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Review: Microbial Colonization of Prosthetic Devices

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Introduction

Modern medical practice is necessarily invasive, and a very large number of plastic and metal prosthetic devices are implanted into patients throughout the world. For example, it is estimated that some 2 to 3 million artificial or prosthetic parts are implanted in the United States each year [31]. The general definition of a prosthesis, which will be adopted in this text, is any material or device that is attached, inserted, or implanted into the body [77].

A broad variety of prostheses is currently used and includes vascular grafts, joint prostheses, cardiac valves and pacemakers, to cite only a few. On the other hand, devices such as intravascular catheters and urinary catheters are not generally seen as true prosthetic devices because they are only inserted into the body for relatively short periods of time. But they are subject to many of the same complications as permanent devices, and can be viewed as temporary prostheses.

Infections remain one of the major complications of the use of prosthetic devices, and treatment of these prosthesis-associated infections often requires removal of the devices since antibiotics alone are usually ineffective [77]. The mechanisms by which the implantation of foreign objects increases susceptibility to infection are incompletely understood; ineffectiveness of local host defense mechanisms has been suggested. Different animal models have been developed to study factors pertinent to foreign body infections [14, 35, 81].

Coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*) are common pathogens in patients with prosthetic devices inserted through the skin or implanted beneath it, while gram-negative rod infections are often associated with devices that are partially or fully exposed to the environment and are subjected to frequent manipulations by hospital personnel (e.g., urinary catheters) [77]. Colonization of the prosthetic devices by such opportunistic microorganisms often precedes overt infection.

Different approaches have been employed to study prosthetic device-associated infections. These include: introduction of bacteria in an experimental animal with an implant [14, 35, 81]; modification of bacterial growth by pros-

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such as chemicals, surfactants, antibodies, and phagocytic leukocytes, and also prevents their removal via host secretions and flow of blood, and mucus [18, 26].

This bacterial strategy thus confers protection on these pathogenic microorganisms, but it also limits their immediate pathogenic impact on the host, and many patients with heavily colonized prostheses experience few overt symptoms [18]. Once a bacterial biofilm has developed on the surface of prosthetic devices, by growth from a septic area or by hematogenous spread, the bacterial populations may persist for extended periods in spite of intact host defenses and aggressive antibiotic therapy. Consequently, the biofilms often act as microbiological reservoirs for infections [18, 25].

Costerton et al. [17] have suggested that the hydrated polyanionic bacterial glycocalyx acts as an ion-exchange resin in binding charged antibiotic molecules and that it thus limits their access to targets within the bacterial cells and cell envelopes. Nickel et al. [59, 60] have assessed the ability of antibiotics to penetrate the biofilm and kill the enclosed bacteria in an in vitro model of colonization of urinary catheters by *Pseudomonas aeruginosa.* Disks of urinary catheter material were exposed to the flow of artificial urine containing cells of *P. aeruginosa,* and a thick adherent biofilm (composed of these bacteria and of their exopolysaccharide products) developed on the latex surface within 8 hours. Cells of a strain of *P. aeruginosa* that have a tobramycin minimal inhibitory concentration of <1.0 μg/ml and a minimal bactericidal concentration of 50 μg/ml survived exposure to 1,000 μg/ml when growing within thick biofilm on the surface of catheter latex. Under usual clinical conditions, levels of plasma tobramycin rarely exceed 8 μg/ml, which usually results in urine tobramycin concentrations of 50–200 μg/ml. Thus, these data may contribute to the explanation of the paradoxal resistance of catheter-associated urinary tract infections to doses of antibiotics that are effective in standard in vitro tests.

Cardiac Prosthetic Valves and Cardiac Pacemakers

Prosthetic heart valves are of two basic types: mechanical (e.g., disc or caged-ball) and bioprosthetic (e.g., porcine heterografts). Regardless of the type, a significant risk of infection exists; staphylococci and micrococci are the most frequently isolated organisms accounting for 43% of all cases of prosthetic valve endocarditis [77].

Bacteria adherent to the surface of various components of cardiac pacemakers infected with *S. aureus* or coagulase-negative staphylococci were examined by electron microscopy [52, 53]. Within developing adherent microcolonies, coccoid cells could be clearly seen to be enveloped by an amorphous material (Fig. 2). Exopolysaccharide formation by coagulase-negative staphylococci growing on pacemakers was considerably greater than that found on intravenous catheters [51], and their morphology of attachment was strikingly similar to that of slime-producing strains adherent to intravenous catheters under experimental conditions [13].

