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FEASIBILITY OF PREVENTING ENCRUSTATION OF URINARY CATHETERS

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Abstract

Colonization of urinary catheters by bacteria which produce urease leads to an increase in urine pH, followed by deposition of the minerals struvite and hydroxyapatite. Adhesion of these encrusting deposits can be reduced, but not prevented, by using catheters with a smooth surface finish. Chemical methods for preventing encrustation are not completely satisfactory. A better way of preventing encrustation would be to prevent colonization of the catheter by bacteria. This might be achieved by controlled release of antimicrobial agents directly into the urine from the catheter itself. Preliminary experiments have demonstrated the feasibility of controlled release from solid silicone. However, a simpler approach is diffusion of an antimicrobial agent from a solution within the retention balloon of the catheter. Further experiments are required to determine the concentrations required and whether they are achievable in practice.

Key Words: Calcification, catheters, controlled release, encrustation, infection.

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Introduction

A mechanism has been proposed for the encrustation of indwelling urinary catheters which involves their colonization by bacteria (Cox *et al.*, 1989a). This paper reviews the evidence for the proposed mechanism and considers its implications for the prevention of encrustation.

Indwelling catheters are used to drain urine from the bladder of patients who are suffering from urinary incontinence or retention (Kunin, 1987). They consist of a natural rubber latex, silicone rubber or PVC tube which is inserted into the bladder. Most latex catheters are coated with silicone elastomer, Teflon or hydrogel to provide a smoother surface finish. The most common design, the Foley catheter, is inserted through the urethra and is retained in the bladder by an inflatable balloon (Fig. 1). The tip allows the catheter to be inserted (with the balloon deflated); the eye is a hole which allows urine to pass into the drainage lumen. The other end of the catheter is connected to a drainage bag to provide a sealed system for the collection of urine. A second lumen (the inflation lumen) connects the inside of the retention balloon to a side arm which terminates in a one-way valve. When the catheter has been inserted, water is injected, through this valve, to inflate the balloon and so retain the catheter in position.

Infection of the urinary tract is believed to be followed by colonization of the catheter surface by bacteria (Kunin and Steele, 1985). Chemical changes then occur in the urine which lead to the formation of encrusting deposits (Bruce *et al.*, 1974; Hedelin *et al.*, 1991). In principle, possible methods for preventing encrustation are to prevent: (i) the adhesion of encrusting deposits to the catheter surface, or (ii) chemical changes occurring in the urine, or (iii) colonization of the catheter by bacteria. Methods (ii) and (iii) involve introducing a chemical agent to the inner surface of the catheter. Controlled release allows the appropriate concentration to be delivered to the appropriate site, whilst relying on minimal nursing care or patient compliance. The catheter itself can provide a suitable vehicle for controlled release.

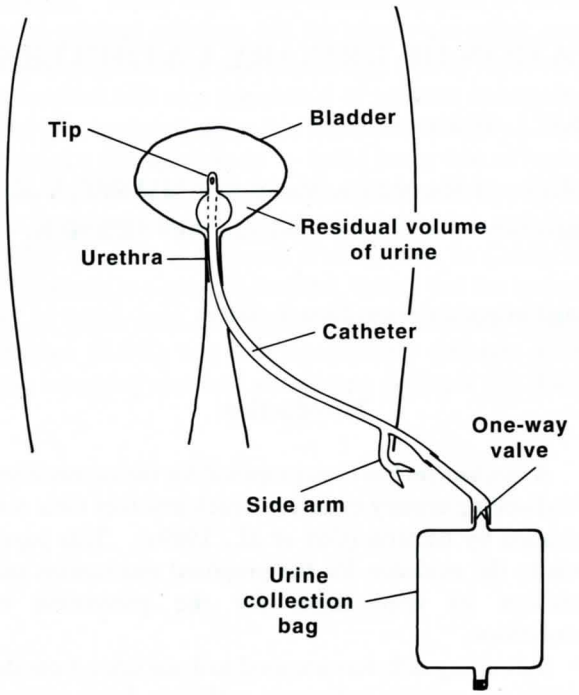

Figure 1. Schematic diagram of a Foley catheter retained in the bladder by an inflated balloon.

$$(NH_2)_2CO + H_2O \xrightleftharpoons{\text{urease}} 2NH_3 + CO_2$$

$$2NH_3 + 2H_2O \rightleftharpoons 2NH_4^+ + 2OH^-$$

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \rightleftharpoons CO_3^{2-} + 2H^+$$

Figure 2. Chemical reactions which lead to an increase in urine pH.

Mechanism of Encrustation

The most common problem which accompanies urinary catheterization is the formation of encrusting deposits on the catheter surface (Getliffe and Mulhall, 1991; Hedelin *et al.*, 1985a; Kunin *et al.*, 1987). These deposits form a hard mass around the eye of the catheter and can cause blockage of the drainage lumen. Analysis of the deposits identified substantial concentrations of ammonium, calcium, magnesium and phosphate ions (Bruce *et al.*, 1974; Hedelin *et al.*, 1984; Holt *et al.*, 1987). The ammonium, magnesium and some of the phosphate ions have been shown, by X-ray diffraction, to be present in the form of the mineral struvite ($NH_4MgPO_4.6H_2O$) (Hukins *et al.*, 1983). It has been suggested that the calcium phosphate is present as brushite ($CaHPO_4.2H_2O$) (Hedelin *et al.*, 1984) but X-ray diffraction, X-ray absorption spectroscopy and stoichiometric calculations based on the results of ion exchange chromatography indicate that it is poorly crystalline hydroxyapatite (Holt *et al.*, 1987; Hukins *et al.*, 1989). Hydroxyapatite (HAP) has the chemical formula $Ca_5(PO_4)_3OH$ but is usually precipitated in an impure form in biological systems.

