for 12 to 96 months.* Each symbol indicates the difference between the observed values during treatment and the pretreatment values for the same patient.

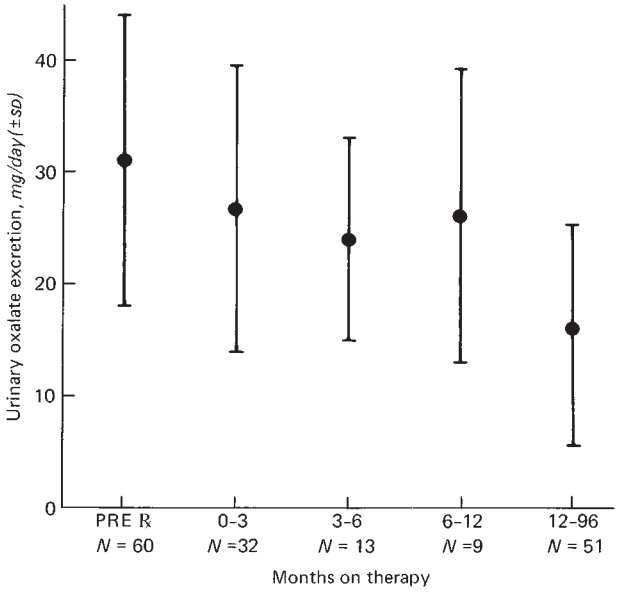

Fig. 4. *Urine oxalate excretion in patients with calcium stones, before and during thiazide therapy.* A significant reduction in urine oxalate excretion occurred after but not during the first year of treatment.

levels are achieved within one month [36]. Although thiazides alter the renal tubular handling of urate, there is no change in the absolute amount of uric acid excreted in the urine. Thus, there is no danger with thiazide of inducing formation of stones of uric acid or calcium oxalate [34, 48] (Coe, this issue). Thiazides have been shown also to decrease the urinary saturation with respect to brushite [36] and calcium oxlate [51] in the majority of patients.

Treatment regimen

All members of the thiazide group of diuretics and related drugs such as chlorothalidone and metolazone possess a hypocalciuric effect. There is no evidence to suggest that any one of this group of drugs is more effective than another in stone prevention, although there is a paucity of information on this subject. The drug employed by us in nearly all our patients has been hydrochlorothiazide, and we have usually employed only one brand (Hydrodiuril®, Merck, Sharp and Dohme) to avoid possible variations in potency and absorption.

The standard dose of hydrochlorothiazide employed by us is 50 mg, twice daily. In some of our early unreported work on this subject, it was found that this dose usually produced the maximum hypocalciuric response, whereas smaller doses often failed to achieve this effect. At the present time, one half the usual dose of hydrochlorothiazide (i.e., 50 mg daily) has been prescribed for 33 patients. Although this reduced dose appears to be adequate for some patients, we have seen a number of patients who continued to form stones on 50 mg per day but not on 100 mg per day. A major difficulty with regard to dosage is that there are no good data relating biochemical response to therapeutic efficacy. Stone formation appears to cease in some patients despite a minimal hypocalciuric response, and as previously indicated, other thiazide-induced changes in the biochemical composition of the urine such as reduced urine oxalate excretion may prove to be just as important or more important in this regard.

To minimize the incidence and severity of thiazide's side effects, which are frequently more severe during the first few weeks of treatment, we no longer initiate therapy with the maximum dose of hydrochlorothiazide but start with 25 mg of hydrochlorothiazide daily for one week and increase the daily dose by 25 mg at weekly intervals until the maintenance dose of 50 mg twice daily is achieved.

It has not been our practice to restrict dietary calcium, oxalate, or sodium chloride in thiazide-treated patients, but excessive intakes of these dietary constituents is corrected. Potassium supplements are not provided as a routine, but patients are provided with an information sheet which outlines the need for an increased intake of potassium-containing foods and emphasizes the importance of correcting potassium deficiency in the event of heart disease, digitalis therapy, or prior to the administration of a general anaesthetic. Potassium supplements are provided to patients with symptoms of potassium deficiency and to asymptomatic patients when serum potassium levels fall below 3.0 mEq/liter.

Before any therapeutic program is initiated, it is important to establish the radiologic status of the patient, with respect to the presence or absence of stones, as precisely as possible. If this is not done, it may be difficult to determine whether stone recurrences during treatment have resulted from progression of the stone problem or from stones which were previously present. In this regard, we have often found that the routine plain film of the abdomen or the i.v. pyelogram is frequently of such poor quality that the presence or absence of stone cannot be established with certainty, and for this reason, renal tomography without dye injection is frequently advisable. Patients who are treated with thiazides for stone prevention should be advised to return for follow-up studies within the first six months of treatment, and then, at annual intervals; in the occasional patient more frequent follow-up may be advisable. At the time of these visits, appropriate radiologic assessment, urinalysis, urine culture, and serum biochemistries are performed as a matter of routine. Serum potassium and uric acid concentrations should be done for obvious reasons, and the serum calcium should also be checked because of the possibility that thiazides may unmask hyperparathyroidism.

