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BIOMATERIALS ASSOCIATED INFECTIONS: THE SCALE OF THE PROBLEM

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Abstract

The biomaterials used in the manufacture of implanted prosthetic devices profoundly impair the host's ability to opsonise and phagocytose invading microbes. As a result, while these devices generally provide effective relief from painful, crippling and life-threatening disorders, they can also induce vulnerability to infection in the recipients. The surfaces of the implants are susceptible to colonisation by microbial biofilms. The cells in the biofilms are further protected against opsonophagocytosis and are also resistant to antibacterials. Device associated infections thus tend to be refractile to antibiotic therapy and in many cases the device has to be removed before the infection will respond to treatment. Infection rates per implantation operation in totally implanted devices, such as, artificial hips and knees, have fallen over the years to 1-2%. Devices that are partly implanted into body cavities or pass transcutaneously into tissues are particularly susceptible to infection. For example, infection rates of 2.3-4 5% have been reported for central line vascular catheters. The incidence of infection is related to the length of time the device is in place. Infection rates for urethral catheters indwelling for more than 28 days approach 100%.

While several ingenious approaches are currently being taken to modify the surfaces of biomaterials, it has not yet proved possible to reduce the deleterious effects on the host or frustrate the surface colonisation mechanisms that microbes have evolved as a basic survival strategy in natural aquatic habitats.

Key Words: Biomaterials, prosthetic device associated infections, bacterial biofilms, nosocomial infections.

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Introduction

The prosthetic devices available to modern medicine provide effective relief from a range of painful, crippling and life-threatening disorders. Some, such as, artificial heart valves and haemodialysis shunts, have become essential for the survival of many patients, others, such as, prosthetic joints, enable patients to regain the ability to perform important physical activities. Artificial devices have been successfully developed and incorporated into nearly all of the body systems and the numbers of patients receiving implants continues to increase. In Wales, for example, a small country with a population of 2 million, from 1989-1994 some 22,000 artificial joints, 4,000 cardiac pacemakers, and 1,500 prosthetic heart valves have been implanted (Fig. 1). Many more patients of course, have undergone vascular or bladder catheterisation. There is no doubt that prostheses have both prolonged and improved the quality of life for millions of individuals.

In the wake of this progress has come the problem of device associated infection, which now accounts for a substantial proportion of the infections acquired in hospitals and other health care facilities. Unfortunately, the biomaterials used in the manufacture of the devices, synthetic polymers, metals and ceramics are vulnerable to colonisation by microorganisms. Contamination can occur during the implantation of the device or later on during its working life and the resulting infections are capable of inducing chronic inflammation, tissue necrosis or even life-threatening septicaemia. Infection of a device can thus transform a substantial health gain into a catastrophe. In addition to the devastating effect of these complications on the individual patients, the costs of the medical care of patients with infected devices are enormous. Sugarman and Young (1989) for example, calculated that the hospital care costs for the treatment of infected joint prostheses in the USA in 1988 was well over $100 million. The scale of the morbidity and mortality together with the costs of treatment, thus provide a strong incentive to prevent these infections.

In the normal healthy individual, the host defences

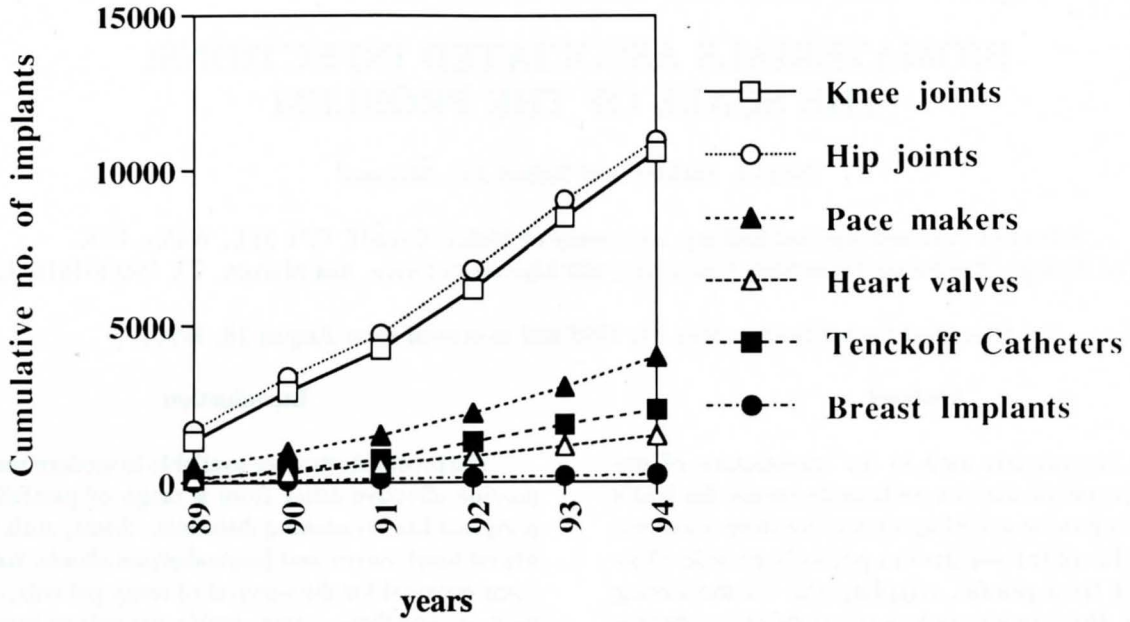

Figure 1. The number of prosthetic devices implanted in patients in Wales over the period 1989-1994; data from the Welsh Health Common Services Authority.

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against infection usually ensure that microbial contamination of tissues and body fluids is rapidly eliminated. The presence of an implanted device, however, seems to reduce the effectiveness of host defence systems so that the numbers of organisms of pathogenic species required to initiate infection is reduced and "non-pathogenic" species such as coagulase negative staphylococci are able to establish infections (Christensen *et al.*, 1989). The colonisation of the devices has profound effects on the phenotypes of the invading microbes, enhancing both their virulence and their ability to resist antibacterial agents. As a result, chronic infections develop and persist despite antibiotic therapy. In many cases, the device has to be removed before infection will respond to therapy (Gristina *et al.*, 1993).

The Effect of Biomaterials on the Host Defence Mechanisms

It is a general observation that implanted devices can provoke chronic localized inflammation which cripples the ability of the host to opsonise and phagocytose contaminating bacteria (Christensen *et al.*, 1989). Shortly after implantation, prosthetic devices attract populations of neutrophils and macrophages. Tang and Eaton (1994) observed that discs of polyester terephthalate preincubated with plasma, attracted phagocytes when implanted intraperitoneally in mice. Precoating the discs with the predominant plasma protein albumin, however, inhibited phagocyte recruitment. The active factor in plasma proved to be fibrinogen. Discs implanted into hypofibrinogenemic mice failed to attract the inflammatory cells unless they were precoated with fibrinogen.