Struvite occurs in urinary calculi when the urine is infected by bacteria (e.g., *Proteus*) which produce the enzyme urease (Griffith *et al.*, 1976; Griffith and Osborne, 1987). Urease catalyses the hydrolysis of urea to produce carbon dioxide and ammonia. Figure 2 shows the chemical reactions which occur, leading eventually to the possible production of several different ions. Since carbon dioxide is a weak acid ($pK_{a1} = 6.4$; $pK_{a2} = 10.3$), but ammonia is a relatively strong base ($pK_b = 4.8$), the urine becomes alkaline, i.e., its pH increases. Above a pH value of 7.2, struvite and HAP are precipitated from urine (Elliot *et al.*, 1958; Lindler and Little, 1986).

It is has been proposed that this mechanism is responsible for catheter encrustation (Cox *et al.*, 1989a). This proposal is consistent with the composition of the encrusting deposits and the elevated pH of urine (up to a value of 8) in catheterised patients (Hedelin *et al.*, 1991; Norberg *et al.*, 1980). Catheter encrustation has been mimicked *in vitro* by adding urease to artificial urine (Hedelin *et al.*, 1985b; Cox *et al.*, 1988, 1989b). Further evidence is provided by the appearance of bacteria in intimate association with the encrusting deposits (Cox *et al.*, 1989a; Stickler *et al.*, 1993a). Furthermore, *Proteus mirabilis* has been identified as the organism most commonly isolated from encrusted catheters (Stickler *et al.*, 1993b). It has also been shown that purified capsular polysaccharides from *Proteus mirabilis* are capable of binding magnesium ions and enhancing struvite formation (Dumanski *et al.*, 1994).

Adhesion of Deposits

Prevention

In principle, adhesion of deposits could be prevented by: (i) inhibiting crystallisation of mineral deposits, or (ii) ensuring that there were no nucleation sites for crystal growth on the catheter surface. The second method has the possible advantage that a surface finish with no nucleation sites would be so smooth that it would be expected to provide a poor surface for bacterial colonisation. Although both methods might be expected to reduce encrustation, they have yet to be explored further, for the reasons given below.

Inhibitors

Controlled release of inhibitors or binding them to the catheter surface might be expected to reduce encrustation. The possibility of preventing HAP deposition on implanted heart valves by controlled release of diphosphonates from silicone rings has been described in the literature (Levy *et al.*, 1985). Substances, such as diphosphonates, inhibit calcium phosphate crystallisation by adsorbing on the surface of crystal surfaces and so prevent further crystal growth (Blumenthal, 1989). Citrate is believed to inhibit HAP deposition in urine (Sutor *et al.*, 1978). Recent studies indicate that oral administration of citrates may significantly reduce crystallisation in urine (Wang *et al.*, 1994). These studies were published after the experimental feasibility studies reported in this paper were completed and may indicate an alternate approach to preventing encrustation.

Unfortunately, substantial encrustation can still occur in the presence of inhibitors. Albumin can be shown to inhibit HAP deposition (Gilman and Hukins, 1994). However, albumin forms part of an *in vitro* model system in which encrustation occurs (Cox *et al.*, 1988, 1989b).

Surface finish

A smooth surface finish is expected to minimise encrustation but it is unlikely that a sufficiently smooth surface will be achieved to completely prevent its occurrence. Hydrogel-coated latex and all-silicone catheters have the smoothest surfaces (Cox, 1987, 1990) but encrusting deposits still adhere to them during *in vitro* experiments (Cox *et al.*, 1988, 1989b). Diamond-like carbon provides a surface which is highly resistant to adhesion of biological materials (Higson and Vadgama, 1993) and so might be reduce encrustation even further. However, it is unlikely that a catheter could be manufactured and introduced into the body without any surface scratches which could provide nucleation sites for crystallisation of encrusting deposits.

Changes in Urine Chemistry

Principles

Changes which occur in the chemistry of urine, following colonization of the catheter surface by bacteria, could be prevented in two ways: (i) by reversing the increase in urine pH, or (ii) by preventing urease from hydrolysing urea. There are two plausible methods for achieving the second aim: to inhibit urease molecules or to remove them from the system.

Changing urine pH

Since deposition of struvite and HA is a result of elevated urine pH, it has been suggested that decreasing the pH by acidifying the urine would prevent encrustation (Hedelin *et al.*, 1991; Kunin, 1987). When acid was added to a mixture of urease and artificial urine, its pH dropped from a value of 8.5 to 6.5, as expected (Bibby and Hukins, 1993). Unfortunately, the pH then increased. The reason is that the pH of the system is controlled by the equilibrium reactions shown in Figure 2. According to Le Chatelier's principle, the equilibrium position shifts to oppose the imposed change, i.e., urease catalyses the conversion of more urea into ammonia and carbon dioxide so that the pH rises again. In order to prevent the rise in pH, all the urea in the urine would have to be converted into ammonia which would then have to be neutralised by a suitable acid. This approach would require an unreasonably large volume of acid and so is not a feasible method for preventing encrustation (Bibby and Hukins, 1993).

