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# Metabolic factors in the causation of urinary tract stones in patients with enterocystoplasties

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**Abstract** Stones are a common complication of the storage of urine in intestinal reservoirs. Previous studies have identified predisposing physical characteristics in the reservoirs. Biochemical and dietary factors have been little investigated. Fifteen patients (6 males and 9 females) who had undergone various enterocystoplasty operations and who had subsequently formed either upper or lower urinary tract stones were investigated. The programme has been previously described and included stone, blood and urine analysis and dietary review. Comparison was made with 15 age- and sex-matched idiopathic stone formers with normal bladders. Stones were infective in origin in 86% of cases, and 14% were sterile. Metabolic screen showed that 80% of enterocystoplasty patients had risk factors for at least three different types of stone. All patients had raised pH (mean 6.93) and hypocitraturia. Five had a raised alkaline phosphatase. Raised serum and urinary calcium, hyperoxaluria and hyperuricosuria were found in 33% of patients. Five had a 24-h urine volume below 1.6 l/day. All patients had a high risk index ($P_{SF}$) for phosphatic stones and 12 also for calcium oxalate stones. Compared to age-and sex-matched idiopathic stone-formers, the urine had a higher pH, sodium and protein excretion and a lower calcium and citrate excretion. Although the patients were already selected as stone-formers, the data show that metabolic and dietary factors are present. They may be as important in the aetiology of the stones, as the already recognised factors of infection and poor reservoir drainage. Investigation should include such factors, the presence of which may be taken into account in a prophylactic regime.

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## Introduction

Stone-formation is a common problem in patients whose urine is stored in an intestinal reservoir. However, it is curious that the incidence is higher in some series than in others and that patients with similar reservoirs appear to have different risks of stone-formation. In most, the incidence is between 12 and 25% of all patients [1–5]. In one report on children with enterocystoplasties, 52.5% had formed a stone at a mean of 4 years follow-up [6]. In many reports the length of follow-up is not given. It would seem that, even with long follow-up, some patients never form stones and some form them repeatedly but at irregular intervals. We have examples of a patient growing stones twice in the first year after reservoir formation and not again in the next 10; another patient went 10 years before producing a single stone.

Work on the aetiology of stones in intestinal reservoirs to date has concentrated on structural characteristics, infection and mucus. It has been generally assumed that urinary infection is the main pre-disposing factor, but there are many other potential aggravating factors that may increase the risk of stone-formation in these patients including metabolism, nutrition, life-style and occupation. There has not been a thorough biochemical investigation to identify the underlying aetiological factors involved in the stone-forming process. In this paper, we attempt to redress this omission.

## Materials and methods

Fifteen patients (6 males and 9 females, aged 15–50), who had undergone various enterocystoplasty operations and who had subsequently formed urinary stones (ESF), were screened at our Stone Clinic for the

potential metabolic and nutritional factors that might have led to their stone-formation. Three had spina bifida. Eleven had had multiple recurrences of stones (between two and five episodes) and four had so far only had a single stone episode. Nine of the patients formed their first stone in the upper urinary tract (ESF-UUT) and six formed their first stone in their pouch or bladder (ESF-LUT). The patients were compared with 15 age- and sex-matched idiopathic recurrent calcium stone-formers (IRSF) also studied at the Stone Clinic. These were included in order to preclude the possibility that the ESF would have formed their stones even if they had not had an enterocystoplasty. All studies were carried out on the patients' free, home diets. The clinical details are shown in Table 1. Only two patients had any possible predisposing factor for stones; one had acid indigestion, self-treated with $CaCO_3$-containing antacids (now stopped) and one had possible hyperparathyroidism secondary to a degree of renal impairment ($C_{Cr} = 48$ ml/min).

The protocol, for which local Ethics Committee approval was obtained, has previously been described as our standard STONESCREEN procedure for determining potential metabolic and nutritional risk factors that might increase the likelihood of the patients forming stones [7]. This consists of:

1. A metabolic screen involving the analysis of a blood and spot urine sample (including a mid-stream urine sample for bacteriological examination) taken at the Out-Patient Clinic.
2. A 7-day Diet Diary completed by the patient on his/her free, home diet.
3. Two 24-h urine samples collected on the final 2 days of the Diet Diary.
4. A quantitative stone analysis (wherever possible).
5. A standard patient history, including details of the surgical and medical history, medication history, demographic profile, occupation, life-style, family history of stone disease and other medical problems and a complete history of each individual patient's stone episodes.