Polymorphonuclear leukocytes (PMNs), that have been in contact with implants, have significantly lower bactericidal activity than PMNs from inflammatory exudates and peripheral blood (Zimmerli *et al.*, 1982). Gristina *et al.* (1993) investigated the effects of polymethylmethacrylate (PMMA) on the antimicrobial oxidative responses of rabbit alveolar macrophages. Contact of the macrophages with PMMA spheres for three hours induced a slow burst of oxidative activity. When these macrophages were subsequently challenged, they were unable to mount a response. Studies using perforated cylinders of PMMA or Teflon implanted subcutaneously into guinea pigs have revealed that contact with the foreign body rapidly (within 6 hours) impairs the PMN oxygen-dependent killing mechanism and causes premature degranulation (Vaudaux *et al.*, 1994). In these early stages, the complement mediated opsonic activity of fluid from the cylinders was adequate, but, after 6 hours contact, it became substantially reduced. It seems therefore that the sequential impairment of the phagocytes, followed by the inhibition of bacterial opsonisation, ensures that opsonophagocytic activity cannot be performed in full in the vicinity of the device at any time after implantation (Vaudaux *et al.*, 1994).

The accumulation of phagocytic cells around devices and their subsequent premature activation and degranulation as they attempt to digest the implant, causes the release of oxidants and degradative enzymes which can damage the biomaterial (Sutherland *et al.*, 1993) and adversely effect the tissue surrounding the device, particularly, in large implants, such as, mammary prostheses (Nelson, 1981).

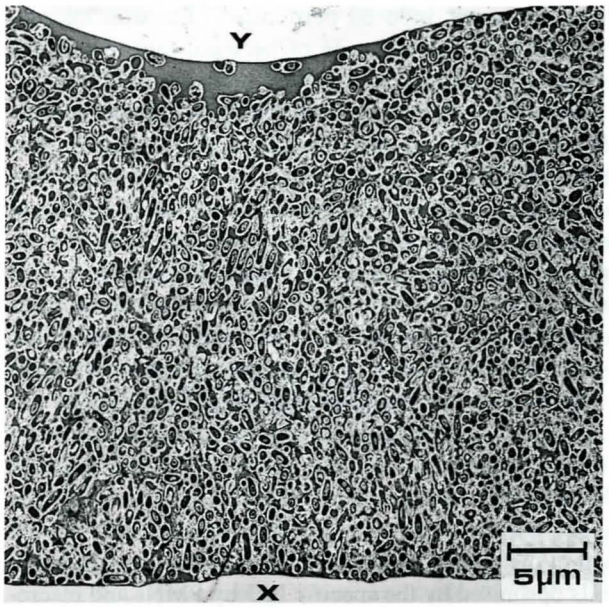

Figure 2. A transmission electron micrograph of a section through a *Pseudomonas aeruginosa* biofilm growing on a urethral catheter. X indicates the edge of the biofilm adjacent to the internal surface of the silicone catheter. Y is the boundary of the biofilm facing the central lumen of the catheter.

The Microbial Colonisation of Biomaterials

The biomaterials used in prosthetic devices have been chosen because their mechanical properties allow them to perform the required function without causing trauma to the surrounding tissues. They are not inert, however, and their surfaces are capable of physical, chemical and biological interactions that facilitate their colonisation by microbes. The geometry of the surface can also induce attachment and cells can become trapped in any surface irregularities (Cheesborough *et al.*, 1985).

Soon after implantation, all biomaterials become coated with glycoproteins from body fluids (Costerton *et al.*, 1987). These conditioning films are formed by proteins such as fibronectin, fibrinogen, vitronectin, laminin and collagen (Vaudaux *et al.*, 1984; Herrman *et al.*, 1988). They then provide receptor sites for the attachment of bacteria. Ohkawa *et al.* (1990), for example, examined the surfaces of Foley urethral catheters and observed the presence of fibrous material which reacted specifically with antihuman fibrinogen fluorescent conjugate. They concluded that the material originated from host tissues injured by the catheterisation process and suggested that it acted as a "glueing substance" trapping bacteria and crystalline material from the urine. Busscher *et al.* (1991) showed that fibronectin formed discontinuous films on biomaterials and speculated that the uncoated surfaces can also provide attractive sites for microbial attachment. Gristina *et al.* (1993) exposed PMMA and teflon to physiological concentrations of human serum albumin and fibronectin. Immunostaining with protein A-gold conjugate revealed that both these proteins had pooled and formed irregular deposits on the polymer surfaces. Observations on titanium implants, however, suggest that host proteoglycans form continuous surface conditioning films (Albrektsson, 1985).

Microbial cells arriving near the implanted surface by direct contamination, transcutaneous spread, or by seeding from infected fluids flowing over the device, are drawn near to the surfaces by forces such as hydrophobic interaction and electrostatic attraction. Attachment to the surface is then consolidated through specific interactions between receptors in the conditioning film and structures, such as, fimbriae and the extracellular polysaccharides of the cell capsule or glycocalyx that protrude on the cell surface (Gristina, 1987).

Staphylococci are particularly important causes of device associated infections, they have surface adhesins which specifically recognize and bind to receptors on serum and tissue fluid proteins. Fibronectin, a large soluble glycoprotein, known to rapidly coat foreign bodies, is a particularly good receptor for *Staphylococcus aureus* (Vaudaux *et al.*, 1984, 1985a) and possibly coagulase negative staphylococci (Christensen *et al.*, 1989). *S. aureus* will also attach itself to surfaces coated with fibrinogen, laminin, vitronectin and fibrinogen (Christensen *et al.*, 1989; Espersen *et al.*, 1990).

Once anchored on the surface of the biomaterial and bathed in tissue fluids, microbes are capable of multiplication and microcolonies of cells develop. Many species are capable of synthesizing extracellular polysaccharides which enclose the clumps of cells in slime. It is significant that *Pseudomonas aeruginosa* and coagulase negative staphylococci, two of the organisms most commonly associated with device associated infections, are noted for their ability to produce these slimes (Christensen *et al.*, 1989; Sutherland, 1995). Scanning electron microscopy has been particularly useful in detecting the colonisation of devices. Direct examination of various prostheses removed from patients have revealed that the extent of microbial contamination ranges from patchy colonisation by microcolonies of cells one or a few cells deep (Elliott, 1988), to confluent layers or "biofilms" up to 1 mm in thickness, and 400-500 cells deep (Ganderton *et al.*, 1992; Stickler *et al.*, 1993a). In some situations, large populations of host cells also become associated with the microbial communities (Ward *et al.*, 1992). Figure 2 shows a transmission electron micrograph of a section through a *Ps. aeruginosa* biofilm colonising the luminal surface of a urethral catheter.