Efficacy of thiazides

In 1970, we reported the results of our first five years' experience with the use of thiazides in the prevention of calcium stone in 72 patients [34]. We divided our patients into two groups. Group I was composed of patients who had no stone *in situ* when treatment started, and group II comprised 34 patients with radiologic evidence of renal stones when therapy was begun. In the group I patients, stone episodes decreased from 0.57 per patient year to 0.03 per patient year during 72 patient years of treatment; only two patients had further stone formation (one stone each) during 64 patient years of treatment. In the group II patients, stone episodes decreased from 1.1 per patient year to 0.53 per patient year; most of

the stone episodes during treatment resulted from stones which were in the urinary tract when treatment started, and there was evidence of new stone formation in only four patients.

In 1973, we reported ten years' experience with this mode of treatment [43]. During the period 1962–1972, thiazide therapy was initiated in 197 patients. Of these, 19 were lost to follow-up, and thiazides were discontinued in 39, leaving 139 patients who remained on long-term treatment with adequate follow-up. Stone progression (i.e., formation of new stones or growth of stones present when treatment started) occurred in only eight patients with noninfected stones who had adhered strictly to the treatment regimen during approximately 700 patient years of treatment. At least six of these eight patients, however, were improved on thiazides and continued to take thiazides. In an additional seven patients, stone formation was arrested during thiazide therapy but was resumed after they had discontinued thiazides or decreased the dose.

At the time of writing, thiazide therapy has been initiated in 346 patients with renal calculi. Progression of stone disease has been identified in 16 patients taking a full dose of hydrochlorothiazide in whom compliance was considered to be excellent. Progression has also occurred in six additional patients for whom a full dose of the drug was prescribed, but in whom compliance was extremely poor. Of the 33 patients for whom only one half the usual dose of hydrochlorothiazide was prescribed, progression has occurred in four patients whose complicance was good and two patients whose compliance was poor.

The clinical histories of the 16 patients in whom there has been evidence of stone progression during thiazide treatment are depicted in Figure 5. A possible or probable explanation for stone progression was identified in three of these patients. Patient number 15 was a case of hypoparathyroidism with marked hypercalciuria due to treatment with pharmacologic doses of vitamin D and supplemental calcium; urinary calcium fell by less than 10% during thiazide therapy, and it is not surprising that stone formation continued under these circumstances. In case #1027, growth of one stone occurred in association with a *Staphylococcus albus* urinary tract infection; when the infection was eradicated, no further progression occurred during the subsequent three and one half years of thiazide therapy. In case #1162, stone progression occurred only at the time when the patient took his hydrochlorothiazide in one daily dose in-

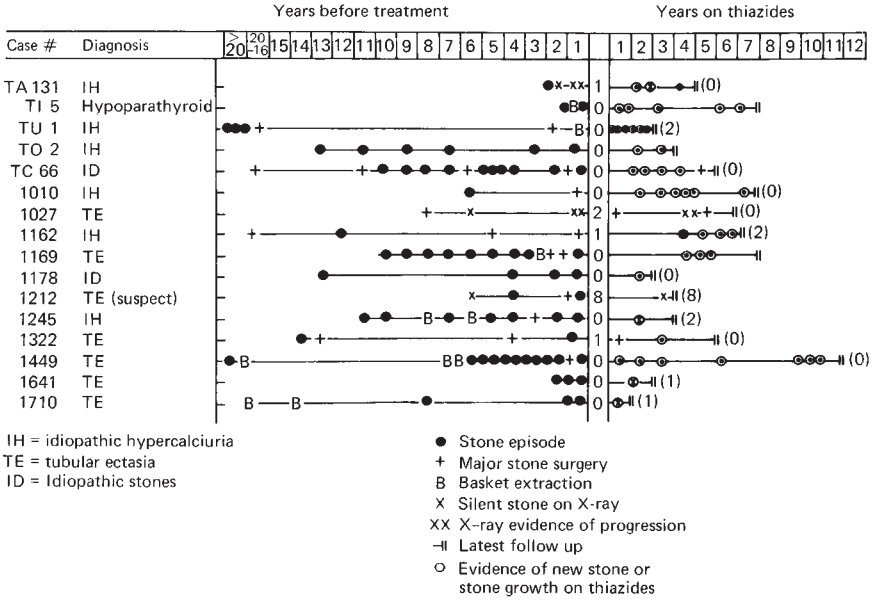

Fig. 5. *The stone histories of 16 patients in whom there has been stone progression during thiazide treatment.* These represent all the treatment-failures identified in patients taking a full dose of hydrochlorothiazide in whom compliance was good. The *figures in the column* separating the pretreatment and treatment data indicate the number of renal calcifications seen on X-ray when treatment started. The *bracketed figures* following the treatment data indicate the number of renal calcifications seen at the time of last follow-up. There is some uncertainty that stone progression has occurred in cases #1178 and #1245, because the X-rays taken when treatment began are not of adequate quality to rule out the presence of stones at that time. A probable explanation for stone progression was identified in cases T.I. 15, #1027, and #1162 (see text). During the treatment period, only the *circled* events were due to new stone formation.