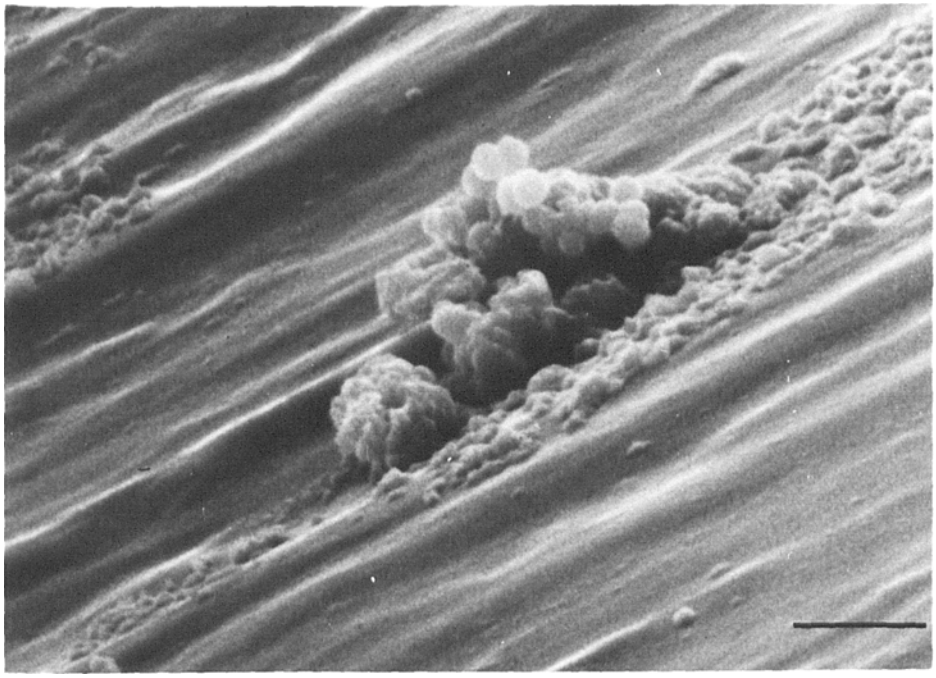

Fig. 2. Scanning electron micrograph of the inner surface of a pacemaker lead from which coagulase-negative staphylococci were isolated on culture. The condensation of the enveloping exopolysaccharide of this adherent microcolony had exposed some coccoid cells, whereas other cells remained buried in its condensed residue. Bar represents 5 μm.

Intrauterine Contraceptive Devices

Several prosthetic devices are inserted so that they comprise a biomaterial "bridge" between a normally colonized mucosal surface and a normally sterile organ. Very common instances of this are urinary catheters that form a bridge between the normally colonized distal urethra and the bladder (see below), and the intrauterine contraceptive devices (IUCDs) that form a bridge between the normally colonized cervix and the uterus.

The mechanisms by which infections of the genital tract are related to IUCDs are not well understood. It is possible that bacteria could be introduced into the uterus at the time of installation of the device or they could ascend along the tail of the device [64, 73, 77]. An experimental study recently done using rabbits tended to incriminate the first possibility [34a].

Surfaces of various IUCDs used for varying lengths of time have demonstrated calcium deposition and the presence of adherent material consisting mainly of macrophages, with some polymorphonuclear leukocytes, erythrocytes, a few platelets, and fibrin fibers [70]. Marrie and Costerton [48] examined IUCDs removed from asymptomatic women and found material adherent to

all types of these devices. They also observed many different morphologic types of bacteria adherent to the devices, often buried in a thick biofilm (Fig. 3).

We investigated the in vitro adherence of different microorganisms to three materials (polyethylene, polypropylene, ethylene/vinyl acetate) used in IUCDs (Jacques et al. in press). We found that the initial attachment of microorganisms to IUCDs appears to involve hydrophobic interactions and lodgment of microbial cells in surface irregularities. We observed a significant correlation ($P < 0.01$) between cell surface hydrophobicity and adherence to the three plastics; the more hydrophobic isolates adhered in larger numbers to the plastics than the less hydrophobic or hydrophilic isolates. The number of adherent microorganisms depended on the type of IUCD material, the type of microorganism, and the duration of contact.