Christensen *et al.* (1994) reviewed the sequential process by which coagulase negative staphylococci colonise medical devices. They concluded that after the cells have been brought into contact with the device by non-specific physicochemical forces, the attachment is promoted by the unavoidable presence of what they call "unique sites" on the surface of the biomaterial. These unique sites may be local variations in surface hydrophobicity, surface irregularities, or the presence of host proteins adsorbed onto the surface of the device. The rare staphylococci that attach to the surface at these sites then proceed to produce extracellular slime. This polysaccharide slime stabilizes cell to surface and cell to cell associations, spreads over the surface, and facilitates the progressive colonisation of the device.

The Properties of Bacterial Biofilms on Biomaterials

The clinical manifestations of biomaterial-associated infection can vary from fulminant sepsis to low grade recurrent fevers and chronic local inflammation. The clinical experience with these device-related infections has been that while antibiotic therapy may control the exacerbations, the chronic infections will generally not resolve until the device is removed. Another common feature, even in immunocompetent individuals, is the failure of the host defence mechanisms to clear the infection. These characteristics stem in part from the inherent properties of bacteria growing as surface colonising biofilms (Finch, 1994).

There is evidence that bacteria in biofilms on the surfaces of implanted devices are protected from host defence mechanisms (Jansen and Peters, 1993). Attachment of *S. aureus* cells to PMMA, for example, has been shown to reduce their susceptibility to killing by fully effective PMNs (Vaudaux *et al.*, 1985b). Johnson *et al.* (1986) demonstrated that the ability of PMNs to phagocytose and kill *Staphylococcus epidermidis* colonising a plastic surface was impaired by the copious extracellular slime produced by this organism. Jensen *et al.* (1990) used a chemiluminescence assay to examine the oxidative burst response of human PMNs against biofilms of *Ps. aeruginosa* that had been grown on silicone discs for 24 hours. They found that the response was slow and only 25% of that produced against planktonic cells of the same test organism.

Ward *et al.* (1992) examined the ability of rabbits to clear intraperitoneal *Ps. aeruginosa* in the presence and absence of a surgically implanted device consisting of Silastic discs on a Teflon rod. In the absence of the implant, an inoculum of 5×10^6 organisms was eliminated from the peritoneal fluid and tissues within 96 hours. The same inoculum in the presence of the implant, however, induced peritonitis. Electron microscopy revealed the presence of bacterial biofilms on the implanted discs and, at 96 hours, more than 10^6 per cm^2 bacteria were recovered from the discs. Bacteria were also recovered from peritoneal fluid after 96 hours. Examination of discs pre-colonised by 10^4 cells/cm^2 after implantation for up to 42 days showed that the adhered organisms had successfully colonised the discs and established biofilms containing 10^7 viable cells/cm^2. The same extent of biofilm development occurred on discs implanted into animals that had been pre-immunised against the test strain of *Ps. aeruginosa* and were shown to have developed high titres of IgG, specific to the test organism. The defences of the peritoneal cavity were clearly undermined by the presence of the implant. Ward *et al.* (1992) suggested that the specific antibodies might not be able to reach the bacterial cells buried within the matrix of the biofilm or that phagocytosis of cells opsonised by the specific IgG by PMNs and macrophages is impaired.

In vitro studies and observations made on colonised devices removed from patients, point to the remarkable resistance of cells in biofilms to antibacterial agents. For example, Gristina *et al.* (1988) found viable biofilm cells colonising a total artificial heart from a patient who had been treated with the maximum tolerable doses of modern antibiotics for extended periods of time (Kunin *et al.*, 1988). Ganderton *et al.* (1992) observed that the luminal surfaces at an indwelling urethral catheter removed from a patient who was being treated with gentamicin was covered in a substantial biofilm some 180 μm thick composed of a viable community (10^8 cfu/cm^2) of *Ps. aeruginosa*, *Providencia stuartii* and *Proteus mirabilis*. Conventional antibiotic sensitivity tests revealed that all the strains were gentamicin sensitive.

Nickel *et al.* (1985a) examined the sensitivity of a strain of *Ps. aeruginosa* growing on discs of latex catheter material to tobramycin. They found that whereas the antibiotic at 50 mg/l completely killed the population of planktonic cells taken from the test system, biofilm populations of 2×10^8 cfu/cm^2 were only reduced to 6×10^6 cfu/cm^2 on 12 hours exposure to 1,000 mg/l. Anwar *et al.* (1989) showed that *Ps. aeruginosa* grown on acrylic tiles for seven days in a chemostat, survived for up to 6 hours in tobramycin at 50 mg/l whereas 5 mg/l was markedly bactericidal to plankton suspensions of the same strain within 2 hours. Pascual *et al.* (1993) reported that attachment of *Ps. aeruginosa* to segments of siliconised latex urinary catheters increased the minimal bactericidal concentrations (MBCs) of amikacin 8-fold, ceftazidime 64-fold, ciprofloxacin 64-fold, and meropenen 2048-fold. They also presented evidence that the catheter material itself reduced the activity of amikacin and meropenem.