The data were entered on to our Stone Database, which automatically calculates various indices of metabolism, renal function and tubular reabsorption and calculates the biochemical risk ($P_{SF}$) of forming different types of urinary calculi [8]. The program also suggests the form of prophylaxis most likely to minimise the risk of stone recurrence in a given patient. The values for $P_{SF}$ are derived from a set of algorithms that calculate the biochemical risk of forming stones from the seven urinary risk factors—24-h urinary volume, pH, and the 24-h urinary excretions of calcium, magnesium, oxalate, citrate and uric acid. The risk is calculated on a probability scale from 0 to 1. Non-stone formers generally have values which are $< 0.5$ but untreated stone patients, particularly recurrent stone-formers, have values $> 0.5$. The greater the value of $P_{SF}$ in a given patient, the higher is his/her stone episode rate [8]. Thus, $P_{SF}$ is a useful index of the risk of stone-formation in a given patient.

Statistical analysis was carried out using the Wilcoxon sum of ranks test for comparing ESF-UUT with ESF-LUT, and the Wilcoxon paired sum of ranks test for comparing the ESF with their age-and sex-matched IRSF.

## Results

All enterocystoplasty patients gave a history of recurring urinary tract infection and 86% of those from whom a stone had been recovered for analysis formed infection stones consisting of various mixtures of calcium phosphate (CaP) and struvite (i.e. magnesium ammonium phosphate [MAP]). Most of the stones contained more CaP than MAP and this is to be expected, as CaP is the first salt to crystallise out in urine as the pH is increased

**Table 1** Clinical details of enterocystoplasty patients with stones included in the study

| Case | Gender | Segment | Length (cm) | Conduit | Drainage | Other predisposing disorders | Time to stone (years) |
|---|---|---|---|---|---|---|---|
| 1 | Female | Sigmoid colon | 20 | No | Urethra CIC | Acid indigestion ($CaCO_3$-antacids) | 19 |
| 2 | Female | R colon | 20 | No | Mitrofanoff/Kock | None | 5 |
| 3 | Female | Ileum/caecum | 10/10 | No | Mitrofanoff | ? Secondary Hyperparathyroid | 9 |
| 4 | Female | Ileum | 12 | No | Mitrofanoff | None | 2 |
| 5 | Female | R colon | 20 | No | Urethra voids | None | 10 |
| 6 | Female | R colon | 20 | No | Mitrofanoff | None | 2 |
| 7 | Female | Ileum | 15 | No | Urethra voids | None | 16 |
| 8 | Female | R colon | 20 | No | Mitrofanoff | None | 5 |
| 9 | Female | R colon | 20 | No | Mitrofanoff | None | 6 |
| 10 | Male | Ileum/caecum | 7/19 | No | Mitrofanoff | None | 12 |
| 11 | Male | Ileum | 15 | No | Urethra voids | None | 8 |
| 12 | Male | Ileum | 15 | No | Urethra voids | None | 3 |
| 13 | Male | Sigmoid colon | 20 | No | Mitrofanoff | None | 7 |
| 14 | Male | Sigmoid colon | 31 | No | Mitrofanoff | None | 9 |
| 15 | Male | Sigmoid colon | N/A | No | Urethra CIC | None | 12 |

*N/A* information not available

above a value of 6.2; MAP only crystallises out at pH values above 7.

The remaining 14% of the enterocystoplasty patients formed sterile stones consisting of a mixture of CaP and calcium oxalate (CaOx). Uric acid was not found in any of the stones analysed. These patients tended to pass urines of pH >6 thereby precluding the risk of precipitation of uric acid.

The metabolic screen showed that four ESF patients had a raised plasma calcium (>2.60 mmol/l) and two of these remained high after correction for serum albumin; one of these had suspected secondary hyperparathyroidism. Five patients had an increased alkaline phosphatase level (>104 U/l). Six patients had a minor degree of renal impairment (calculated creatinine clearance <80 ml/min) and two were hyperuricaemic (>412 μmol/l), one of whom had a low GFR.