Table 1. Urine composition before and during thiazide in treatment-failure patients

Patient no.	Sex	Diagnosis[a]	Urine volume *ml/24 hr*		Urine creatinine *mg/24 hr*		Urine calcium *mg/24 hr*		Urine magnesium *mg/24 hr*	
			Before	During	Before	During	Before	During	Before	During
TA 131	M	IH	1547	1730	2143	2360	440	205	156	143
TU 1	M	IH	3420	3110	2080	1790	713	443	87	54
TU 2	M	IH	1300	1400	1810	1830	346	309	88	124
TC 66	M	IS	1487	1484	1871	2076	311	150 (yr 1) 268 (yr 2) 306 (yr 3)	167	111
1010	M	IH	1430	1934	2080	2121	557	223	155	179
1169	M	TE	1865	2585	1617	1798	559	301	85	119
1212	M	IS	2125	1910	1770	1893	299	168	142	121
1322	M	TE	3020	2710	2470	2447	757	366	45	89
1449	M	TE	1115	1822	1915	1991	466	353	63	87
1641	M	TE	1300	1110	1935	1645	311	193	145	90
1710	M	TE	1107	1330	1833	1942	455	259	97	135
Mean ± SEM			1792 ± 232	1920 ± 191	1957 ± 69	1990 ± 74	474 ± 48	270 ± 28	112 ± 13	114 ± 10

[a] Abbreviations used are: IH, idiopathic hypercalciuria; IS, idiopathic stone-former; TE, tubular ectasia.
[b] ND means "not done."

stead of two divided doses as instructed; the hypocalciuric response to thiazide was considerably diminished during that period of time. Two additional patients, case #1178 and case #1245, are included for the sake of completeness, although we are uncertain that stone progression occurred during thiazide treatment in either of them, because the X-rays taken when treatment was initiated are of such poor quality that stones may well have been present at that time.

In the remaining 11 patients, we are confident that stone progression has occurred during thiazide therapy, and there is no obvious explanation for the treatment failures. The clinical and biochemical data in these patients are summarized in Table 1. The group consists entirely of male patients, and the incidence of tubular ectasia which was present in five of the 11, is considerably higher than in the treatment group as a whole; moreover, some of our earlier patients diagnosed as having idiopathic hypercalciuria or idiopathic calcium stones might also have had tubular ectasia, because it is only in recent years that we have made an intensive search for ectatic tubules in patients having stone disease. The mean 24-hr urine volume, creatinine, calcium, oxalate, phosphate, and uric acid for the group was significantly greater than for normal male subjects studied under similar conditions, but the 24-hr urinary excretion of magnesium, citrate, zinc, and sodium did not differ significantly from normal (Table 2). Of greater interest, perhaps, is a comparison of these 11 patients with 31 consecutive male hypercalciuric stone patients who have been treated successfully with thiazides (Table 2). The urinary excretion of calcium, phosphorous, and uric acid was greater in the treatment-failure group, but no other significant differences were observed. Thus, a greater degree of hypercalciuria is characteristic of the treatment-failure group than in hypercalciuric male patients successfully treated with thiazides, and in addition urine phosphorous and uric acid excretions were significantly greater than normal, which was not the case in the successfully treated group of patients. The increased urinary excretion of uric acid in the treatment failure group is of particular interest in view of the report of Coe and Kavalach that stone formation ceased in all but two of 27 patients with idiopathic hypercalciuria and associated hyperuricosuria during combined thiazide and allopurinol treatment [52]. In their report, hyperuricosuria was defined as a 24-hr urinary uric acid excretion in excess of 800 mg in male patients on unrestricted diets; 24-hr urinary uric acid excretion exceeded 800 mg in 9 of the 11 patients in our treatment-failure group and in 13 of the 31 patients sucessfully treated with thiazides. The upper limit of normal for urinary uric acid excretion in our normal male subjects studied on unrestricted diet on the ambulant basis, however, is 1065 mg/24 hr, and on this basis most of these patients would be more properly classified as having uric acid excretion in the high normal range rather than as true hyperuricosurics. These remarks emphasize the potential importance of hyperuricosuria in the pathogenesis of calcium oxalate stones (Coe, this issue).

The biochemical response to thiazide administration in the 11 patients who continued to form stones during thiazide treatment is seen in Table 1. The thiazide-induced changes in urinary calcium, oxalate, and citrate excretion were qualitatively and quantitatively similar to those observed in the treatment group as a whole.