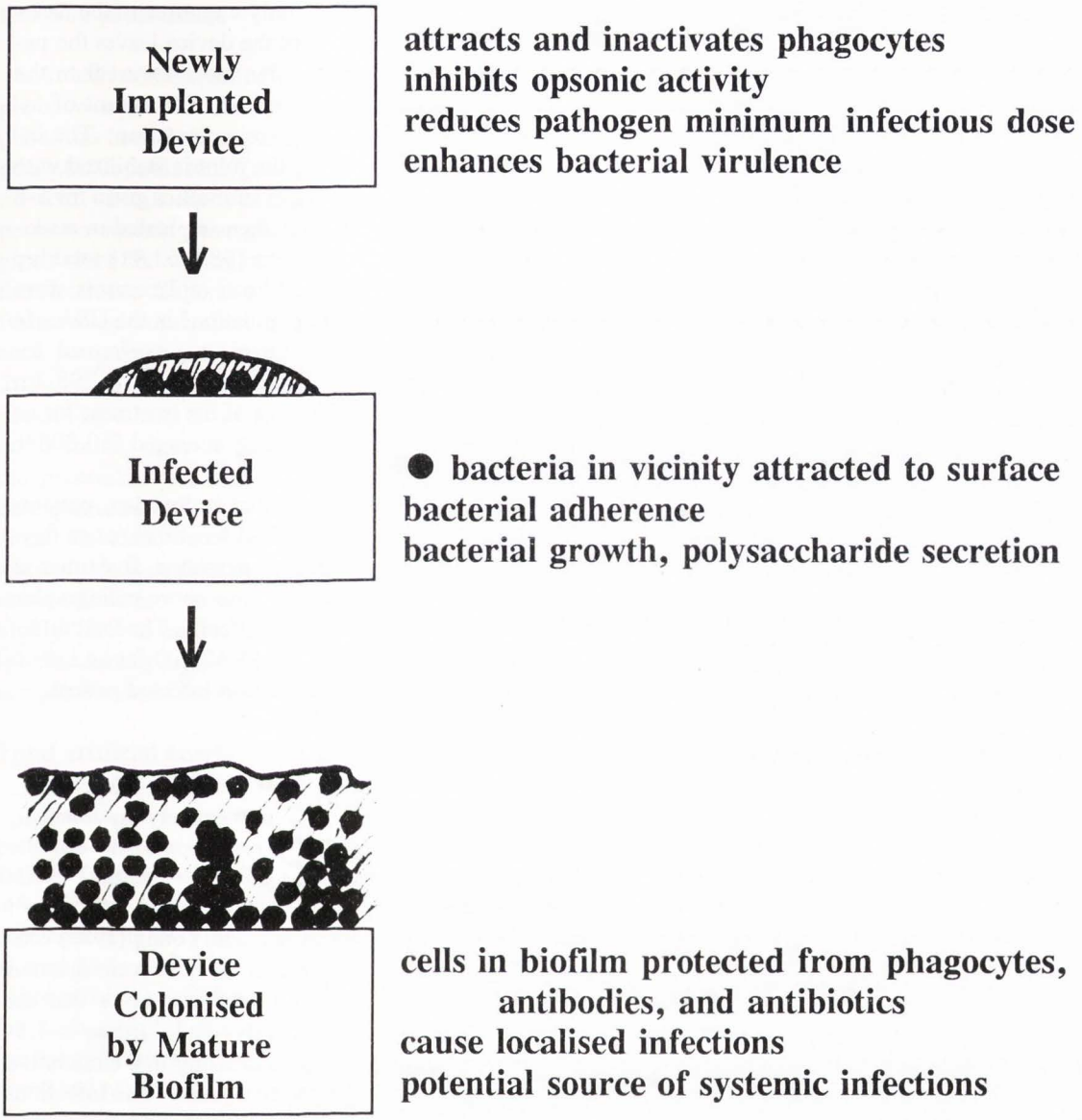

Figure 3. A summary of the effects of an implanted prosthetic device on host defence systems and of the consequences of prosthesis colonisation by biofilm.

Nafcillin-sensitive coagulase negative staphylococci that had colonised polyvinylchloride catheters for up to 24 hours, were able to survive exposure to bactericidal concentrations of the drug (Sheth *et al.*, 1985). This effect was particularly marked with slime producing strains. Evans and Holmes (1987) developed biofilms of *S. epidermidis* on discs of silicone elastomer. The test strain had an MBC for vancomycin of 6.25 mg/l but cells that had grown on the discs for 72 hours survived continuous exposure to 25 mg/l for up to 10 days. Gristina *et al.* (1989) examined the sensitivity of coagulase negative staphylococci adherent to stainless steel, polyethylene, and PMMA. They found that the MBC of adherent cells were 4-fold greater for vancomycin and up to 32-fold greater for gentamicin. Naylor *et al.* (1990) reported that the adherence of strains of both coagulase positive and negative staphylococci to various biomaterials enhanced their resistance to nafcillin, daptomycin, vancomycin and gentamicin. The effect was not dependent on slime production but was related to the type of material, being more pronounced on PMMA than on stainless steel. Figure 3 is a diagram summarizing the effects of an implanted device on host defence systems and the consequences of biofilm formation on protheses.

Specific Prosthetic Device Infections

Device associated infections may be severe or silent depending on factors, such as, the location and depth of implantation, nature of the surrounding tissue, the virulence of the infecting organism, and the immuno-competence of the individual. Infection is a relatively rare complication of the totally implanted devices, it is however, much more prevalent in those devices that are only partially inserted into tissues or body cavities.

Joint implants

The replacement of joints destroyed by arthritis or injury is now performed routinely worldwide. Hip, knee, shoulder, and elbow joints are regularly reconstructed with artificial devices. In the surgical procedure for hip joints, the acetabulum is enlarged and a high density polyethylene cup, sometimes with a metal backing is fitted into the new cavity. The femoral head is replaced by a smaller metal or ceramic sphere attached to a stern which is then located in the medullary canal of the femur. The devices are cemented to the skeleton using methylmethacrylate or by a layer of hydroxyapatite. Prosthetic knee joints are constructed from the same materials.

Infection has been the major cause of failure of these devices. Infection rates per hip implantation operation have reduced from about 6.8% in the 1960s to about 1% by the 1990s (Kaplan and Wilson, 1994). Knee and elbow replacement has slightly higher risks of infection, reported rates being 2% and 6-9%, respectively (Fitzgerald, 1989; Huo and Sculco, 1990). Contamination of the artificial joints usually takes place during surgery or from superficial perioperative wound infection that progresses to the device. Some infections present longer than 24 months after surgery with the onset of acute joint pain. These are believed to be subsequent to episodes of bacteraemia from other sources such as dental, genito-urinary procedures, or abdominal surgery (Dickinson and Bisno, 1993).

Sanderson (1991) and Karchmer (1992) have reviewed the microbiology of infected hip, knee and elbow infections. *S. aureus* and coagulase-negative staphylococci were by far the most commonly isolated organisms, followed by streptococci, *Pseudomonas* species, *Escherichia coli*, *Proteus sp.*, and obligate anaerobes, such as, *Bacteroides* and peptococci.

The clinical manifestations of artificial joint infections range from pain and loosening of the prosthesis, to acute inflammation, swelling and fever (Kaplan and Wilson, 1994). Treatment of these infections is difficult and costly. Antibiotic suppression is used for patients who are poor risks for surgery. The results are disappointing, being successful in only a quarter of the cases (Rand, 1993). The removal of the device leaves the patient with physical disability often more severe than the original. The most popular method of treatment of infected prosthesis is a two stage reimplantation. The infected prosthesis is removed, the joint is stabilized with a cement spacer and intravenous antibiotics given for 5-6 weeks. The new prosthesis is then implanted in a second operation (Wilde, 1994). In 1989, 62,918 total hip replacements and 80,647 total knee replacements were performed in the "Medicare population" in the USA. In the same year, 1,395 procedures were performed for removal of infected total hip implants and 1,795 for infected knee implants. The cost of the treatment for an infected total hip in New York City averaged $50,000 to $60,000 (Wilde, 1994).

Bengtson (1993) reported that in Sweden, patients with infected knee prostheses had ten times more days in hospital, three times as many operations, five times as many outpatient visits, and four times more radiographic examinations than non-infected patients. The total direct costs at 1991 prices averaged US$ 62,100 for an infected patient and US$ 8,600 for a non-infected patient.