A summary of the metabolic data from the various groups is shown in Table 2. This shows that there were no significant differences between those ESF who had their first stone removed from the upper urinary tract and those who had their first stone removed from the lower urinary tract. The ESF as a whole tended to have slightly poorer renal function, with significantly higher plasma urea ($P<0.01$) and creatinine concentrations ($P<0.05$) and lower creatinine clearances ($P<0.05$) than the IRSF. The ESF also had significantly lower bicarbonate concentrations ($P<0.01$) and significantly higher alkaline phosphatase values ($P<0.05$) than the IRSF, suggesting a tendency to very mild acidosis but only four patients had a real reduction in serum bicarbonate (<22 mmol/l).

The 24-h urine studies showed that all ESF had a raised urinary pH (>6.3; mean value 6.93) consistent with their predisposition to urinary tract infection. Five patients had low urinary volumes (<1.6 l/day), and three of these had volumes <1.4 l/day, generally as a result of an inadequate fluid intake. Five patients were hypercalciuric (>6 mmol/day), all of whom had a renal leak of calcium (notional $Tm_{Ca}/GFR<2$ mmol/l GF). Five patients had mild hyperoxaluria (>0.45 mmol/day), including one with enteric hyperoxaluria (0.86 mmol/day). All the patients studied were hypocitraturic (<2 mmol/day) and the majority (67%) were markedly so (<0.7 mmol/day). Five patients were hyperuricosuric (>4 mmol/day) as a result of a high purine intake and five had low magnesium excretions (<3.5 mmol/day), two of which were very low (<2 mmol/day). All the patients had some degree of proteinuria (>12 mg/mmol creatinine) ranging from 17 to 157 mg/mmol creatinine.

A summary of the 24-h urine data from the various groups is shown in Table 3. This shows that the average urine volume of the ESF as a whole was significantly higher than that of the IRSF ($P<0.01$), reflecting the tendency to higher fluid intakes among the ESF (Table 4), although this difference was not significant. The ESF also had significantly higher urinary pH values ($P<0.01$), sodium excretions ($P<0.01$) and protein levels ($P<0.01$) than the IRSF. Conversely, the ESF had slightly lower calcium excretions ($P<0.05$) and much lower citrate excretions ($P<0.001$) than the IRSF.

As a consequence of the urinary abnormalities described above, all patients with an enterocystoplasty

**Table 2** Summary of the metabolic data in enterocystoplasty stone-formers (ESF) and in age- and sex-matched idiopathic recurrent calcium stone-formers

| Variable | ESF (all) (mean ± SEM) ($n=15$) | ESF (UUT stones) (mean ± SEM) ($n=9$) | ESF (LUT stones) (mean ± SEM) ($n=6$) | IRSF (UUT stones) (mean ± SEM) ($n=15$) | Normal range |
|---|---|---|---|---|---|
| Plasma | | | | | |
| Urea (mmol/l) | 6.3 ± 0.7** | 6.7 ± 0.9 | 5.7 ± 1.2 | 4.6 ± 0.4 | 2.8–7.6 |
| Creatinine (μmol/l) | 90.4 ± 8.3* | 89.4 ± 9.3 | 91.8 ± 10.8 | 79.4 ± 3.9 | 70–115 |
| Bicarbonate (mmol/l) | 25.6 ± 0.8** | 26.0 ± 1.2 | 25.1 ± 1.0 | 29.0 ± 0.6 | 20–30 |
| Sodium (mmol/l) | 143 ± 0.7 | 143 ± 1.2 | 143 ± 0.5 | 141 ± 0.5 | 136–145 |
| Potassium (mmol/l) | 4.4 ± 0.08 | 4.5 ± 0.11 | 4.4 ± 0.13 | 4.4 ± 0.08 | 3.5–5.1 |
| Albumin (g/l) | 47.8 ± 0.9 | 49.3 ± 1.0 | 45.8 ± 1.5 | 46.7 ± 0.7 | 35–50 |
| Calcium (mmol/l) | 2.53 ± 0.06 | 2.58 ± 0.06 | 2.46 ± 0.11 | 2.50 ± 0.02 | 2.2–2.6 |
| Magnesium (mmol/l) | 0.84 ± 0.02 | 0.84 ± 0.03 | 0.84 ± 0.03 | 0.83 ± 0.01 | 0.6–1.1 |
| Phosphate (mmol/l) | 1.20 ± 0.05 | 1.22 ± 0.05 | 1.16 ± 0.10 | 1.17 ± 0.06 | 0.7–1.45 |
| Alkaline phosphatase (U/l) | 103 ± 16* | 107 ± 22 | 97 ± 24 | 73 ± 6 | 30–120 |
| Urate (μmol/l) | 288 ± 30 | 303 ± 41 | 269 ± 48 | 282 ± 29 | 140–400 |
| Renal function | | | | | |
| Creatinine clearance (ml/min) | 87 ± 9* | 86 ± 15 | 87 ± 11 | 97 ± 4 | 80–150 |
| $Tm_{Ca}/GFR$ (mmol/l GF) | 2.11 ± 0.06 | 2.14 ± 0.09 | 2.06 ± 0.08 | 2.05 ± 0.04 | 2.0–2.2 |
| $Tm_P/GFR$ (mmol/l GF) | 1.32 ± 0.07 | 1.24 ± 0.05 | 1.42 ± 0.14 | 1.34 ± 0.10 | 0.8–1.6 |