Intravascular catheters

Direct examination of stratified squamous epithelia, including human skin, has shown that these tissues comprise an ecosystem within which bacteria adhere, proliferate, and penetrate into the intercellular spaces among the distal keratinized cell layers [12]. All devices that traverse the skin, such as intravascular (IV) catheters, peritoneal dialysis catheters (see below), and sutures (see below), are therefore subject to colonization by native cutaneous microorganisms. But microbial colonization of IV catheters is a complex phenomenon and it has been suggested that it results from contamination of the fluid infused, manipulation of the IV delivery system, hematogenous "seeding" of the catheter tip, as well as invasion of organisms present at the insertion site along the catheter [8]. It was found that comparatively shorter catheters used for arterial access combined with the faster intraarterial flow rate account for the diminished colonization rates of arterial versus central venous catheters [69].

Semiquantitative [47] and quantitative [16] culture techniques were developed to study IV catheter-related infections. While the majority of the studies suggest that the insertion site was the portal of entry for skin commensal microorganisms [1, 8, 11, 16], the work of Michel et al. [55] supports the theory of hematogenous spread from remote foci.

The surfaces of IV catheters are imperfect [2, 5, 11, 42, 51]. Such imperfections may be due to protruding material, scratches, troughs, scales, lacunae, or adhering particles [5]; infusates can also leave residue on the surface of the catheters [65].

Locci et al. [42] examined by scanning electron microscopy 10 commercially available (on the German market) unused IV catheters. Different types of irregularities in the external and internal surface could be detected in all catheters examined. They speculated that such irregularities are large enough to trap 0.5–1.0 μm large particles.

Peters et al. [62] examined by scanning electron microscopy 42 nonselected, naturally infected IV catheters. In many catheters an amorphous substance could be detected; the thickest layers of such a substance were found in catheters