Inhibition of urease

Urease can be inhibited by acetohydroxamic acid (AHA) or hydroxyurea (Hamilton-Miller and Gargan, 1979; Carmignani *et al.*, 1980). Only AHA has been used as a pharmaceutical agent (to prevent formation of urinary tract calculi as a result of infection); its recommended dosage is 250 mg, three to four times daily. However, *in vitro* experiments suggest that a concentration of AHA of greater than 3.8 mg cm^{-3} is required to prevent a rise in urine pH (Griffith *et al.*, 1973). Although AHA has been successfully used to reduce catheter encrustation, patients suffered from side effects which can include loss of appetite, mental depression, nausea and vomiting (Burns and Gauthier, 1984). It may be that the risk of side effects would not be so great if AHA were delivered directly to the site of bacterial colonization. However, the seriousness of these side effects suggests that AHA is unlikely to be acceptable for routine prevention of encrustation.

Removal of urease

In principle, the problem could be solved by digesting urease molecules with an proteolytic enzyme. Early research on the action of proteolytic enzymes produced ambiguous results (Sumner, 1951), perhaps because pure, well characterised enzymes and substrates were not then available. We have updated this research using a selection of enzymes which are active at neutral or alkaline pH values: trypsin, chymotrypsin, papain, ficin, proteinase k and subtilisin Carlsberg.

All enzymes were obtained from Sigma Chemical Company (St. Louis, Missouri, US). Ficin was a crude preparation; all other proteolytic enzymes were crystallized and lyophilized by the supplier. Jack bean urease was dissolved in 0.02 M sodium phosphate buffer (pH 7) which was adjusted to the optimum pH of the proteolytic enzyme being investigated by addition of sodium

hydroxide. The concentration of the urease was 15 $mg.cm^{-3}$, corresponding to an activity of approximately 855 $IU.cm^{-3}$. Urease solution was incubated at 37°C before adding protease and all digestions were performed at this temperature. The proteolytic enzyme was added so its mass was 1/30 times that of the urease. This ratio of proteolytic enzyme/urease was chosen arbitrarily, although it ensured that the substrate (urease) was present in excess. Although the same mass was used for each of the six proteolytic enzymes, they may have had different activities. However, the aim of this experiment was to compare the effects of each enzyme in its commercially available form. The activity of the urease solution was determined before the addition of proteolytic enzyme from the mean of four assays (Bibby and Hukins, 1992). Two samples were removed from the solution at time periods of 5, 15 and 25 minutes; the urease activity at each time was determined as the mean assay from the two samples. A control sample of the original urease solution was incubated at 37°C with no enzyme and the activity determined after a period of 30 minutes (mean of two assays). Digestion experiments were repeated four times for enzymes which were found to reduce urease activity to less than 80% of its initial value.

Three proteolytic enzymes (subtilisin Carlsberg, chymotrypsin and proteinase k) reduced urease activity to less than the 80% level in the time period of the experiment. Proteinase k was the only enzyme which reduced the activity to less than 60%; its results are shown in Figure 3a. For both subtilisin Carlsberg and chymotrypsin, the reduction was to not less than the 70% level. These results are consistent with proteinase k being especially active towards native enzymes and suggests that it could prove useful in removing urease.

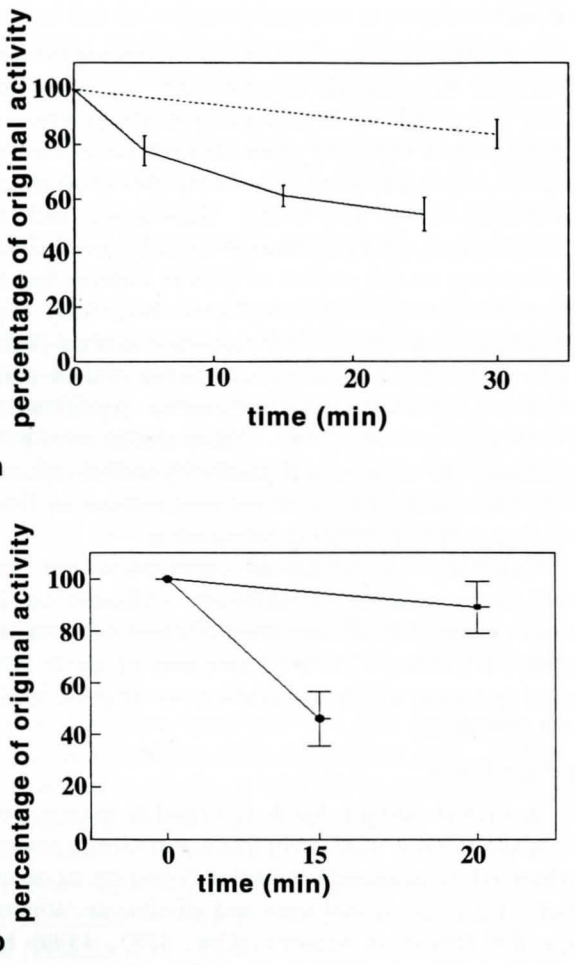

Figure 3. Effect of proteinase k on the activity of urease in solution. In (a) the proteinase k was also in solution, in (b) it was immobilised. Further details are given in the text.

Application of immobilised proteinase k

There are two reasons for using proteinase k in an immobilised form: (i) to prevent it being flushed from the catheter, and (ii) to prevent it digesting itself. Loss of proteolytic enzyme would lead to depletion of supply; compensating for this loss with excess enzyme could prove an expensive solution to the problem. Enzymes are commonly immobilised on to hydrogels, so there should be no problem in immobilising proteinase k on to the surface of the drainage lumen of a hydrogel-coated catheter. Therefore, the experiments described in the previous section were repeated with immobilised proteinase k.