*ESF* enterocystoplasty stone-formers, *IRSF* age- and sex-matched idiopathic recurrent calcium stone-formers, *UUT* upper urinary tract, *LUT* lower urinary tract, $Tm_{Ca}/GFR$ notional tubular maximum reabsorption of calcium in mmol/l GF (normal range 2.0–2.2), $Tm_P/GFR$ notional tubular maximum reabsorption of phosphate in mmol/l GF (normal range 0.8–1.6)

*$P<0.05$ (ESF vs. IRSF)

**$P<0.01$ (ESF vs. IRSF)

**Table 3** Summary of the 24-h urine data in enterocystoplasty stone-formers (ESF) and in age- and sex-matched idiopathic recurrent calcium stone-formers

| Variable | ESF (all) (mean ± SEM) ($n=15$) | ESF (UUT stones) (mean ± SEM) ($n=9$) | ESF (LUT stones) (mean ± SEM) ($n=6$) | IRSF (UUT stones) (mean ± SEM)\| ($n=15$) | Normal range |
|---|---|---|---|---|---|
| Volume (l/day) | 1.99 ± 0.16** | 1.95 ± 0.21 | 2.04 ± 0.25 | 1.56 ± 0.25 | 1.3–3.3 |
| Creatinine (mmol/day) | 11.2 ± 1.3 | 11.4 ± 1.9 | 10.9 ± 1.8 | 11.1 ± 0.7 | 8–18 |
| pH | 6.93 ± 0.10** | 6.91 ± 0.10 | 6.97 ± 0.21 | 6.59 ± 0.51 | 5.0–7.4 |
| Calcium (mmol/day) | 5.25 ± 0.45* | 5.15 ± 0.62 | 5.42 ± 0.70 | 6.73 ± 0.51 | 2.5–6.0 |
| Magnesium (mmol/day) | 3.88 ± 0.44 | 4.37 ± 0.65 | 3.15 ± 0.40 | 3.95 ± 0.34 | 2.5–6.0 |
| Phosphate (mmol/day) | 22.9 ± 2.7 | 25.5 ± 4.2 | 18.9 ± 2.0 | 24.1 ± 2.5 | 15–40 |
| Oxalate (mmol/day) | 0.38 ± 0.04 | 0.39 ± 0.07 | 0.37 ± 0.06 | 0.33 ± 0.02 | 0.25–0.45 |
| Citrate (mmol/day) | 0.78 ± 0.16*** | 0.76 ± 0.24 | 0.79 ± 0.22 | 2.50 ± 0.37 | 2.0–4.5 |
| Uric acid (mmol/day) | 3.09 ± 0.37 | 2.89 ± 0.49 | 3.37 ± 0.60 | 3.23 ± 0.22 | 2.0–3.5 |
| Sodium (mmol/day) | 156 ± 17** | 163 ± 28 | 147 ± 14 | 138 ± 10 | 40–220 |
| Potassium (mmol/day) | 63 ± 6 | 64 ± 10 | 61 ± 6 | 61 ± 4 | 15–120 |
| Protein (g/day) | 0.57 ± 0.07** | 0.55 ± 0.11 | 0.60 ± 0.09 | 0.21 ± 0.06 | 0–0.15 |
| $P_{SF}$ (CaOx) | 0.53 ± 0.08 | 0.51 ± 0.10 | 0.56 ± 0.15 | 0.61 ± 0.08 | < 0.5 |
| $P_{SF}$ (CaOx/CaP) | 0.79 ± 0.06 | 0.79 ± 0.07 | 0.77 ± 0.11 | 0.78 ± 0.05 | < 0.5 |
| $P_{SF}$ (CaP) | 0.92 ± 0.01** | 0.91 ± 0.02 | 0.93 ± 0.02 | 0.76 ± 0.05 | < 0.5 |
| $P_{SF}$ (MAP) | 0.72 ± 0.04*** | 0.72 ± 0.04 | 0.71 ± 0.08 | 0.013 ± 0.005 | < 0.5 |