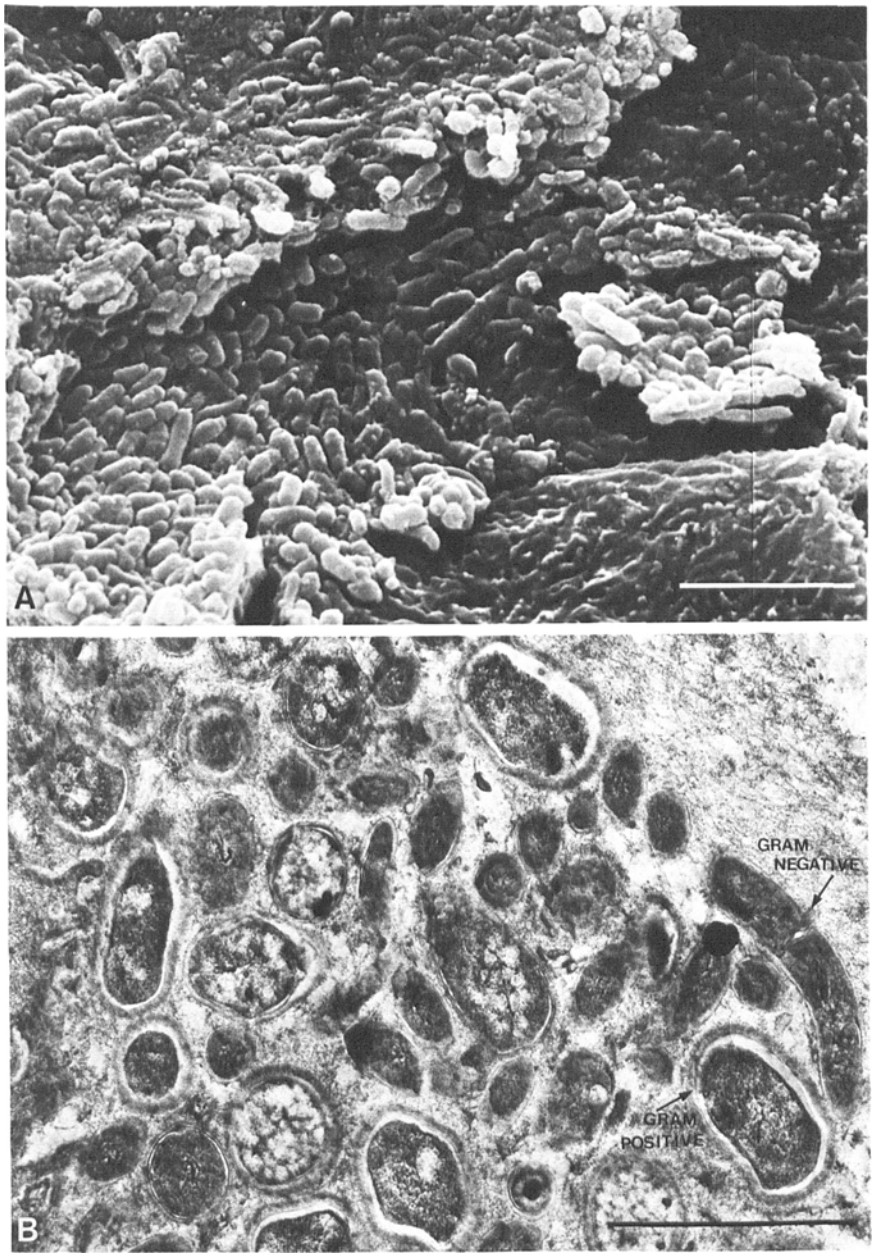

Fig. 3. (A) Scanning electron micrograph of the intrauterine portion of an IUCD. Note that bacteria are present in the surface of this thick biofilm (bar represents 5 μm). **(B)** Transmission electron micrograph of material scraped from the surface of an IUCD. The biofilm on this device was composed of gram-positive and gram-negative bacteria in an extensive network of fibrous material (bar represents 1 μm).

infected by coagulase-negative staphylococci. Among the microorganisms colonizing the lumen of these devices, eukaryotes were also observed [44]. IV catheters infected by *Candida albicans* displayed proliferation in situ despite an absence of mycelial structures and chlamydospores.

Marrie and Costerton [51] recovered bacteria or yeasts from 38 of 63 catheters examined, and *S. epidermidis* was present on 29 of the 38 colonized catheters. Electron microscopic examination of the colonized IV catheters showed a very extensive amorphous accretion, on both the lumenal and the external plastic surfaces, in which bacterial and yeast cells were entrapped (Fig. 4).

Sheth et al. [71] examined 687 Teflon catheters and found by culture that 6.9% were positive for microbial growth, compared with 24.6% of the 77 polyvinylchloride (PVC) catheters examined. Colonization by coagulase-negative staphylococci on PVC was more important than on Teflon. They concluded that the type of catheter material may be important in determining the incidence of catheter-related infections and in selective colonization by coagulase-negative staphylococci.

Franson et al. [21] observed a diffuse amorphous material covering the entire surface of infected catheters, and showed the presence of bacteria which appeared to be anchored to that surface by several means including slime layer, "foot" processes, and lodgment in surface irregularities. Surface defects were also shown by Cheesbrough et al. [11] to be associated with microbial colonization which occurred either as isolated colonies or in association with a cellular fibrinous matrix.

Locci et al. [43] have carried out in vitro bacterial colonization of IV catheters by artificial perfusion with known suspensions of staphylococci for a period of 24 hours. The first step of bacterial attachment was associated with the different irregularities of the inner surface of the catheter. When the duration of the experiment was extended, regular sampling of specimens, for up to 96 hours, demonstrated adhesion of bacteria to the catheter surface followed by cell proliferation, and production of a slimy material covering the bacterial colonies [63].

In an outbreak of *S. epidermidis* IV catheter-associated sepsis, Christensen et al. [13] noted that 63% of clinically implicated strains produced a slime. When grown in vitro, slime producers accumulated on the surface of IV catheters as macrocolonies, whereas nonproducers did not. Electron microscopic examination showed slime producers to be encased in an adhesive layer on the catheter surface, whereas nonproducers were not encased. These results suggest that slime-mediated adherence and consequent protection from host defense factors may be a critical factor in the pathogenesis of *S. epidermidis* infections of medical prostheses.

Ludwicka et al. [46] also investigated slime production and attachment of a coagulase-negative staphylococcal strain to different chemically pure polymers. According to their results, attachment of staphylococci and slime production seem to be independent of the presence of organic additives (acting as plasticizers, stabilizers) in biomaterials. In a further study, they demonstrated that adherence of hydrophobic strains of *S. epidermidis* was dependent on the surface-free energy of the substrata; a decrease in attachment with an increase