Proteinase k immobilised on agarose was purchased from Sigma Chemical Company. Its activity was comparable to that of the free enzyme. However, in this experiment, the ratio of proteolytic enzyme to urease was 1/60, by mass. The mixture was incubated for 15 minutes at 37°C and the immobilised enzyme was then removed by centrifugation for 5 minutes. A control contained no proteolytic enzyme and was incubated for 25 minutes. Four experiments were performed.

Figure 3b shows that the immobilised enzyme caused an even greater and more rapid digestion of urease than the free enzyme. However, a problem still remains in preventing catheter encrustation by immobilising proteinase k on the surface of the drainage lumen. Urease is present in the urine of patients infected with the bacteria which produce it, as a result of cell lysis (Griffith and Osborne, 1987). It has been suggested that this extracellular urease is important in the formation of kidney stones (Griffith and Osborne, 1987). However, the pH of the urine surrounding bacteria which produce urease can rise without cell lysis, i.e., intracellular urease may also be important (Griffith *et al.*, 1973).

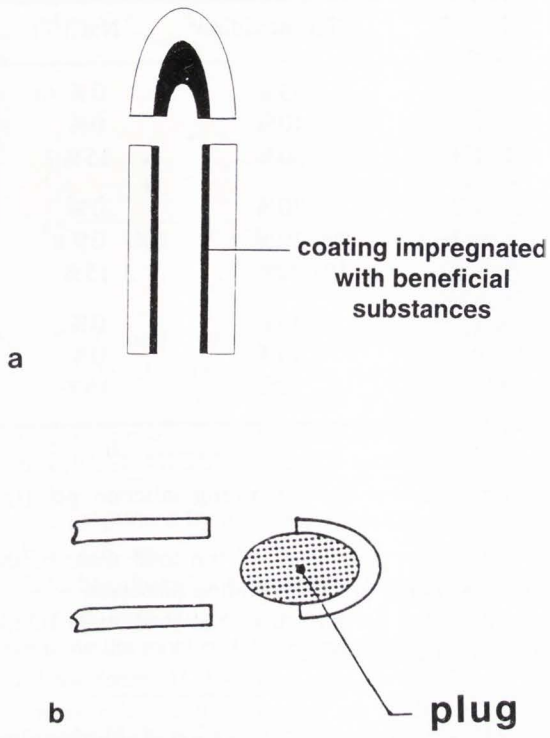

Figure 4. Incorporation of a controlled release matrix as (**a**) a lining and (**b**) a plug near the eye of the catheter.

Thus, extensive studies of the relative importance of intracellular and extracellular urease would be needed before this approach was proved to be of value.

Prevention of Bacterial Colonization

Background

Since improving the surface finish of a catheter is unlikely to prevent encrustation and the chemical methods described above all present problems, it appears reasonable to solve the problem at its source, i.e., to prevent the colonization of the catheter by bacteria. Prevention of infection would prevent encrustation. Infection of the urine in a catheter is already perceived as a problem, albeit separate from that of encrustation, in the catheterized patient (Kunin and Steele, 1985; Slade and Gillespie, 1985). It is believed to occur by two different routes: (i) through the drainage system (intraluminally), and (ii) between the outer surface of the catheter and the urethral mucosa (periurethrally) (Brehmer and Marsden, 1972; Kunin, 1987). Rigorous cleansing routines reduce periurethral infection (Brehmer and Marsden, 1972) and closed drainage systems minimise intraluminal infection (Gillespie *et al.*, 1967; Kunin, 1987); however, once infection is introduced into the system, closed drainage serves no purpose. Application of bladder washout solutions also breaks closed drainage systems (Kirk *et al.*, 1979; Warren *et al.*, 1978). If intraluminal infection is prevented, infection still proceeds by the periurethral route (Gillespie *et al.*, 1983).

The antimicrobial properties of silver (Foye, 1977) have been exploited in two ways. A randomized clinical trial of catheters coated with silver showed a statistically significant decrease in the incidence of bacteriuria after 6 days (Liedberg and Lundeberg, 1990). Such a catheter may have a short-term effect in minimising encrustation, but the long-term effects are unknown. A plug which contains silver has been introduced for attaching the catheter to the drainage bag (Silverline, Clinimed, High Wycombe, U.K.). This antimicrobial layer may prevent migration of bacteria from the drainage bag into the catheter but does not address the problem of periurethral infection.

An alternative approach to preventing infection and, hence, encrustation, is the prophylactic application of antimicrobial agents. Controlled release of these agents has several advantages: (i) application of the agents to the site of infection, (ii) avoidance of breaking a closed drainage system, (iii) reduction in nursing care, and (iv) use of the catheter as a means of introducing the agent. A possible problem with this approach is that the routine use of antimicrobial agents may give rise to resistant strains (Britt *et al.*, 1977; Butler and Kunin, 1968a; Dudley and Barriere, 1981). However, this is likely to be more of a problem with bladder washout solutions where the agent must be applied intermittently. It has been found that catheters impregnated with antimicrobial agents lose their activity within 48 hours (Butler and Kunin, 1968b). More recent work on release from linings of the walls of catheters provides little detail (Huajin, 1988; Mochizuki *et al.*, 1985). An alternative approach involves ionically bonding antimicrobial agents to the catheter wall; molecules are released as the bonds break (Sakamoto *et al.*, 1985).

Here the construction of the catheter is exploited as a means of releasing antimicrobial agents into the urine. One approach involves impregnating silicone with the agent. This is achieved by mixing liquid silicone with the agent; the mixture subsequently cures so that the agent is incorporated into solid silicone. The silicone could be introduced as a plug within the tip of the catheter (Fig. 4a) or as a lining in the drainage lumen (Fig. 4b). The other approach exploits the catheter balloon as a reservoir for a solution of antimicrobial agent which

could then diffuse through the wall of the balloon into the residual urine in the bladder and then pass through the drainage lumen.