Table 1 (*continued*). Urine composition before and during thiazide in treatment-failure patients

	Urine oxalate[b] *mg/24 hr*		Urine phosphorus[b] *mg/24 hr*		Urine citrate *mg/24 hr*		Urine uric acid[b] *mg/24 hr*		Urine zinc[b] *μg/24 hr*		Urine sodium[b] *mEq/24 hr*	
Patient	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During
TA 131	47	ND[b]	ND	ND	265	301	946	1056	ND	ND	ND	ND
TU 1	27	ND	1090	ND	248	132	951	ND	ND	ND	ND	ND
TU 2	36	ND	1134	ND	520	381	890	927	ND	ND	ND	ND
TC 66	48	36	ND	785	226	151	591	801	ND	ND	ND	ND
1010	ND	33	1170	1138	699	724	834	847	ND	1310	ND	195
1169	55	12	1155	1200	375	192	1042	985	450	1079	122	199
1212	26	27	1285	1099	427	273	1019	644	1072	1292	229	328
1322	ND	ND	1457	1249	590	319	1648	1191	1579	1900	256	220
1449	33	ND	924	823	240	228	765	805	ND	882	ND	248
1641	34	16	1022	877	591	359	816	709	430	463	177	258
1710	20	22	923	1186	680	497	848	973	393	771	151	202
Mean	36 ± 4	24 ± 4	1124 ± 64	1045 ± 66	442 ± 55	323 ± 51	941 ± 80	894 ± 52	785 ± 235	1099 ± 175	187 ± 25	263 ± 31

There is a commonly held misconception that for patients having calcium stones, the use of thiazides should be restricted to patients with hypercalciuria. For some years now, we have stated that this mode of therapy is equally effective in normocalciuric patients. We have not previously reported, however, the data on which this opinion is based. The clinical histories of 28 normocalciuric patients with calcium stones before and during thiazide therapy are depicted in Figure 6. There was no evidence of new stone formation in any of these patients during 103 patient years of observation. A total of 10 stone episodes occurred in five patients after thiazides were begun, but in every instance these episodes were due to stones which were present when therapy was instituted. Another most interesting feature evident from this study, one that we have not previously commented on, is that there was, during treatment, a reduction in the number of renal calcifications evident on X-ray in eight patients who had not experienced

Table 2. Biochemical composition of urine[a]

	Normal male subjects		Stone patients with progression on thiazides[b]		Stone patients with no progression on thiazides (male, hypercalciuric)
	Mean ± SEM	*P*	Mean ± SEM	*P*	Mean ± SEM
Volume, *ml/24 hr*	1269 ± 103	<0.025	1792 ± 232	NS	1761 ± 120
N	31		11		31
Creatinine, *mg/24 hr*	1796 ± 58	<0.05	1957 ± 69	NS	1882 ± 52
N	30		11		31
Calcium, *mg/24 hr*	221 ± 16	<0.0005	474 ± 48	<0.05	396 ± 13
N	29		11		31
Magnesium, *mg/24 hr*	93 ± 7	NS	112 ± 13	NS	111 ± 7
N	16		11		31
Oxalate, *mg/24 hr*	18 ± 3	<0.0005	36 ± 4	NS	31 ± 4
N	14		9		29
Phosphorus, *mg/24 hr*	932 ± 41	<0.01	1124 ± 64	<0.025	1007 ± 43
N	21		9		30
Citrate, *mg/24 hr*	521 ± 52	NS	442 ± 55	NS	487 ± 49
N	16		11		29
Uric acid, *mg/24 hr*	761 ± 39	<0.05	941 ± 80	<0.025	780 ± 32
N	16		11		30
Zinc, *μg/24 hr*	587 ± 30	NS	785 ± 235	NS	685 ± 50
N	29		5		18
Sodium, *mEq/24 hr*	174 ± 13	NS	187 ± 25	NS	190 ± 7
N	27		5		27

[a] Most 24-hr urine specimens were collected on an out-patient basis on unrestricted diets. Patients values are pretreatment values.
[b] The urine composition of the individual patients in this group is described in Table 1.