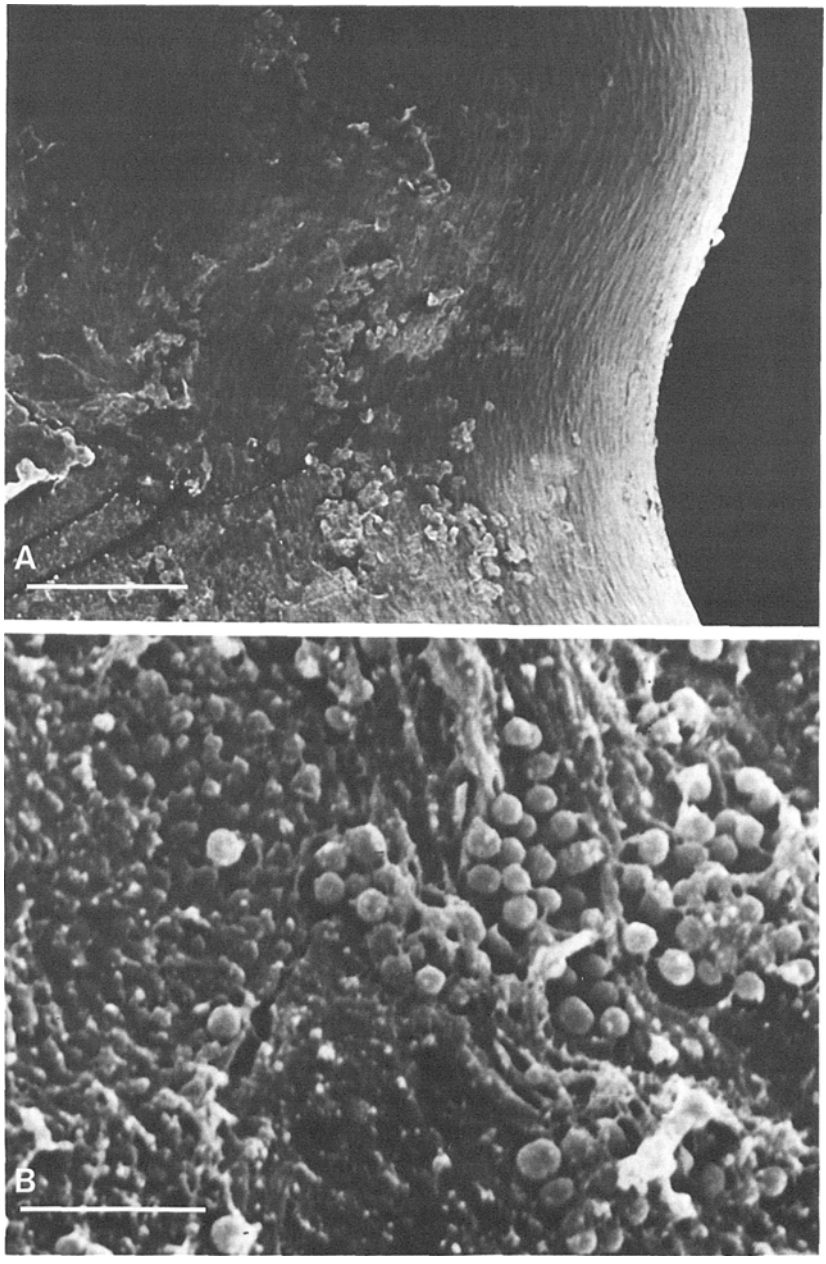

Fig. 4. Scanning electron micrographs of the outer surface of an intravenous catheter recovered from a patient and from which *Staphylococcus epidermidis* was isolated on culture. **(A)** Flakes of material are present on the surface (bar represents 50 μm). **(B)** At higher magnification, bacterial cells are evident (bar represents 5 μm).

in surface-free energy was observed [45]. The attachment of more hydrophilic strains did not show such relationship to surface-free energy. They concluded that the interaction of staphylococci with synthetic polymers is a multifactorial event. Both hydrophobic and hydrophilic interactions as well as electrostatic forces seem to mediate attachment. Ashkenazi and Mirelman [2] also observed the importance of bacterial cell surface hydrophobicity in adherence to IV catheter materials.

Upon brief immersion of catheters in suspensions of *S. aureus,* coagulase-negative staphylococci, and *Escherichia coli,* organisms adhered to catheter surfaces, replicated, and formed colonies [72]. Adherence was greater on PVC catheters than on Teflon catheters for coagulase-negative staphylococci, and D-mannosamine inhibited their adherence to PVC catheters [22]. The reasons why coagulase-negative staphylococci appear to have greater in vitro [22, 72] and in vivo [71] affinity for PVC than for Teflon are not clear; intrinsic catheter surface features, presence of trace materials, surface charge differences, and/or microbial traits such as glycocalyx may be involved. It was also observed that *C. albicans* and *C. tropicalis* adhered in vitro to both PVC and Teflon IV catheters, and that both adhered more extensively to PVC than to Teflon [68].