Prosthetic heart valves

About 40 different types of prosthetic heart valves are available for use, some are entirely mechanical, manufactured from metal alloys, carbons, and durable plastics, others are made up of tissue but do include metallic struts or rings for structural support (Wellford and Wellford, 1994). Sugarman and Young (1989) estimated that some 120,000 of these devices were inserted worldwide in 1986. Actuarial analysis shows that the cumulative rate of prosthetic valve endocarditis is 1.5-3.0% one year after surgery, increasing to a cumulative rate of 3.2-5.7% after four to five years. The infections induce valve disfunction, regurgitant blood flow, persistent bacteraemia, and fever. They are highly invasive conditions and can progress to myocardial abscess and annulus infection. The infections are refractile to treatment with prolonged bactericidal agents and valve replacement surgery is required to eliminate infection and restore effective valve function in 50-65% of cases. A recent prospective multi-centre study of prosthetic valve endocarditis in 74 patients revealed 46% mortality at six months. Surgical replacement of the infected valve reduced mortality rates to 23% compared to 56% in patients who received medical therapy alone (Yu *et al.*, 1994). Karchmer (1992) reported that while a wide range of microbes from fungi to mycobacteria, *Legionella*, *Listeria* and mycoplasmas have been isolated from the artificial heart valves, staphylococci, particularly coagulase negative strains, were predominantly responsible for the infections.

Cardiac pacemakers

It has been estimated that more than a million people have implanted cardiac pacemakers. Infectious complications have been reported to occur in up to 15% of patients (Coppola and Yealy, 1994). The infections can involve various sites along the device including the pocket containing the generator, the subcutaneous regions along the wiring, and the cardiac tissue alongside the electrode. Generator pocket infections usually result from wound contamination at surgery. Patients experience pain, erythema and swelling at the generator site. *S. aureus* is responsible for about 70% of the infections presenting within 2 weeks of surgery, while *S. epidermidis* causes most of the later infections. Infection of the pacemaker wires and electrodes can be caused by contiguous spread from an infected generator pocket, from the skin, or from bacteraemia with a distant source. Endocarditis and septicaemia can develop from these infections. As conservative antibiotic treatment is highly likely to fail and exposes the patient to the risk of life threatening septicaemia, the recommended approach is replacement of the entire apparatus (Karchmer, 1992).

Total artificial hearts

The initial experience with total artificial hearts as permanent cardiac replacements was an infection rate of 100% (Kunin *et al.*, 1988). Since then, the incidence of infection has declined, particularly in short-term recipients. Burns (1993) reported that infection rates are now around 33%. Infection is the greatest threat to these patients and is one of the most important factors limiting the further exploitation of these devices. The surgical trauma associated with the implantation, the contact with blood and other body fluids, and the transcutaneous penetration of vascular conduits or power transmission systems all contribute to the likelihood of infection. Kunin *et al.* (1988) reported on the infectious complications in four long-term recipients of the Jarvik-7 artificial heart. They found that infections spread along the drive lines to the periprosthetic surfaces. *S. epidermidis*, *Ps. aeruginosa*, *S. aureus* and *Candida* were the common organisms. Once the drive lines became contaminated and bacteraemia was established, it was not possible to eradicate the infections even by intensive therapy with powerful antibiotics. Continued use of the antibiotics was associated with the emergence of resistant organisms. In two cases, intensive therapy temporarily suppressed the infection but eventually all four died of their infections. Post-mortem microbiological examination revealed extensive polymicrobial colonisation of the device and drive lines (Dobbins *et al.*, 1988; Gristina *et al.*, 1988).

Vascular catheters

One of the most common invasive procedures performed in modern medicine is the insertion of catheters into peripheral and central veins and arteries. The catheters are made of synthetic polymers, such as, polyvinylchloride, polyethylene, polyurethane, or silicone. They are used to deliver fluids, medications and nutrients, to perform haemodialysis, plasmaphoresis, and to monitor medications. The majority of medical and surgical in-patients in acute care hospitals will have at least one intravenous line. To try and reduce the risk of infection, these catheters are usually tunnelled partially beneath the skin before they enter the vascular system. Unfortunately, these devices are commonly associated with infections which may be systemic or localized at the site of entry. A multi-national European study of over 10,000 patients reported that bacteraemia developed in 0.4% of patients with peripheral catheters but in 4.5% of patients with central catheters (Nystrom *et al.*, 1983). Estimates of the scale of the problem in the USA range from 50,000-200,000 patients developing systemic sepsis from this source per annum (Maki, 1991; Raad and Sabbagh, 1992). A comprehensive prospective study from Australia (Collignon, 1994) recently revealed that of 4,957 separate episodes of bacteriaemia or fungaemia occurring in 15 hospitals, 809 were identified as intravascular catheter related. The problem was greater with central line catheters, systemic sepsis with peripheral vein catheters occurred with 0.36 of every 1,000 catheters, the equivalent figure for central vein devices was 23 episodes per 1,000 catheters. It was calculated that at least 3,000 cases of intravascular sepsis occurred per year in Australia. In two of the hospitals with well documented follow-up of patients, the associated case fatality rate was 24%. This figure compares with estimates of 20-40% from the USA.

Microbiological and direct microscopic studies have indicated that microbes from the patient's skin flora at the site of insertion can migrate along the outer surface of the catheter (Elliott, 1988; Bjornson, 1993). An important route of contamination is the inside surface of the catheter hub resulting in colonisation of the catheter lumen and tip (Maki *et al.*, 1977; Cooper and Hopkins, 1985; Fan *et al.*, 1988). Organisms can also contaminate the catheter tip at the time of insertion. Haematogenous contamination of the intra-vascular part of the catheter can also occur during bouts of transient bacteraemia secondary to a distant focus of infection (Bjornson, 1993). Contamination of infusion fluids can also occasionally produce infection (Elliott, 1988).

Using scanning electron microscopy, Passeroni *et al.* (1992) observed that extensive bacterial biofilm formation was common even on catheters that had been in

place for only 24 hours. A variety of microbial species are involved in catheter related sepsis. Collignon (1994), for example, reported that the most commonly isolated organisms were *S. aureus* (38%), coagulase negative staphylococci (27.5%), *Klebsiella* spp. (4.8%), *Candida albicans* (4.8%), and *Pseudomonas* spp. (3.6%). Elliot and Faroqui (1992) examined 156 infected catheters and found that the organisms most commonly colonising catheters were coagulase negative staphylococci (60%), *S. aureus* (14%), *Ps. aeruginosa*, *Enterococcus faecalis*, coliforms and *Candida* being amongst the other organisms isolated. The incidence of infectious complications is related to the length of time the catheter is *in situ* (Elliott, 1988). The clinical consequences of vascular catheter associated infections range in severity from local inflammation and discomfort at the skin site of entry to septicaemia. Eighty-two percent of 2,073 cases of bacteraemia occurring in the Center for Disease Control's National Nosocomial Infection Surveillance study, were found to be associated with intravenous catheters (Dickinson and Bisno, 1993).