Preliminary experiments were performed with chlorhexidine (in solid silicone plugs) and mandelic acid (in solution, filling the retention balloon of all-silicone catheters). Mandelic acid has the advantage that it is effective against *Proteus* in the biofilms which coat the drainage lumen of encrusting catheters (Stickler and Hewett, 1991; Stickler *et al.*, 1991). These biofilms consist of a mixture of bacteria, macromolecules and minerals; the bacteria are protected from antibiotics by the barrier provided by their environment (Cox *et al.*, 1989a; Nickel *et al.*, 1985; Ramsay *et al.*, 1989). A further advantage of mandelic acid is that it does not give rise to resistant strains (Robertson and Norton, 1990). However, *Proteus mirabilis*, which was the commonest species colonizing a sample of encrusted catheters (Stickler *et al.*, 1993a,b), is especially sensitive to trimethoprim, cefuroxime, nalidixic acid and norfloxacin (Garrod *et al.*, 1981); it would, therefore, be worth investigating controlled release of these antibiotics from catheters in future experiments.

Chlorhexidine release from silicone

Chlorhexidine has been claimed to reduce infection on latex catheters (Zinsser *et al.*, 1968). However, some species of *Proteus* are not very susceptible. The controlled release of chlorhexidine diacetate from ethyl cellulose, hydrogels, latex and biodegradable protein have been investigated (Friedman and Golomb, 1982; Mirth *et al.*, 1989; Mochizuki *et al.*, 1985; Steinberg *et al.*, 1990). Most of the devices have been developed for dental applications. Factors which affect the rate of release of chlorhexidine include: (i) the mass of chlorhexidine incorporated, (ii) the surface area, and (iii) the permeability of the matrix (Friedman and Golomb, 1982; Mirth *et al.*, 1989; Mochizuki *et al.*, 1985; Steinberg *et al.*, 1990). Permeability of silicone matrices for the release of diphosphonates has been increased by adding polyethylene glycol (PEG); the PEG is then dissolved out in acetone, leaving pores in the matrix (Golomb *et al.*, 1987). However, we found that chlorhexidine prevents silicone from curing in the presence of PEG. In our experiments, attempts were made to increase the porosity of the matrix by adding sodium chloride. The sodium chloride was expected to dissolve in water, introducing pores into the matrix. Experiments were performed with three formulations of silicone: (i) Dow Corning silicone elastomer (MDX4-4210; Dow Corning Corp., Medical Products, Midland, Michigan, USA), (ii) Provil L dental silicone (Bayer Dental, Leverkusen, Germany), and (iii) Dow Corning silicone gel (Q7 2218). All three silicones are prepared by mixing two components; in each case, incorporation of chlorhexidine diacetate produced a stronger, more rigid solid. The experiments tested release from one side of discs of material, to simulate release from the surface lining of a catheter.

Table 1. Compositions of the samples used for controlled release experiments.

Silicone[1]	Chlorhexidine[2]	NaCl[3]
MDX4	33%	0%
MDX4	40%	0%
MDX4	30%	15%
Provil L	20%	0%
Provil L	30%	0%
Provil L	20%	15%
Q7	30%	0%
Q7	40%	0%
Q7	30%	15%

[1]Dow Corning silicone elastomer (MDX4-4210), Provil L dental silicone or Dow Corning silicone gel (Q7 2218).
[2]Expressed as the percentage of the total mass of the specimen consisting of chlorhexidine diacetate.
[3]Expressed as the percentage of the total mass of the specimen consisting of NaCl.

Table 1 lists the compositions of the specimens used. The particle size of the chlorhexidine diacetate was determined by image analysis; 97% of the area occupied by 1250 particles consisted of particles whose area was less than 24 μm^2. For the sodium chloride added to some specimens, the corresponding particle area was less than 80 μm^2. All samples were thoroughly mixed and cast as sheets; air bubbles were removed by placing the mixtures in a vacuum for 15 minutes. Since Dow Corning Q7 takes at least 24 hours to cure at room temperature, these samples were rotated at 0.7 $rad.s^{-1}$ to prevent settling of chlorhexidine diacetate. Samples were tested as discs of area 1.77 cm^2 which were backed with an impermeable coating to ensure that release was restricted to a single face.

Each disc was placed in a fixed volume of distilled water in a conical flask that had been treated with Sigmacote (Sigma, St. Louis, MO), because chlorhexidine is believed to be affected by glass (E. Chantler, personal communication). For each of the formulations listed in Table 1, six discs were tested . Other flasks contained solutions of chlorhexidine to monitor its stability during the course of each experiment. Samples were removed periodically and the concentration of chlorhexidine

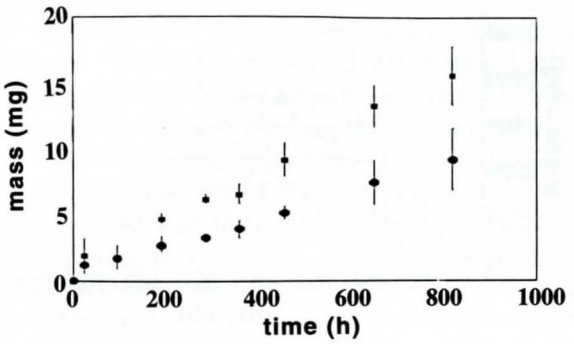

Figure 5. Cumulative mass of chlorhexidine diacetate released from silicone gel Q7 for specimens containing 30% (circles) and 40% (squares) loadings (Table 1). Error bars represent one standard deviation.