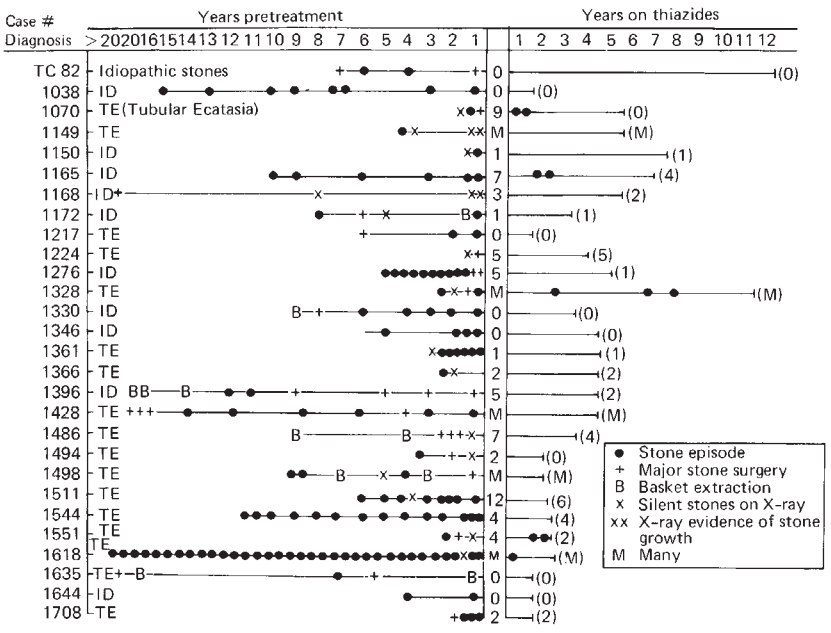

Fig. 6. *Clinical histories of 28 normocalciuric stone patients before and during thiazide treatment, in which the out-patient 24-hr urine calcium values measured on unrestricted diets did not exceed 300 mg in males or 250 mg in females.* The *figures in the column* separating the pretreatment and treatment data indicate the number of renal calcifications seen on x-ray when treatment started. The *bracketed figures* following the treatment data indicate the number of renal calcifications seen at the time of last follow-up. There was no evidence of stone progression during treatment in any of these patients; the episodes which occurred during treatment were all due to stones which had been present when treatment started. In cases #1070, 1165, 1276, 1396, 1486, 1494, and 1511, a significant reduction in the number of renal calcification occurred during treatment despite the fact that the patients were unaware of having passed stones to account for this. Abbreviations of diagnoses are the same as in Figure 5.

renal colic and who were unaware of having passed gravel or stones during the treatment period.

It will be noted from Figure 6 that in 17 of the 28 normocalciuric patients successfully treated with thiazides some degree of tubular ectasia (medullary sponge kidney) was evident in the i.v. pyelogram. Stone progression has also ceased in 30 hypercalciuric patients with tubular ectasia who were treated with thiazides.

We have previously referred to the fact that the failure to observe the usual degree of hypocalciuric response following the initiation of thiazide therapy does not necessarily signify that thiazides will be ineffective in stone prevention. We are following a small group of 10 patients who fall into this category who have shown no evidence of stone progression during 42 patient years of treatment.

Our favourable experience with the use of thiazides in stone prevention has been confirmed by Coe and Kavalach who reported new stone formation in only two of 37 patients with idiopathic hypercalciuria during 740.5 months of treatment with trichlormethiazide (4 mg/day) [52]. Rose and Harrison report that they have a very strong clinical impression that renal stone formation has not progressed in patients with idiopathic hypercalciuria in whom the control of urinary calcium has been achieved and maintained [53].

Side effects

The incidence of side effects in thiazide-treated patients is in the order of 30 to 35% [34]. These tend to be most severe during the initial phase of thiazide therapy and frequently disappear with the passage of time. In an earlier report, we indicated that side effects necessitated discontinuation of thiazide therapy in approximately 10% of our patients [43]. As a result of two changes in our treatment regimen, however, it has been necessary to discontinue thiazide because of side effects in only 16 or our last 225 patients. The first of these changes is the practice of initiating thiazide therapy with a small dose and increasing dosage gradually until the maintenance dose is achieved. The second measure is to reduce the dose of hydrochlorothiazide to 25 mg twice daily if side effects are a problem; this usually results in disappearance or marked reduction in the severity of

symptoms, and in most cases stone growth has not resumed as a result of the dose reduction.

Weakness, fatigue, loss of energy and lassitude, frequently accompanied by mental irritability and an increased need for sleep are by far the most common thiazide side effects and are most often those which necessitate the discontinuation of this form of treatment. These symptoms are sometimes related to potassium deficiency and may be relieved by the provision of potassium supplements, but in other cases they are not alleviated by the correction of hypokalemia. Other side effects which have necessitated termination of treatment include skin rashes, severe headaches, dizziness, mental depression, loss of libido, and pancreatitis. Gout has developed in a few of our patients, but in this situation it has been our practice to add allopurinol to the therapeutic regimen rather than discontinue thiazides. The development of diabetes during thiazide therapy does not necessitate discontinuation of therapy, but thiazide-induced hypokalemia should be corrected by the provision of potassium supplements.

A gradual decline in serum magnesium levels has occurred in a few patients during chronic thiazide therapy. The lowest level which we have observed is a total serum magnesium concentration of 1.04 mg/100 ml (normal range, 1.60–2.45 mg/100 ml) with a corresponding decrease in the serum ultrafiltrable magnesium concentration to 0.56 mg/100 ml (normal range, 1.05–1.55 mg/100 ml). So far, we have not observed any clinical disturbances attributable to this biochemical abnormality. Nonetheless, this finding is obviously a matter of concern; now it seems advisable to measure serum magnesium at intervals during long-term thiazide therapy, and the provision of magnesium supplements may sometimes be necessary.