The treatment recommended for catheter associated infections depends on a number of important considerations, including the nature of the organism recovered from the catheter or blood, the status of the patient's host defence mechanisms, the presence of other prosthetic devices, and other conditions such as valvular heart disease or diabetes that would increase the risk of metastatic spread of the infection (Bjornson, 1993; Howell, 1994). *S. aureus* infection of catheters is associated with a high rate of metastatic complications and should be managed by intravenous antistaphylococcal antibiotics for a minimum of 14 days and catheter removal (Raad and Sabbagh, 1992). Bjornson (1993) has pointed out that there is little information about optimal management of catheter infections caused by *S. epidermidis*, Gram-negative bacilli or fungi, his recommendation, however, was, in most cases, to remove the catheter and treat with appropriate antibiotics. In the case of *S. epidermidis* infections in the immuno-competent patient, removal of the catheter was generally effective.

Breast implants

It has been estimated that since the development of silicone gel-filled implants in 1963, one to two million women in America have received breast implants. Some 65% for cosmetic augmentation and 35% for reconstruction after mastectomy for breast cancer (Payne, 1994). Early studies of patients receiving breast implants indicated infection rates in the region of 1-4% (Sugarman and Young, 1989). While a recent study of 54,000 implants performed by 73 plastic surgeons reported infection rate of 0.1% (Brand, 1993), evidence has been presented that about 5% of mammary prostheses are "subclinically" infected with *S. epidermidis* causing chronic pain and movement of the device (Parsons *et al.*, 1993). The most common organisms cultured from "clinically" infected breast implants are *S. aureus* (75%) and *S. epidermidis* (10%). The silicone implant becomes encapsulated by a collagen sheath and infection is believed to contribute to a process of capsular contraction which produces distortion of the implant and disfigurement of the breast (Payne, 1994).

Cerebrospinal shunts

In patients with hydrocephalus, the equilibrium between the production and reabsorption of cerebrospinal fluid (CSF) is disturbed, increasing intracranial pressure and dilating of the ventricles of the brain. The main form of treatment involves the mechanical shunting of the fluid. A silastic catheter is implanted into a surgically created conduit from the ventricle of the brain. There is usually a reservoir and valve in the drainage system to facilitate sampling of the fluid or drainage and pumping. Drainage continues either into the peritoneal cavity or into the central circulation via the jugular vein (Jordan, 1994). It has been estimated that 180,000 CSF shunts are implanted each year worldwide (Sugarman and Young, 1989). The rate of CSF infection ranges from 1-10% (Bisno and Sternau, 1994). Most of the infections present within six weeks of surgery. Staphylococci, particularly coagulase negative strains, are the main problem, but infections can also be produced by Gram-negative bacilli and obligate anaerobes. The clinical manifestations vary from rigorous fever, malaise, and lethargy to meningitis, peritonitis, and endocarditis. The overall mortality associated with these infections is as high as 60%. Antibiotic therapy alone is not as effective as the combination of shunt removal and antibiotics (Jordan, 1994).

Peritoneal dialysis devices

Many patients with end-stage renal disease are treated by continuous ambulatory peritoneal dialysis (CAPD) as an alternative to haemodialysis. The technique involves the surgical implantation of a Tenckoff catheter through the lower abdominal wall. From the cutaneous entry site, the catheter is tunnelled for about 10 cm through the subcutaneous tissues before it enters the peritoneal cavity. It is secured in position by a Dacron cuff placed sub-cutaneously at the entry site and another at the portal of entry in the peritoneal wall. The intraperitoneal end of the catheter lies in the pelvic gutter and its multiple perforations allows the drainage of peritoneal fluid. The instillation and subsequent drainage of dialysis fluid is usually repeated four times a day, seven days a week. CAPD, thus, involves the use of a catheter which traverses the skin and is repeatedly manipulated, putting the patient at risk of infection. Peritonitis is the

most common complication of CAPD. Refinements in the technique have reduced the incidence of infection, even so, the peritonitis rate in CAPD patients is around one episode per 16 patient months (Ludlam, 1991). Symptoms may vary from mild non-specific complaints to severe abdominal pain, nausea, vomiting and fever. Infection of the peritoneum usually occurs by organisms migrating along the transcutaneous catheter track, or through the catheter lumen after a break in sterile technique contaminates the delivery system (Vas, 1994). A variety of bacterial and fungal species have been reported to have caused sporadic cases of CAPD peritonitis, it is clear, however, that 40% of the episodes are caused by coagulase negative staphylococci. *S. aureus* accounts for a further 10-20% of cases. Streptococci, *Pseudomonas*, *E. coli* and other Gram-negative enterobacteria are the other main organisms (Ludlam, 1991; Karchmer, 1992). Scanning electron microscopy (Marrie *et al.*, 1983; Dasgupta *et al.*, 1987) and confocal laser scanning microscopy (Gorman *et al.*, 1993) have confirmed the presence of adherent bacteria embedded in a mucoid matrix on the surfaces of Tenckoff catheters removed from patients. It has been suggested that biofilm contamination of the lumen or surface of the catheters is common and that spread of the biofilm along the catheter can result in peritonitis (Dasgupta *et al.*, 1993). The role of the biofilm in initiating peritonitis has been questioned, however, some workers consider that its presence on the catheter does not necessarily lead to symptomatic infection and that other factors are involved (Vas, 1994). The progression of peritoneal contamination to peritonitis is probably facilitated by the repetitive large volume dilution of immunoglobulins, complement and macrophages that takes place in the peritoneal fluid (Vas, 1994). In light of the difficulties usually associated with the treatment of infected prostheses, antibiotic treatment of CAPD peritonitis is surprisingly successful (Niezgoda and Wolfson, 1994). Ludlam (1991), for example, reported that only 5% of patients treated at the St. Thomas's Hospital CAPD unit were refractory to antibiotics. The conventional management of cases resistant to treatment is to remove the catheter and replace it 1-3 weeks later during which time antibiotics are given to eradicate the infecting organisms before the new catheter is implanted.

Urinary drainage devices

Indwelling urethral catheters, generally made from silicone or silicone coated latex, are used worldwide on an enormous scale to relieve anatomical or neurophysiological obstruction of the urethra, to provide an accurate measure of urinary output from unconscious patients in intensive care units, to promote repair to the urethra after prostatic or gynaecological surgery, and to manage long-term urinary incontinence in the elderly and patients with spinal cord injuries. The prevalence study of Jepsen *et al.* (1982), carried out in eight European countries, reported that 11% of hospital patients were undergoing indwelling bladder catheterisation. Warren *et al.* (1989) reported that in Maryland, 9 4% of women and 6.4% of men in nursing homes were undergoing indwelling urethral catheterisation and a prevalence study in Denmark found that 4.9% of patients in nursing homes and 3.9% of those in home care had indwelling urinary catheters (Zimakoff *et al.*, 1993). These catheters pass from the periurethral skin site, which commonly has a rich microbial flora, into the bladder, and it is inevitable that organisms will gain access via the catheter or its connected tube and bag drainage system to the reservoir of urine maintained in the bladder by the positioning of the catheter. In this excellent growth medium, bacteria contaminating the urine will multiply rapidly. The risk of acquiring an infection increases with time, during the first week of catheterisation, the risk being about 5% per day. Patients undergoing long-term catheterisation (more than 28 days), even with modern closed drainage systems and careful management, will inevitably develop bacteriuria (Kunin, 1987). The numbers of patients undergoing this form of bladder management is so large that catheter associated urinary tract infection is the most common of the hospital acquired infections (Haley *et al.*, 1985).