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diacetate monitored by ultraviolet absorbance at a wavelength of 276 nm.

Chlorhexidine diacetate was released from all the formulations listed in Table 1 but Dow Corning Q7 was shown to be the most suitable matrix for this application. The release from MDX4 was comparatively slow (cumulative mass released was about 2 mg in 300 hours for a 40% loading) when compared with Q7 (over 5 mg in 300 hours for 40% loading) and Provil L (about 5 mg in 300 hours for 30% loading). However, Provil L showed an initial rapid release, while that from Q7 was highly linear ($r = 0.99$), as shown in Figure 5. Furthermore, it was found possible to achieve a higher loading of chlorhexidine diacetate in Q7 (40%) than in Provil L (30%). All experiments on samples containing sodium chloride were discontinued because of their rapid physical deterioration.

The concentration of chlorhexidine released into the urine of a catheterised patient can be estimated. From the slope of Figure 5 (0.0204 ± 0.0008 mg.h^{-1}), the concentration of chlorhexidine in the urine of an elderly patient passing typically 800 cm^3 per day would be 0.006 mg.cm^{-3}. Although this is less than in bladder washout solutions (0.2 mg.cm^{-3}), it is possible that lower concentrations would be effective in continuous application.

Mandelic acid release from the balloon

The experiments described in this section show that mandelic acid can diffuse through the retention balloon of an all-silicone catheter. Thus, the catheter itself can be used as the vehicle for controlled release. The advantages of using mandelic acid for controlling catheter infection have been described above.

An all-silicone Foley catheter (size 16 or 18; Bard Ltd., Clacton-on-Sea, U.K.) was introduced through a

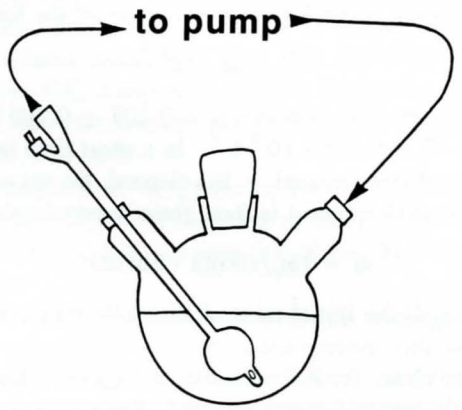

Figure 6. Apparatus used to investigate release of mandelic acid from an inflated retention balloon.

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screw adapter into one of the side necks of a triple-necked flask (250 cm^3 capacity), as shown in Figure 6. Distilled water (125 cm^3) was added to the flask and circulated through the drainage lumen of the catheter by means of a peristaltic pump. (A limited number of experiments using artificial urine yielded closely similar results.) The balloon was inflated with mandelic acid solution (30 cm^3). Concentrations of 0.025, 0.050, 0.075, 0.100 and 0.125 g.cm^{-3} were used. Six catheters were used for each concentration studied. Samples (0.08-0.5 cm^3) of the circulating water were removed periodically through the central neck of the flask. The mandelic acid concentration was monitored by ultraviolet absorption at a wavelength of 256 nm. Sink conditions were maintained throughout by changing the circulating liquid every time the mandelic acid concentration exceeded 0.016 g.cm^{-3}. (This ensured that the release of the mandelic acid from the balloon was not inhibited by its concentration in the surrounding liquid. Thus, the experiments mimicked release into the drainage lumen of a catheter where the substance released would be flushed into the collecting bag.) Six different catheters were used for each mandelic acid concentration investigated.

Figure 7 shows that mandelic acid diffuses through the catheter balloon; Figure 7a compares the results for all five concentrations used. The results for the most concentrated mandelic acid solutions are incomplete because the balloons persistently ruptured. However, a separate series of experiments showed no decrease in balloon strength, as measured by bursting pressure, after exposure to mandelic acid solution. In Figure 7b, the results for all concentrations are shown to lie on a single

smooth curve when the cumulative mass of mandelic acid released is expressed as a percentage, P, of the initial mass in the balloon. This curve can be represented by the second-order polynomial of the form:

$$P = at - bt^2 \quad (1)$$

when t is the time in hours, $a = 0.207 \pm 0.005\ h^{-1}$ and $b = (1.32 \pm 0.08) \times 10^{-4}\ h^{-2}$. In a short time interval, $\Delta\tau$, after a time interval, τ, has elapsed, the mass, m, of mandelic acid released is then given approximately by:

$$m = (m_o/100)(a - 2b\tau)\Delta\tau \quad (2)$$

where m_o is the initial mass of mandelic acid in the balloon.

It is clear, from the results of Figure 7, that mandelic acid was still being released after a period of over 4 weeks. Eq. 2 shows that between days 10 and 11, the mass of mandelic acid diffusing through the balloon was 0.104 g for a filling solution with a concentration of 0.1 $g.cm^{-3}$. For an elderly person expressing an average of 800 cm^3 of urine per day, this corresponds to a mandelic acid concentration of 0.13 $mg.cm^{-3}$. Mandelic acid is bactericidal in urine at a concentration of 5 $mg.cm^{-3}$ (Rosenheim, 1935). Further research needs to be performed to determine: (i) the minimum concentration at which it would be effective for preventing encrustation, (ii) methods for increasing the diffusion rate, and (iii) methods for increasing the concentration of mandelic acid in the balloon. Also, there are many other potentially useful antimicrobial agents whose diffusion properties have yet to be investigated. Release through a membrane can also be achieved when drugs are encapsulated into micelles or reversed micelles (Juni *et al.*, 1978).