*ESF* enterocystoplasty stone-formers, *IRSF* age- and sex-matched idiopathic recurrent calcium stone-formers, *UUT* upper urinary tract, *LUT* lower urinary tract
*$P < 0.05$ (ESF vs. IRSF)
**$P < 0.01$ (ESF vs. IRSF)
***$P < 0.001$ (ESF vs. IRSF)

had high indices ($P_{SF}$) of risk for forming phosphatic stones (both CaP and MAP, but particularly CaP). This was mainly due to the combination of the high urinary pH and hypocitraturia found in the group as a whole, accentuated in those patients who had hypercalciuria and/or a low urinary volume. In addition, 12 of the patients had a high risk of forming CaOx-containing stones (both "pure" CaOx and CaOx mixed with CaP) arising mainly from the observed hypocitraturia but accentuated in those patients with hypercalciuria, a low urinary volume, hyperuricosuria and a low urinary magnesium excretion.

Comparison of the biochemical indices of the risk of stone-formation between ESF and IRSF showed that both groups had an equally high risk of forming CaOx-containing stones but the ESF had a much higher risk of forming both CaP ($P < 0.01$) and MAP ($P < 0.001$) stones than the IRSF.

**Table 4** Summary of the dietary data in enterocystoplasty stone-formers (ESF) and in age- and sex-matched idiopathic recurrent calcium stone-formers

| Variable | ESF (all) (mean ± SEM) ($n=15$) | ESF (UUT stones) (mean ± SEM) ($n=9$) | ESF (LUT stones) (mean ± SEM) ($n=6$) | IRSF (UUT stones) (mean ± SEM) ($n=15$) | Normal range |
|---|---|---|---|---|---|
| Total fluids (l/day) | 2.66 ± 0.18 | 2.76 ± 0.23 | 2.52 ± 0.30 | 2.30 ± 0.20 | 1.5–3.5 |
| Calcium (mmol/day) | 20.1 ± 2.1 | 21.9 ± 3.2 | 17.3 ± 2.2 | 23.2 ± 2.8 | 15–25 |
| Magnesium (mmol/day) | 12.4 ± 0.8 | 12.8 ± 1.1 | 11.8 ± 1.3 | 13.7 ± 0.9 | 10–25 |
| Phosphate (mmol/day) | 37.8 ± 2.8 | 40.3 ± 4.4 | 34.1 ± 1.8 | 45.3 ± 4.1 | 10–60 |
| Oxalate (mmol/day) | 1.97 ± 0.19 | 2.09 ± 0.29 | 1.80 ± 0.19 | 1.94 ± 0.18 | 1.2–2.0 |
| Total protein (g/day) | 71.1 ± 5.4 | 75.4 ± 8.6 | 64.7 ± 4.3 | 77.8 ± 5.4 | 55–90 |
| FVC protein (g/day) | 28.6 ± 2.0 | 29.6 ± 3.1 | 27.0 ± 2.3 | 30.8 ± 1.7 | 15–40 |
| Animal protein (g/day) | 42.5 ± 4.3 | 45.8 ± 6.2 | 37.7 ± 5.1 | 47.0 ± 4.3 | 30–60 |
| MFP protein (g/day) | 29.7 ± 3.6 | 31.9 ± 4.8 | 26.8 ± 5.8 | 33.2 ± 3.3 | 15–45 |
| Dairy protein (g/day) | 12.8 ± 2.1 | 13.9 ± 3.1 | 10.9 ± 2.6 | 13.8 ± 1.8 | 10–30 |
| Purine (mg/day) | 179 ± 14 | 179 ± 19 | 179 ± 22 | 181 ± 12 | 130–220 |
| Fibre (g/day) | 17.6 ± 1.4 | 18.1 ± 2.1 | 16.9 ± 1.5 | 19.2 ± 1.3 | 14–25 |
| Refined CHO (g/day) | 116 ± 9 | 119 ± 13 | 112 ± 13 | 128 ± 13 | 70–120 |
| Sodium (mmol/day) | 173 ± 16 | 181 ± 26 | 160 ± 12 | 159 ± 8 | 100–220 |
| Potassium (mmol/day) | 74 ± 5 | 74 ± 7 | 73 ± 7 | 79 ± 4 | 40–100 |