There is also a possibility that long-term thiazide treatment may induce zinc deficiency in a few patients as a result of the sustained increase in urine zinc excretion associated with this form of therapy. We have found serum zinc concentrations below the normal range (85 to 135 μg/100 ml) in eight of our patients, the lowest value recorded to date being 62 μg/100 ml. In this patient, the serum zinc concentration decreased gradually but remained within the normal range for the first five years of treatment. No untoward effects of the low serum zinc concentrations have been detected in any of these patients.

We have never encountered metastatic calcification during chronic thiazide therapy, and we are unaware of any reports of this complication in the medical literature. The fact that the positive calcium balance following the institution of thiazide therapy is only a temporary phenomenon suggests that there need be no fear of this theoretical danger. There is no evidence that metastatic calcification is responsible for the induction of pancreatitis.

Selection of patients

The decision to institute thiazide therapy in a patient with recurrent calcium stones is not always an easy one. The first consideration is whether the severity of the stone problem warrants the institution of a program of drug administration which will likely be lifelong, and the second is the choice between available agents of known efficacy. At the present time, there does not appear to be an overwhelming consensus among stone experts with respect to either question. We are of the opinion that the association of hypertension and recurrent calcium stones nearly always warrants treatment with thiazide if diseases such as primary hyperparathyroidism and renal tubular acidosis have been excluded. In the normotensive patient, the decision to embark on an effective prophylactic program is based on several considerations, including *1)* the frequency of stone recurrence, *2)* the history of major stone surgery, *3)* the presence or absence of renal calcifications, and *4)* the patient's reaction to the possibility of further stone episodes. If on the basis of these considerations, an effective prophylactic regimen is warranted, the choice of an agent is at the present time largely a matter of personal preference. It is our current practice to begin treatment with a thiazide and to switch to orthophosphates if the patient is unable to tolerate the drug. As has been previously pointed out, we do not believe that the presence or absence of hypercalciuria should have a bearing on this decision, since thiazides are effective in both normocalciuric and hypercalciuric patients. Moreover, we do not believe that it is necessary to distinguish between absorptive and renal hypercalciuria, because thiazides are effective in both situations. The association of hyperuricosuria with hypercalciuria does not in our opinion warrant combined allopurinol-thiazide therapy at the outset, since approximately 40% of our male hypercalciuric patients successfully treated with thiazide treatment fall within this category; our findings indicate, however, that most thiazide treatment failures may be found within this group of patients, and in such cases the addition of allopurinol may prove beneficial at some future time. Gout and diabetes are not absolute contraindications to the use of thiazides for stone pre-

vention. A number of our patients who have developed gout prior to or during thiazide therapy are being successfully treated with the combination of allopurinol and a thiazide. Furthermore, the administration of a thiazide is not likely to aggravate the severity of diabetes if thiazide-induced hypokalemia is corrected. In the patient with suspected primary hyperparathyroidism, there is a preference for the use of thiazides which might unmask the disorder, whereas orthophosphates would tend to mask the disorder; in other patients the low cost and convenience of thiazides must be balanced against the probability of fewer immediate side effects with phosphates.

Summary

On the basis of almost 15 years of experience with thiazide treatment in 346 patients with calcium stones, we believe that the following conclusions are justified: *1)* Stone progression ceases in at least 90% of patients who take hydrochlorothiazide (50 mg, twice daily) on a regular basis. *2)* A reduced dose of hydrochlorothiazide, i.e., 25 mg twice daily, appears to be effective in a significant proportion of patients. *3)* Thiazides are effective in normocalciuric as well as hypercalciuric patients and in most patients with tubular ectasia (medullary sponge kidney). *4)* Side effects necessitate discontinuation of thiazide treatment in approximately 7% of patients. The incidence and severity of side effects is reduced by initiating treatment with a small dose and by increasing the dose progressively until the full maintenance dose is achieved. A trial with a reduced dose is warranted in patients who are unable to tolerate the regular maintenance dose. *5)* The therapeutic efficacy of thiazides in stone prevention cannot be accurately predicted by the degree of hypocalciuric response. Stone prevention may cease despite a minimal hypocalciuric response, whereas stone progression may occur when an adequate hypocalciuric response has taken place. *6)* In addition to the hypocalciuric action, thiazides reduce urine oxalate excretion and increase urine zinc and (probably) magnesium; these effects probably contribute to the efficacy of this agent in stone prevention.