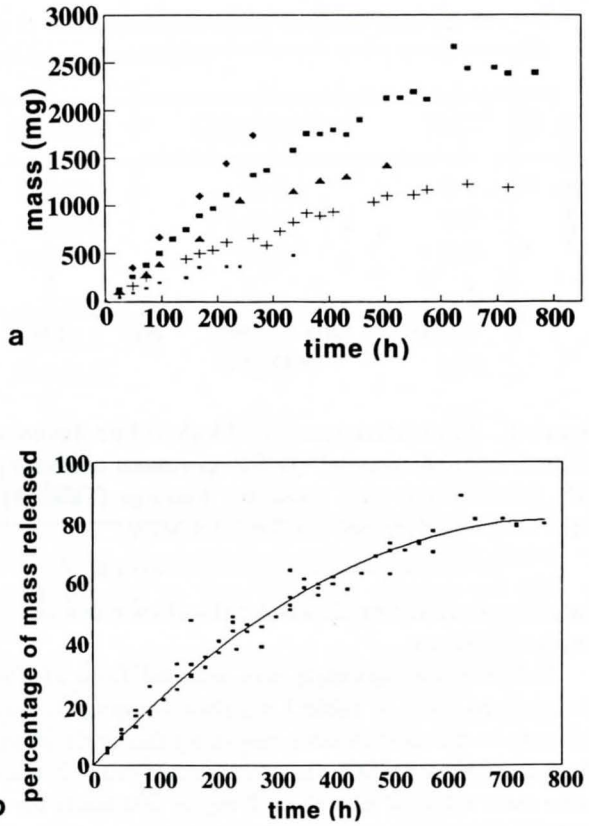

Figure 7. (a) Cumulative mass of mandelic acid released from a silicone retention balloon filled with solutions of concentration: 0.125 (diamonds), 0.100 (large squares), 0.075 (triangles), 0.050 (crosses) and 0.025 (small squares) $g.cm^{-3}$. (b) When the results for all concentrations are expressed as a percentage of the mass of mandelic acid available for release, they lie on the same smooth curve.

Conclusions

There do not appear to be any satisfactory chemical methods for preventing catheter encrustation. Although acidic bladder washout solutions may be helpful for removing encrusting deposits, once they have formed (Getliffe, 1994), acidification of the urine cannot prevent encrustation (Bibby and Hukins, 1993). The reason is that the effect of adding acid is rapidly reversed by the enzyme urease, produced by the bacteria which colonize the catheter surface. It is the reactions which are catalysed by urease (Fig. 2) which are responsible for encrustation in the first place. Urease inhibitors which are presently available have side effects that make them unsuitable for routine administration (Burns and Gauthier, 1984). However, if a safe and effective urease inhibitor could be developed, it might have considerable potential for preventing encrustation. Proteolytic enzymes, especially proteinase k, can digest urease. Although there is extracellular urease in infected urine, as a result of bacterial cell lysis, intracellular urease may also be important (Griffith *et al.*, 1973). Enzymes could be immobilised on the catheter surface to digest the extracellular urease, but it is difficult to devise a method to digest intracellular urease. One possibility is to also immobilise an enzyme which digests bacterial cell walls to the catheter surface. However, this possibility has not been seriously investigated.

Smooth catheter surfaces are less likely to be encrusted than rough surfaces. However, some encrustation occurs on the smoothest surfaces currently available (Cox *et al.*, 1988, 1989b). Thus, smooth surfaces, e.g., those of all-silicone or hydrogel-coated latex catheters, are beneficial but cannot prevent encrustation completely.

The most promising approach to preventing encrustation is to prevent the catheter from being colonized by the bacteria which are ultimately responsible for the problem. Controlled release of antimicrobial agents would ensure that they targeted the site of infection and is expected to be more effective than intermittent application. In any case, application of antibiotic bladder washout solutions breaks the closed drainage system, and so, could lead to renewed infection (Kirk *et al.*, 1979; Warren *et al.*, 1978). Preliminary experiments show that controlled release is feasible. However, it has yet to be determined whether it can deliver concentrations of antimicrobial agents which are sufficiently high to prevent encrustation.

Using the retention balloon of the catheter as the reservoir for controlled release has the advantage that no change in the design of the conventional Foley catheter is required. In a patient, the release of antimicrobial agent in the urine could be monitored by periodically determining the concentration remaining in the solution filling the balloon. If it had fallen to an unacceptably low level, it could be replenished without disturbing the catheter. However, further experiments need to be performed to develop suitable solutions.

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Discussion with Reviewers

K.A. Getliffe: Urinary catheters have been manufactured with a range of coatings designed to combat catheter-associated infection and/or encrustation. Where success has been demonstrated, it tends to be in the short-term only. It seems likely that this may be due to deposition of proteins from body fluids on the catheter surface where they then mask the specially applied coating. What are your views on this?

R.J.C. McLean: Throughout this paper, considerable attention is given to the properties of catheter surfaces and their influence on bacterial and crystal adhesion. One must consider that in a dirty system such as the urinary tract, any surface will encounter urine components and may, thus, acquire a conditioning film of macromolecules (Reid *et al.*, 1992). Such a film will mask the underlying surface and interfere with any crystal-preventing properties that it has.