*ESF* enterocystoplasty stone-formers, *IRSF* age- and sex-matched idiopathic recurrent calcium stone-formers, *UUT* upper urinary tract, *LUT* lower urinary tract, *FVC* protein = fruit + cereal + vegetable protein, *MFP* protein = meat + fish + poultry protein
*$P < 0.05$ (ESF vs. IRSF)
**$P < 0.01$ (ESF vs. IRSF)

Dietary excesses in terms of animal protein and purine, calcium, oxalate and sodium were contributory factors in the generation of the urinary abnormalities described above in six of the patients and low intakes of fluid, fibre or magnesium important in a further eight. A summary of the dietary data from the various groups is shown in Table 4. No significant differences were found in the dietary intakes of any of the constituents between the ESF and IRSF, although the IRSF tended to consume more of almost every dietary factor measured with the exception of fluids and salt.

## Discussion

Urolithiasis is generally considered to be a multi-factorial problem, influenced by metabolism, life-style, occupation, nutrition, clinical status and medication. The main initiating cause of stones is the formation in urine of crystals and aggregates of one or more of the insoluble salts and acids that turn up in kidney stones. If this occurs frequently, the probability is increased of one of these particles becoming trapped at some narrow section of the urinary tract or by adhesion to some area of the renal epithelium damaged by the passage of crystals or by infection and there forming the nucleus of a stone. The factors that lead to crystal formation are numerous and include urinary volume and pH, the urinary concentrations of all the stone-forming constituents (calcium, oxalate, phosphate, ammonium, magnesium, uric acid, cystine etc). Conversely, adequate concentrations of protective inhibitors (citrate and magnesium) can reduce the rate of crystal growth and the agglomeration of crystals of calcium salts (but not that of crystals of cystine, uric acid or MAP). The balance between these factors in a given urine determines the net risk of forming stones [8].

The presence of staples in the reservoir strongly predisposes to stone-formation. In practice, this is only a problem with the Kock pouch, which was used in only one of the patients in this series (Table 1). In an earlier study, we showed that the presence of a Kock nipple in the pouch caused a 50% incidence of stones [9]. The dissolving staples used in the construction of some pouches are unlikely to be relevant beyond the first 3 months by which time they have dissolved.

In patients with an enterocystoplasty (or ileal conduit), the risk of forming stones is increased mainly as a result of recurring urinary tract infections. If the infection involves a urea-splitting organism, there is an increase in the urinary concentration of ammonium ions (from the breakdown of urea) and an increase in urinary pH. This, in turn, increases the risk of forming stones consisting of calcium phosphate and magnesium ammonium phosphate. The former usually predominates, because, as outlined above, CaP is the first salt to crystallise out in urine as the pH is increased above a value of 6.2; MAP only crystallises out at pH values above 7. Indeed, "pure" MAP stones are very rare in patients with urinary tract infections. The results from this study showed that all patients gave a history of recurring urinary tract infection and 86% of those from whom a stone had been recovered for analysis formed infection stones consisting of various mixtures of calcium phosphate (CaP) and struvite (i.e. magnesium ammonium phosphate [MAP]). Most of the stones contained more CaP than MAP, as expected.

It is well documented that patients with enterocystoplasty are prone to form phosphatic stones, often in association with mucus [1–5]. In this study, however, 14% of the patients formed sterile stones consisting of a mixture of CaP and CaOx. Uric acid was not found in any of the stones analysed. This is not surprising since the patients tended to pass urines of pH $>6$ thereby precluding the risk of precipitation of uric acid itself. There may be a slight theoretical risk, however, of the more hyperuricosuric patients in the group forming ammonium urate stones since, when they have urinary infections, they will pass their "total uric acid" in the form of urate ions and their ammonia excretion may be high enough to allow the formation of ammonium urate crystals. Although ammonium urate-containing stones have been reported in a small percentage of patients with urinary tract infection [10] and in some patients with Kock pouches [11], none of the ESF in this study was found to have such a stone.