As one can see, naturally and artificially infected IV catheters have been extensively studied but the mechanisms whereby microorganisms colonize these catheters remain uncertain. In summary, recent in vitro studies have suggested that surface defects favor bacterial attachment and subsequent colonization [2, 11, 43]. The production of slime may promote such colonization [13, 63]. Coating with host substances and thus attachment of microorganisms to fibrin rather than to the catheter surface may also be an important factor [11, 21, 51]. It should also be noted that these studies have examined the initial stages of biofilm formation (<1 day), whereas the later stages of biofilm formation almost certainly involve bacterial aggregation more than bacteria-biomaterial colonization.

Orthopedic Prostheses

Electron microscopic examination of infected material showed unequivocally that bacteria grew predominantly in coherent microcolonies in an enveloping matrix of anionic fibrous exopolysaccharides [25, 26]. Gristina et al. [27, 28] first suggested that the biomaterials used in orthopedic prostheses serve as suitable substrata for adherent bacterial growth. Their proposed etiology of bacterial infections states that bacteria contact biomaterial via surgery or hematogenous spread, form glycocalyx-enclosed microcolonies that are resistant to antibiotics and antibodies, and that burgeoning bacterial biofilm on biomaterial provides an inoculum for tissue invasion [25].

Peritoneal Dialysis Catheters

Marrie et al. [54] examined Tenckhoff peritoneal catheters removed from uninfected patients, and from patients with exit site infections and/or peritonitis.

Colonization of the catheters was uneven; bacteria tended to occur in clusters, and extensive matrix formation was evident in several instances. They did not observe any major morphological differences in the adherence of bacteria to the Dacron fibers of the cuff (a relatively dry environment) or to the silicone rubber tubing (continuously bathed by the dialysate), nor did they observe any differences between the exterior and interior surfaces of the catheters.

Suture Materials

Bloomstedt et al. [9] investigated the transport of bacteria by suture materials and found that immobile bacteria can propagate inside multifilamentous materials; bacterial spreading was correlated with the capillary properties of the threads.

The effects of physical configuration and chemical nature of various suture materials on the preferential adherence of different microorganisms has been investigated [15, 37, 76]. It was found that the amount of adherent bacteria depended on the type of suture material, the type of bacteria, and the duration of contact. For example, the nylon monofilament [37, 76] and the new synthetic adsorbable monofilamentous suture PDS (made of polydioxanone) [15] exhibited a low affinity towards the adherence of bacteria, whereas braided materials such as braided Dexon (made of polyglycolic acid) had the highest affinity towards adherence of bacteria [15, 37, 76]. Therefore, infection is more likely to occur around multifilament than monofilament material and least likely to occur around nylon [77]. Gristina et al. [29] have recently examined the surfaces of >100 sutures and staples removed serially in an orthopedic practice and have found that most were heavily colonized by gram-positive cocci (predominantly *S. epidermidis*) but that these had not caused either inflammation or infection. This observation supports the general consensus that transcutaneous devices are routinely colonized by native cutaneous organisms and that, while they constitute potential foci of infection, colonization is not synonymous with infection.

Urinary Catheters, Urine Droppers, and Collecting Systems

Multiple factors are probably important in the development of catheter-acquired bacteriuria. Bacteria may be introduced into the bladder from the urethra at the time of catheterization; they may ascend within the catheter lumen or enter via the catheter-meatal interface [38, 50]. The predominant current concept concerning the development of catheter-acquired bacteriuria is that the urethra becomes colonized with gram-negative rods and enterococci derived from the fecal flora [38] and that these bacteria enter the bladder through the mucosal sheath around the catheter. However, recent data generated in animal models, using auxotrophically marked strains of uropathogenic bacteria [57], have indicated that the luminal "route" of bacterial invasion is faster than the periurethral "route."

Kunin and Steele [38] obtained cultures from 398 patients with sterile urine,

and observed that catheter surfaces were colonized less often in males than in females. In both sexes, gram-positive species (mainly *S. epidermidis* and *Streptococcus faecalis*) were isolated more frequently than gram-negative species.

Extensive microbial colonization has been shown to appear on the surface of urine droppers and urine collecting systems from bacteriuric patients (Fig. 5A [50]. A thick biofilm was found on the surface of a Foley catheter removed from a woman with antibiotic-resistant bacteriuria (Fig. 5B) [58]. The biofilm was thicker on the outer surface of the catheter. Sessile bacteria were surrounded by an extensive exopolysaccharide glycocalyx which appears to be fundamental in the pathogenesis of catheter-associated urinary tract infections and their resistance to systemic antibiotherapy.