In early stages of catheterisation, infection is generally by pure cultures of *S. epidermidis*, *Enterococcus faecalis*, *E. coli*, or *Pr. mirabilis* (Bultitude and Eykyn, 1973; Gillespie *et al.*, 1983). The longer the catheter remains *in situ*, the greater the variety of organisms that will appear and the long-term patients become infected with complex mixed communities of mainly Gram-negative nosocomial species. Organisms, such as, *Pv. stuartii*, *Ps. aeruginosa*, *Pr. mirabilis*, and *Klebsiella pneumoniae* are particularly common and persistent (Clayton *et al.*, 1982). These polymicrobial infections are extremely difficult to eliminate with antibiotic therapy while the catheter remains in place (Clayton *et al.*, 1982). It is common practice not to treat these infections until clinical symptoms indicate that the infection has reached the kidneys or the blood stream (Warren, 1994).

Scanning electron microscopy of catheters taken from patients has revealed that they are commonly colonised, particularly on the luminal surfaces, by bacterial biofilms (Nickel *et al.*, 1985b; Ramsay *et al.*, 1989; Ohkawa *et al.*, 1990; Ganderton *et al.*, 1992). Ganderton *et al.* (1992), for example, observed biofilms on 44 of 50 catheters that had been indwelling from 3-83 days. Using a simple freeze-fracturing technique to produce cross-sections of the catheters, it was shown that the

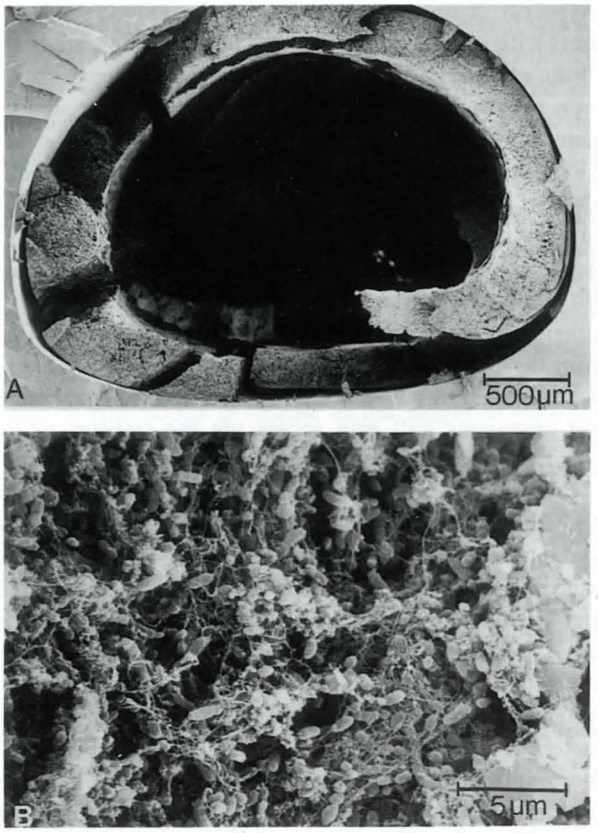

Figure 4. Scanning electron micrographs of a urethral catheter that had been indwelling in the bladder of a patient for six weeks. **(A)** A freeze dried preparation of a freeze-fractured cross-section of the catheter. **(B)** A fixed, critical point dried preparation of the same catheter showing the layers of small bacilli in a fibrous matrix. (From Stickler and Winters, 1994, with permission of the editors).

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biofilms varied in thickness from patchy monolayers of cells to extensive films some 400 cells deep. Scanning electron micrographs of such a biofilm are shown in Figure 4. Even though the sample preparation has produced some shrinkage, it is still 500 μm thick. The biofilm extended along the whole length of the catheter and bacteriological analysis showed it to be a pure culture of *Ps. aeruginosa* (5 x 10^9 cfu/cm^2 of luminal surface area).

There is evidence that the adherent biofilm can creep along the luminal and external surfaces of the catheters and initiate bladder infections (Nickel *et al.*, 1994). The innate resistance of the bacteria in biofilms contributes to the refractility of these infections to both systemic antibiotics and antiseptic bladder instillations (Nickel *et al.*, 1985a; Stickler *et al.*, 1987). Biofilms that contain *Pr. mirabilis* become encrusted with calcium and magnesium salts (Stickler *et al.*, 1993b). This precipitates one of the major complications of long-term catheterisation, blockage of the catheters (Hukins *et al.*, 1983; Getliffe and Mulhall, 1991). These blockages, if not dealt with promptly, can induce painful urinary retention and can lead to pyelonephritis and septicaemia (Kunin, 1987).

Although patients with indwelling bladder catheters are generally asymptomatic, they are at risk from a range of complications which make them more vulnerable than non-catheterised patients. The recent prospective survey by Kunin *et al.* (1992) of 1540 patients in nursing homes in Ohio, clearly demonstrated the significantly higher morbidity and mortality rates in catheterised patients than in matched non-catheterised patients. It was found that in comparison with non-catheterised patients, catheterised patients in nursing homes, whatever their status in relation to age, their ability to perform the activities of daily living, cancer, heart disease, diabetes or skin condition, were three times more likely to receive antibiotics, three times more likely to be hospitalized, and three times more likely to be dead at the end of a year. The specific complications that can afflict these patients include pyelonephritis, bacteraemia, bladder cancer, and kidney and bladder stone formation (Stickler and Zimakoff, 1994).

Bladder drainage via a small catheter introduced through the anterior abdominal wall has been used as an alternative to urethral catheterisation in patients with urethral stricture or fistula (Slade and Gillespie, 1985). It has also been argued that the lower density of bacteria on the abdominal skin will result in a lower incidence of bacteriuria than is associated with urethral catheters (Warren, 1990). Although it has its advocates, suprapubic catheterisation is not as popular as other methods of bladder management. Warren *et al.* (1989) for example, reported that 0.5% of 4,259 elderly patients in nursing homes in Maryland had suprapubic catheters compared to 8.3% of patients with indwelling urethral catheters. The evidence suggests that prolonged drainage by suprapubic catheter is inevitably associated with bacteriuria (Newman and Price, 1977).