Although urinary infection is undoubtedly the main problem in these patients, this study shows that there are several other factors that also may accentuate the risk of forming CaP- and CaOx-containing stones. These include moderate to severe hypocitraturia, an increased tendency to hypercalciuria and mild hyperoxaluria, a low urine volume, hyperuricosuria and a low urinary magnesium excretion. In patients with a normal endocrine system, the biochemical changes could be due to transport in either direction across the reservoir wall or changes in intestinal absorption due to removal of bowel segments. No relationship was found between the biochemical profiles and the type or length of bowel used, though the numbers for each combination in this study are too small to enable a firm conclusion to be drawn.

Of the urinary risk factors identified in these patients, the hypercalciuria appears to be mainly due to a renal leak of calcium in those patients consuming a high salt diet. The low urine volume is due to a low fluid intake (some patients have difficulty in maintaining a high fluid intake). The effect of enterocystoplasty on fluid balance has been investigated. Those with an ileal reservoir tend to lose water while a colonic reservoir has little effect on fluid balance [12]. It is unlikely, however, that the effect of the ileal reservoir would override the requirement of the body to maintain osmotic balance so that thirst would ultimately force the patient to drink. The hyperuricosuria is due to a high purine intake and the low urinary magnesium excretion to a low magnesium intake.

The relationship between calcium metabolism and bone growth has been extensively studied in our Unit

and by others, with contradictory results. In children, it seems clear that storage of urine in intestinal reservoirs does not impair growth height [13]. In an experimental study in rats, it was found that storage in an ileal reservoir in addition to resection of a further length of ileum reduced bone strength [14]. It seems likely that this phenomenon is due to intestinal malabsorption, possibly secondary to renal impairment, rather than to a direct effect of the enterocystoplasty. The clinical significance is unknown. In the current study, only two patients were $<20$ years old (15 and 19, respectively). In fact, the metabolic screen showed that four of the ESF patients actually had a raised plasma calcium ($>2.60$ mmol/l) and two of these remained high after correction for serum albumin; one had suspected hyperparathyroidism secondary to renal impairment. Five patients had an increased alkaline phosphatase level ($>104$ U/l). The tendency to hypercalcaemia may be due, in part, to the reported reabsorption of calcium from urine passing through the implanted intestinal tissue from the mucosal to the serosal side [15].

The hypocitraturia is partly related to a low intake of potassium but is probably also due to the tendency to urinary tract infection in these patients [16]. However, it may still be important for bladder stones since if bladder urine is low in citrate, stones may be initiated at that site as the supersaturation of the urine with respect to calcium phosphate is increased. The mild hyperoxaluria may be due to two factors. First, removal of small bowel for the purposes of the urinary implant may lead to mild enteric hyperoxaluria for the same reasons as in any patient who undergoes small bowel resection [17].

Second, there is the possibility that because these patients are often treated with antibiotics for their recurring urinary tract infections, this will knock out in the colon *Oxalobacter formigenes*, the only gut flora that is known to metabolise oxalate. Furthermore, it is apparently very difficult to re-colonise the gut with this anaerobe once it is removed. This results in a higher concentration of free oxalate in the colon where it is known to be absorbed passively into the bloodstream and hence out in the urine resulting in mild hyperoxaluria [18].

In this context, it is interesting that there has been a marked increase in the incidence of CaOx stones in young women during the past 30 years and that this has been associated with an increase in urinary oxalate in that age group [19]. Over 70% of these patients gave a history of urinary tract infection but did not form infection stones because they were treated quickly with antibiotics which would probably have eliminated intestinal *O. formigenes*, thereby allowing an increase in the passive absorption of oxalate in the colon. In support of this hypothesis, it has been observed that young female stone-formers treated with antibiotics for urinary infections have higher urinary oxalate levels than an equivalent group with no history of urinary infections [20].

It has already been shown that some physical characteristics of the reservoir predispose to stone-formation. The most generally accepted is the presence of a foreign body. The Kock pouch relies on multiple rows of staples to maintain its two nipple valves. In a single unit experience of 72 patients with a Kock pouch and 54 with an Indiana pouch (which does not have staples), the stone incidence was 43% compared to 13%. Furthermore, no patient with an Indiana pouch formed a stone after 4 years, but those with a Kock continued to do so at a steady rate to the end of follow up at 8 years [11].