Sugarman [75] demonstrated in vitro that *E. coli* and *Klebsiella* sp. adhere readily to latex and latex-Teflon and less well to silicone catheters. Marrie and Costerton [49] studied the kinetics of attachment of various uropathogens to the surface of plastic droppers (made of polyethylene). Of the uropathogens tested, *P. aeruginosa* adhered most avidly and formed the most extensive glycocalyx around its adherent microcolonies. They concluded that uropathogens display a highly varied capacity to adhere to a polyethylene surface and that the production of extracellular polymers appears to be as important in the colonization of inert surfaces as it is in nature.

Vascular Grafts

In the absence of fibrin coating, the differences in structure of various vascular grafts such as bovine heterograft (a plain prosthesis), polytetrafluoroethylene (microporous and highly hydrophobic), and Dacron velour (resembling a trellis) account for differences in bacterial adhesion [74]. The fibrin coating enhances the ability to entrap bacteria. Goeau-Brissoniere et al. [24] designed an experimental model to reproduce, in vitro, hematogenous seeding of various grafts with *S. aureus*, and observed that the prosthetic grafts entrapped large numbers of bacterial cells which were mainly located on irregular fibrin strands and on surface defects of the grafts.

Miscellaneous Prosthetic Devices and Biomaterials

The staphylococci most often found in colonized Holter shunts (cerebrospinal fluid shunts) belong to subdivision SIIA [34]. Bayston and Penny [6] showed that these staphylococci produce a large amount of mucoid substance during their growth. This substance was produced in vivo when the staphylococci colonized Holter shunts, and it was suggested that this mucoid substance played a part in maintaining colonization by enabling microcolonies to adhere to the shunt wall, and that it protected the organisms from the action of lysozyme and antibiotics.

Scanning electron microscopic examination of myringotomy tubes demonstrated significant surface morphologic irregularities [36]. Fluorocarbon tubes