Other devices

There are, of course, many other types of prosthetic devices that are subject to bacterial colonisation and infection. The intraocular lenses for example, that are normally inserted at the time of cataract operation can become infected (Scribbick and Scribbick, 1994). While these infections are rare, they can produce serious pathologies and can result in loss of vision (Sugarman and Young, 1989). Silicone rubber voice prostheses are used for voice rehabilitation after laryngectomy. They are implanted into an environment with a rich microbial

flora and rapidly become colonised by microbial biofilms. Leakage of food or liquid and an increase in air flow resistance caused by the biofilm necessitates the replacement of the devices at about four month intervals (Neu *et al.*, 1994). Biliary stents (Sung *et al.*, 1993), extended wear contact lenses (Slusher *et al.*, 1987), a range of genitourinary implants (Shandera and Thompson, 1994) and dental implants (Saadoun *et al.*, 1993) are similarly infected.

Prevention of Biomaterial-Associated Infections

It is clear that the skin organisms *S. aureus* and the coagulase negative staphylococci are by far the most common causes of prosthesis associated infection. Meticulous attention to skin preparation, hand-washing, and use of sterile technique during the insertion and manipulation of devices will reduce the infection rates (Ludlam, 1991; Bjornson, 1993; Maki, 1994). The provision of ultra-clean air in operating theaters has been shown to produce a tenfold reduction of airborne bacterial counts and reduce sepsis rates by half (Lidwell *et al.*, 1987). While the evidence from controlled trials on its efficacy is not conclusive, the use of short term perioperative antibiotic prophylaxis is standard practice for the implantation of prosthetic material (Learmouth 1993; Haas and Kaiser, 1994). Despite all these precautions, infections still occur, and it is clear that the development of a biomaterial which did not compromise host defences and resisted microbial contamination would be a major advance.

Surface modification is the key to improving the biomaterials available for the manufacture of prosthetic devices (Gristina *et al.* 1993). Irradiation techniques have been used to introduce new functional groups at the surfaces of polymeric materials. These modifications have generated altered physicochemical surface properties and altered interactions with proteins and cells. Polyurethanes with more hydrophilic surfaces have been produced, for example, which seem to reduce *S. epidermidis* adherence and preferentially adsorb albumin rather than fibrinogen from plasma (Jansen and Peters, 1991). These sort of modifications might also encourage rapid host cell colonisation and tissue integration which would then provide protection against bacterial contamination for some types of implant (Gristina, 1987).

A second approach has been to incorporate antimicrobial agents into biomaterials. Flucloxacillin for example, has been incorporated into polyurethane and iodine into polyvinyl fluoride (Jansen and Peters, 1991). Surface coatings, such as, benzalkonium chloride on polyurethane (Tebbs and Elliott, 1993) or thin multi-metal films on butyl and silicone rubber (McLean *et al.*, 1993) have also been developed. This general strategy could be neutralised by the shielding effect of the conditioning films that rapidly coat biomaterials *in vivo*. It is also possible that while antibacterial surfaces might kill the pioneering bacterial colonisers, these dead cells and resulting cell debris could provide a foundation for subsequent colonisation shielded from the antimicrobial agent (Stickler *et al.*, 1994).

The recent work of Bayston (1995) suggests that a method for incorporating antibiotics into silicone elastomers (Bayston *et al.*, 1989) has produced an antibacterial biomaterial which is not easily inactivated. Silicone catheters were immersed in a chloroform solution of the antibacterial agent. The chloroform causes the elastomer to expand to 2.5 times its volume, carrying the antibiotic into the matrix of the polymer. Under in-use conditions, the antibacterial is released steadily and slowly over long periods with no deleterious effects on the mechanical properties of the polymer. The ability of these catheters to resist multiple discrete challenges with contaminating bacteria was tested under conditions of constant perfusion. The combination of clinadamycin and rifampicin gave total protection against colonisation by some 24 strains of both coagulase positive and negative staphylococci and corynebacteria over a six week period. This activity remained even when the impregnated catheters had been coated with conditioning film proteins from blood. Clinical trials of these catheters are currently underway. The use of antibiotics in this way, of course, provokes concern about the possible selection of antibiotic resistant strains. Bayston (1995) claims, however, that the release kinetics from these polymers are such that the antibiotics are not detectable in blood or urine on animal implantation, so that selection of resistance is not likely to be a problem. Experience with these materials will no doubt show whether reservations about their use are justified.

Elliott *et al.* (1990) devised a novel means of protecting devices against colonisation using low amperage electric currents. They were able to show that a negative electric current repelled organisms from the surface of a vascular catheter. It was also demonstrated that catheters acting as cathodes, prevented the migration of organisms along both the internal and external surfaces (Crocker *et al.*, 1992). In further experiments, it was established that the electrical currents not only repelled microorganisms but were also bactericidal against *S. epidermidis* already colonising vascular catheters (Liu *et al.*, 1993). This *in vitro* experimentation has of course to be confirmed *in vivo* but it does open up the prospect of a simple physical method for preventing and controlling infection of some types of devices. Another application for electrical energy has been suggested by Costerton *et al.* (1993) who reported that the inherent resistance of biofilm bacteria to antibacterial agents can

be entirely overcome in the presence of a weak electrical field. It is possible that this "bioelectric effect" could also be exploited in the control of device related bacterial infections.

While some of the recent developments in the fight to control prostheses associated infections are encouraging, it is clear that microbes are formidable and highly adaptive opponents. It will take considerable ingenuity to develop biomaterials that do no harm the body's defences against infection and are also capable of frustrating the surface colonisation mechanisms that microbes have evolved as a basic survival strategy in natural aquatic habitats (Costerton *et al.*, 1987).

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Discussion with Reviewers

W.W. Nichols: What is the estimated annual cost of device-associated infections world-wide in 1994, or estimated for 1995?

Authors: We know of no estimates of the costs of device associated infections worldwide in 1994 or 1995.

W.W. Nichols: Are there any well-controlled (preferably blind) clinical trials that compare ordinary devices with devices possessing modified surfaces (e.g., in an attempt to prevent bacterial binding) or that have been pre-treated with antibacterial agents?

Authors: There have been controlled trials of silver coated urethral catheters but the results are rather contradictory. Liedberg and Lundeberg (1990) reported a randomized trial in a population of patients undergoing short-term catheterisation (six days) after surgery. They recorded a significantly ($p < 0.01$) lower rate of bacteriuria in patients with silver-coated latex catheters (10%) than in patients with control teflonised latex catheters (37%). In contrast, Johnson *et al.* (1990), in a study of 482 patients in a general hospital, found that the overall rate of bacteriuria in recipients of silver-oxide coated catheters (9.0%) was not significantly different from those receiving standard all-silicone catheters (10.0%).

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