Authors: This problem is likely to occur when films of proteins, polysaccharides or other organic deposits are formed on the catheter. Ideally, one would wish to develop a surface coating with a sufficiently low surface energy to inhibit the adhesion of these deposits. Thus, we are concerned to minimize the adhesion of all foreign substances, including macromolecules as well as inorganic crystals and bacteria. Note also that a smooth surface coating on the catheter will cover inhomogeneities in the bulk material which might otherwise act as nucleation sites for crystallization of struvite or hydroxyapatite.

K.A. Getliffe: There is some evidence, from animal studies, that acidic solutions disrupt the mucus layer lining the bladder mucosa. Would continuous slow release of mandelic acid from the catheter balloon present an unacceptable risk of damage to the bladder tissue?

Authors: The answer to this question depends on how the pH of the urine affects disruption of the mucus layer and would have to be answered experimentally. However, there are two important points to note. One is that infected urine may have an abnormally high pH value so that acidification would not then be expected to have an adverse effect. The problem of damage by acidification could then be overcome by filling the balloon with an acid solution only when the urine showed signs of elevated pH. The other point is that intermittent acidification with bladder wash-out solutions is likely to lead to much lower pH values, if it is to be effective in removing encrusting deposits, than those arising from gradual controlled release of mandelic acid.

D.J. Stickler: There are reports in the literature of the poor activity of chlorhexidine against *Proteus mirabilis* in urine (e.g., Stickler *et al.*, 1987). Dance *et al.* (1987) also reported a large outbreak of urinary tract infections by a chlorhexidine resistant strain of *Proteus mirabilis* in catheterized patients in a hospital where the catheter care policy involved the extensive use of chlorhexidine. It seems to me that the release of this antiseptic from catheters, as suggested by the authors, could

be counter productive and select for precisely the species that produces the problem of encrustation. Would the authors please comment on this possibility?

Authors: Chlorhexidine was chosen to test the feasibility of controlled release of an antimicrobial agent from a catheter. The reason for this choice was that it has been claimed to reduce infection on catheters, is a component of some bladder wash-out solutions and can be released from a range of solid matrices, as described in the text. However, we did not wish to imply that it was the most suitable antimicrobial agent for preventing infection by *Proteus mirabilis*. Resistance and related problems are important considerations, as we outlined in the main text. The references cited by the reviewer imply that an alternative agent should be used in further studies of controlled release.

D.J. Stickler: How does mandelic acid pass from the catheter balloon into the urine? Could the authors comment on the nature of the chemical agents that are likely to be able to diffuse in this way?

Authors: We believe that the mechanism is diffusion through the material of the balloon. Therefore, we would expect that the diffusion rate would be greater for low molecular weight compounds with hydrophobic groups which would improve their miscibility with the balloon material. Oil soluble dyes, such as Sudan IV, can diffuse through a silicone membrane whilst methylene blue, a water soluble dye, cannot (Chien, 1980). Preliminary studies on diffusion through catheter balloons showed that molecular weight (in the range 36-898) did not limit the ability of a substance to diffuse, although it may have influenced the rate of diffusion (Bibby, 1992). The most important factor was whether the substance had some hydrophobic nature. For example, oil red O, a large hydrophobic molecule (molecular weight, 408), was found to diffuse through the membrane, while hydrochloric acid did not.

D.J. Stickler: What concentrations of mandelic acid were achieved in the bladder when artificial urine was used as an alternative to distilled water? Have you used human urine in these experiments?

Authors: Substituting artificial urine for distilled water made no appreciable difference to the results presented in Figure 7a. It is important to note that these results cannot be directly related to mandelic acid concentration in the bladder because experiments were performed under sink conditions, i.e., the liquid was changed whenever the mandelic acid concentration exceeded a value of 0.016 $g.cm^{-3}$. The reasons for this experimental design are given in the text. We have not used human urine because its composition is not constant, and, therefore, its use introduces a hidden variable into the design of the experiment.

R.J.C. McLean: It has been our experience that catheter surfaces become colonized quite rapidly by biofilm-forming bacteria. Any adhesion of a microorganism or its surface region, e.g., capsule, will alter and influence catheter chemistry. When growing as biofilms, bacteria can create microenvironments in their immediate vicinity which can be chemically quite different from the bulk urine environment (McLean *et al.*, 1991). In addition, surface polymers of bacteria can also influence struvite crystal growth (Clapham *et al.*, 1990; Dumanski *et al.*, 1994). While catheter chemistry is important in controlling mineralization, it needs to be addressed in context with other chemical and biological features.

Authors: This supports our conclusion that the most promising approach to preventing encrustation is to prevent the catheter from being colonized by the bacteria which are ultimately responsible for the problem.

R.J.C. McLean: Do the authors have any information on the physical structure of the catheter surface as it directly pertains to nucleation of struvite and/or hydroxyapatite (i.e., do different catheter materials promote or inhibit mineral growth)?

Authors: We are not aware of any materials suitable for coating the surface of catheters which inhibit growth of mineral crystals. However, a smooth surface is less likely to provide nucleation sites for crystallization than a rougher surface. Scanning electron micrographs of silicone catheters encrusted *in vitro* show struvite crystallizing at the intersection of surface ripples with hydroxyapatite deposits between the crystals of struvite (Cox, 1988). However, during an *in vitro* test lasting for 11 weeks, there was no significant difference between the mass of mineral deposited on hydrogel-coated latex, latex coated with silicone elastomer and all-silicone catheters (Cox *et al.*, 1989b).

R.J.C. McLean: The data pertaining to the kinetics of antibiotic release from catheters is interesting. Have the authors tested any of these?

Authors: We have not tested any of these ideas on systems containing bacteria. Optimizing the system being used could well prove to be an important part of any such testing programme.

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