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References

1. LAMBERG BA, KUHLBACK B: Effect of chlorothiazide and hydrochlorothiazide on the excretion of calcium in urine. *Scand J Clin Lab Invest* 2:351–357, 1959
2. LICHTWITZ A, PARLIER R, DESEZE S, HIOCO D, MIRAVET L: L'effect hypocalciurique des sulfamides diuretiques. *Sem Hop Paris* 37:2350–2362, 1961
3. SEITZ H, JAWORSKI ZF: Effect of hydrochlorothiazide on serum and urinary calcium and urinary citrate. *Can Med Assoc* J 90:414–420, 1964
4. DUARTE CG, BLAND JH: Calcium phosphorus and uric acid clearances after intravenous administration of chlorothiazide. *Metabolism* 14:211–219, 1965
5. YENDT ER, GAGNE RJA, COHANIM M: The effects of thiazides in idiopathic hypercalciuria. *Trans Am Clin Climatol Assoc* 77:96–110, 1965
6. EDWARDS BR, BAER PG, SUTTON RAL, DIRKS JH: Micropuncture study of diuretic effects on sodium and calcium reabsorption in the dog nephron. *J Clin Invest* 52:2418–2427, 1973
7. COSTANZO LS, WEINER IM: On the hypocalciuric action of chlorothiazide *J Clin Invest* 54:628–636, 1974
8. SUKI WH, HULL AR, RECTOR FC JR, SELDIN DW: Mechanism of the effects of thiazide diuretics on calcium and uric acid (abstr.). *J Clin Invest* 46:1121, 1967
9. BRICKMAN AS, MASSRY SG, COBURN JW: Changes in serum and urinary calcium during treatment with hydrochlorothiazide: Studies on mechanisms. *J Clin Invest* 51:945–954, 1972
10. PARFITT AM: The interactions of thiazide diuretics with parathyroid hormone and vitamin D. Studies in patients with hypoparathyroidism. *J Clin Invest* 51:1879–1888, 1972
11. MIDDLER S, PAK CYC, MURAD F, BARTTER FC: Thiazide diuretics and calcium metabolism. *Metabolism* 22:139–146, 1973
12. SUKI WN, EKNOYAN G, MARTINEZ-MALDONADO M: Control of idiopathic hypercalciuria with diuretics and salt restriction, in *Current Controversies in Urologic Management*, edited by SCOTT R JR, Saunders, Philadelphia, 1972, pp. 345–350
13. JORGENSEN FS: The effects of bendroflumethiazide on the renal excretion of calcium and sodium in normal, parathyroidectomized and thyroparathyroidectomized rats. *Acta Pharmacol Toxicol* 30:296–307, 1971
14. BRICKMAN AS, COBURN JW, KOPPEL MH, PEACOCK M, MASSRY SG: The effect of hydrochlorothiazide administration on serum and urinary calcium in normal, hypoparathyroid and hyperparathyroid subjects: Studies on mechanisms. *Isr J Med Sci* 7:518–519, 1971
15. COE FL, CANTERBURY JM, FIRPO JJ: Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. *J Clin Invest* 52:134–142, 1973
16. STOTE RM, SMITH LH, WILSON DM, DUBE WJ, GOLDSMITH RS, ARNAUD CD: Hydrochlorothiazide effects on