The role of mucus in stone-formation is uncertain. Reservoirs made of stomach are almost never complicated by stones; only one case was seen in 44 patients at a median follow-up of 9.8 years [21, 22]. Although there is no mucus, the acidic pH may be relevant in protection from stone-formation.

Patients and doctors tend to blame an excess of mucus for almost everything that goes wrong with an intestinal reservoir. Patients may be forgiven but doctors should know better. Patients have only their own experience of mucus and have no objective means of measuring the output other than casual inspection. Even in the laboratory, it is difficult to measure and in clinical practice almost impossible [23, 24]. Scanning electron microscopy and energy dispersive X-ray spectrometry show that the mucus of stone formers has increased calcium, phosphate, magnesium and calcium to phosphate ratio than that of non-stone formers [25].

Although washouts of mucus are widely recommended for the prevention of stones, it may be that the only advantage is to clear fragments of 'sand' before a stone can be formed. In the only prospective trial of weekly washouts, the incidence of stone in 30 children was no different from that in historical controls [26].

Even in a urinary tract that has not been reconstructed, a stagnant urine residual is known to predispose to stone-formation. Where urine drains out from the bottom of the reservoir stone-formation is rare, whilst drainage from the top, in our experience, greatly increases the risk of stone-formation. This is most graphically shown in children who have an augmented bladder. Those who void 'naturally' through the urethra seldom, if ever, form stones; those who empty by urethral CISC have a 9% stone incidence; those who perform CISC through a Mitrofanoff conduit entering the top of the augmented bladder form a stone in 21–100% of cases [5, 25]. Although these data seem strong, it must be said that others have shown little difference in stone risk between these two types of drainage (6% in urethral catheterisers v 10% in Mitrofanoff catheterisers) [27]. Nurse et al. found that stones occurred ten times more often in patients with augmented bladders who were on CISC compared to those who voided [28].

The data from the present series are derived from our patients who often formed stones, some of whom were subjects in an earlier paper [5]. They therefore came from a group the physical characteristics of whose reservoirs predisposed them to stone-formation. The metabolic abnormalities were different in some respects, from those in IRSF patients, with a higher incidence of

hypocitraturia than in the IRSF. There are no control patients from a non-stone forming group with enterocystoplasty. Nonetheless, it is possible to conclude that, in enterocystoplasty patients who form stones, there are biochemical and dietary factors present that are known predispose to stone-formation in otherwise normal subjects. Investigation should, therefore, extend beyond a simple examination of the anatomy of the reservoir. Metabolic factors may explain why some patients form stones and others with an identical reservoir do not. Similarly, unconscious changes in diet might alter the stone risk in individual patients.

Furthermore, the data may be used to devise a prophylactic regime. The predisposition to recurring urinary infections requires that patients be treated frequently with antibiotics. Although this may reduce the risk of forming infection stones, it may increase their risk of forming CaOx-containing stones, by the elimination of *O. formigenes*. It is desirable to keep the use of antibiotics to the minimum possible both in dose and duration. A *consistently* high fluid intake (not less than 2.5 l/day) is a prerequisite for prophylaxis, if it can be tolerated. They must minimise their intake of salt and salty foods, such as ham, bacon, sausages, crisps and other salted snacks, sauces and pre-prepared foods. This will help to reduce their risk of hypercalciuria. They should also keep to a minimum their intake of high oxalate-containing foods, such as rhubarb, spinach, beetroot, okra, yams, soya beans and soya products, nuts, peanut butter, chocolate and tea without milk. This will reduce the risk of mild hyperoxaluria. Otherwise, they should maintain a well-balanced diet with more fruit and vegetables (other than those with a high oxalate content) and choose brown bread rather than white bread. This combined approach will increase their intake of fibre, potassium and magnesium and thereby increase the excretion of protective factors in urine, such as citrate and magnesium. This holistic approach should help to reduce their risk of forming further stones, provided that they can also keep clear of urinary tract infections. An alternative is to prescribe potassium citrate supplements in order to try to increase the urinary excretion of citrate and to reduce the urinary excretion of calcium. However, the downside of this approach is that it will alkalinise the urine of these patients still further and so may possibly increase the net risk of forming phosphatic stones rather than decrease it.

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