serum calcium and immunoreactive parathyroid hormone concentrations. *Ann Intern Med* 77:587–591, 1972
17. MOORE PF: The effects of diazoxide and benzothiazide diuretics upon phosphodiesterase. *Ann NY Acad Sci* 150:256–260, 1968
18. NASSIM JR, HIGGINS BA: Control of idiopathic hypercalciuria. *Br Med J* 1:675–681, 1965
19. HARRISON AR, ROSE, GA: The effect of bendrofluazide on urinary and faecal calcium and phosphorous. *Clin Sci* 34; 343–350, 1968
20. HARRISON JE, HITCHMAN JW, FINLAY JM, FRASER D, YENDT ER, BAYLEY TA, MCNEIL KG: Effect of treatment on calcium kinetics in metabolic bone disease. *Metabolism* 20:1107–1118, 1971
21. EHRIG U, HARRISON JE, WILSON DR: Effect of long term thiazide therapy on intestinal calcium absorption in patients with recurrent renal calculi. *Metabolism* 23:139–145, 1974
22. HARRIS WH, HEANEY RP: Skeletal renewal and bone disease. *N Engl J Med* 280:253–259, 1969
23. LAFFERTY FW, SPENCER GE, PEARSON OH: Effects of androgens, estrogens, and a high calcium intakes on bone formation and resorption in osteoporosis. *Am J Med* 36:514–528, 1964
24. SCHWARTZ E, PANARIELLO VA, SAELI J: Radioactive calcium kinetics during high calcium intake in osteoporosis. *J Clin Invest* 44:1547–1560, 1965
25. YENDT ER: Renal calculi. *Can Med Assoc J* 102:479–489, 1970
26. JORGENSEN FS, NIELSEN SP: Effects of long term administration of bendroflumethiazide on bone metabolism in the rat. *Acta Pharmacol Toxicol* 31:521–28, 1972
27. JORGENSEN FS, TRANSBOL I, BINDER C: The effect of bendroflumethiazide on total, ultrafiltrable and ionized calcium in serum in normocalcemic renal stone formers and in hyperparathyroidism. *Acta Med Scand* 194:323–326, 1973
28. DUARTE CG, WINNACKER JL, BECKER KL, PACE A: Thiazide-induced hypercalcemia. *N Engl J Med* 284:828–830, 1971
29. PARFITT AM: Chlorothiazide induced hypercalcemia in juvenile osteoporosis and hyperparathyroidism. *N Engl J Med* 281:55–59, 1969
30. PICKLEMAN JR, STRAUSS FH II, FORLAND M, PALOYAN E: Thiazide-induced parathyroid stimulation. *Metabolism* 18:867–873, 1969
31. HAHN TJ, AVIOLI LV: Effects of parenteral thiazide administration on parathyroid function (abstr.). *Clin Res* 18:31, 1970
32. MUKAI T, HOWARD JE: Some observations on the calcification of rachitic rat cartilage by urine. *Johns Hopkins Med J* 112:279–290, 1963
33. DESMARS JG, TAWASHI R: Dissolution and growth of calcium oxalate monohydrate: I. Effect of magnesium and pH. *Biochim Biophys Acta* 313:256–267, 1973
34. YENDT ER, GUAY FG, GARCIA DA: The use of thiazides in the prevention of renal calculi. *Can Med Assoc J* 102:614–620, 1970
35. JORGENSEN FS, TRANSBOL I: The effects of bendroflumethiazide on the renal handling of calcium, magnesium and phosphate in normocalcaemic renal stone formers and in hyperparathyroidism. *Acta Med Scand* 194:327–334, 1973
36. PAK CYC: Hydrochlorothiazide therapy in nephrolithiasis: Effect on the urinary activity product and formation product of brushite. *Clin Pharmacol Ther* 14:209–217, 1973
37. COHANIM M, YENDT ER: Zinc excretion in patients with renal calculi (abstr.). *Clin Res* 19:807, 1971
38. PAK CYC, RUSKIN B, DILLER E: Enhancement of renal excretion of zinc by hydrochlorothiazide. *Clin Chim Acta* 39:511–517, 1972
39. COHANIM M, YENDT ER: The effects of thiazides on serum and urinary zinc. *Johns Hopkins Med J* 136:137–141, 1975
40. BIRD ED, THOMAS WC JR: Effect of various metals on mineralization in vitro. *Proc Soc Exp Biol Med* 112:640–643, 1963
41. EUSEBIO E, ELLIOT JS: Effect of trace metals on crystallization of calcium oxalate. *Invest Urol* 4:431–453, 1967
42. GLAZENBURG J: The effect of hydrochlorothiazide on the renal excretion of oxalic acid and on the formation of oxalate stones in the urinary tract. *Arch Chir Neerl* 23:217–223, 1971
43. YENDT ER, COHANIM M: Ten years' experience with the use of thiazides in the prevention of kidney stones. *Trans Am Clin Climatol Assoc* 85:65–75, 1973
44. MARSHALL RW, BARRY H: Urine saturation and the formation of calcium-containing renal calculi, in *Urinary Calculi: International Symposium on Renal Stone Research,* Madrid 1972, Karger, Basel, 1973, pp. 164–169
45. COHANIM M, YENDT ER: Reduction of urine oxalate excretion during chronic thiazide therapy (abstr.). *Clin Sci* 24:685A, 1976
46. MARSHALL RW, COCHRAN M, HODGKINSON A: Relationship between calcium and oxalic acid intake in the diet and their excretion in the urine of normal and renal-stone-forming subjects. *Clin Sci* 43:91–99, 1972
47. 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, HENCH LL, SMITH LH, Washington D.C. National Academy of Sciences, 1972, pp. 79–95
48. GARCIA DA, YENDT ER: The effects of probenecid and thiazides and their combination on the urinary excretion of electrolytes and on acid-base equilibrium. *Can Med Assoc J* 103:473–483, 1970
49. EVANS BM, MACINTYRE I, MACPHERSON CR, MILNE MD: Alkalosis in sodium and potassium depletion: With especial reference to organic acid secretion. *Clin Sci* 16:53–65, 1957
50. RUSSELL RGG, HODGKINSON A: Urinary excretion of pyrophosphate by normal subjects and patients with renal calculus. *Clin Sci* 31:51–62, 1966
51. WOELFEL A, KAPLAN RA, PAK CYC: Effect of hydrochlorothiazide therapy on the crystallization of calcium oxalate in urine. *Metabolism* 26:201–205, 1977
52. COE FL, KAVALACH AG: Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. *N Engl J Med* 291:1344–1350, 1974
53. ROSE GA, HARRISON AR: The incidence, investigation and treatment of idiopathic hypercalciuria. *Br J Urol* 46:261–274, 1974