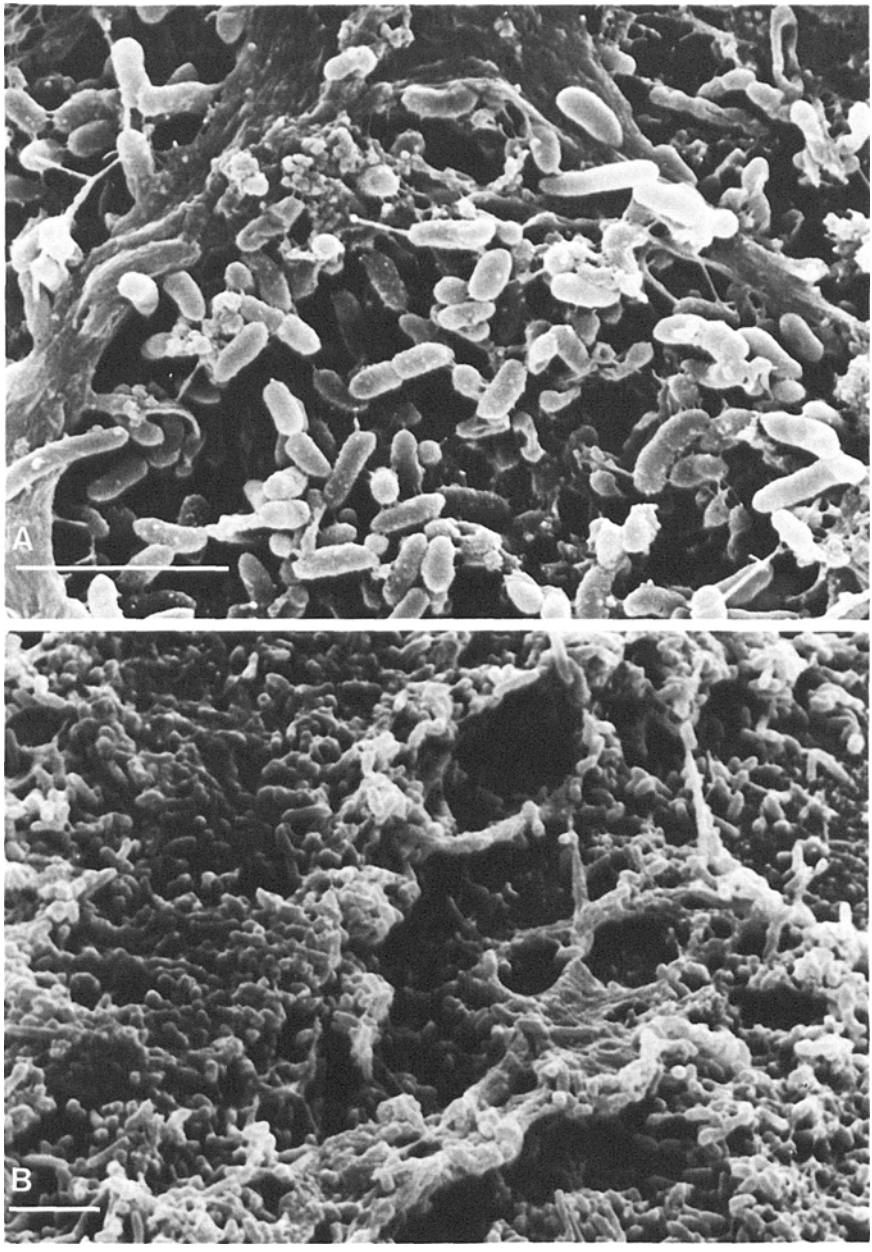

Fig. 5. (**A**) Scanning electron micrograph of the inner surface of a reservoir bag of urine-collecting system that had been in use for 5 days. Note the extensive colonization of the surface of the bag (bar represents 5 μm). (**B**) Scanning electron micrograph of luminal surface of a Foley catheter removed from a patient with antibiotic-resistant bacteriuria. Note the bacteria adhering to the catheter surface (bar represents 5 μm).

appear to be smoother than silicone tubes and also show a lower incidence of infection (11% vs. 28%). Whether the basis for this is the nature of the polymer, its surface smoothness, or both is not certain.

Leake et al. [41] designed a technique, using chemotaxis chambers, to study bacterial colonization of biomaterials. They observed abundant growth of *S. aureus* and *P. aeruginosa* on four biomaterials frequently used in orthopedic surgery (methylmethacrylate bone cement, polyethylene, stainless steel, and Vitallium), after 24 hours of incubation [40]. They believe that the type of colonization seen on the biomaterials studied in their experiments represents a surface colonization which involves the presence of profuse amounts of bacterial glycocalyx.

Botta et al. [10] investigated the adherence of different microorganisms to polytetrafluoroethylene and to polyethylene. They found that the latter had a higher affinity for the bacteria tested than the former. Hogt et al. [32, 33] studied the in vitro adhesion of coagulase-negative staphylococci (*S. epidermidis* and *S. saprophyticus*) to poly(tetrafluorethylene-co-hexafluorpropylene) (FEP), a hydrophobic material used in vascular grafts, IV catheters, and trachea prostheses, and to cellulose acetate, a more hydrophilic material used for the coating of sorbents in haemoperfusion systems. They found that the strong interaction between *S. epidermidis* and FEP is mainly caused by hydrophobic bonding.

A study by Vaudaux et al. [78] suggested that fibronectin (a multifunctional animal glycoprotein) may be an important mediator of the adherence of *S. aureus* to polymethylmethacrylate, and thus may contribute to the pathogenesis of foreign body infection.

Infection-resistant Prosthesis

The extensive search for a material that is inherently resistant to bacterial colonization will likely continue to be futile. Even metals with demonstrable toxicity against bacteria (e.g., copper, silver) are colonized avidly by biofilm-forming bacteria.

Controlled clinical trials have confirmed that antibiotics administered at the time of prosthetic implantation do, indeed, reduce the incidence of prosthetic infections [77]. Future developments in the design of prosthetic devices may influence their susceptibility to infection. One of the techniques used to render prosthetic devices resistant to infection involves the bonding of an antibiotic to it. Methods for the passive adsorption of antibiotics onto prosthetic surfaces have been described [66]. Most antibiotics are extremely water soluble, and therefore are rapidly eluted from the surface of an implanted prosthetic device. Rifampin has a high lipid solubility and has been shown to retain its activity for up to 48 hours when Dacron grafts are soaked in it prior to their implantation (Powell, TW. 8th annual meeting Southern Association for Vascular Surgery, Scottsdale, Arizona, January 1983).

Antibiotics admixed with bone cements leach out from the hardened plastic by diffusion [77]. This leaching phenomenon varies quantitatively among the variety of bone cements and antibiotics available. Wahlig and Dingeldein [79]

compared several antibiotics and different bone cements. The mixture of polymethylmethacrylate with gentamicin proved to be the most suitable as far as a high and sustained release of the antibiotic from the resin is concerned. A continuous leaching of gentamicin was observed for more than 5 years. Theoretical problems in the clinical application of antibiotic-impregnated bone cement have centered on three issues: (1) possible loss of the structural integrity of the bone cement; (2) systemic toxicity of diffusing antibiotics; and (3) protracted hypersensitivity reactions to the sustained release of potentially allergenic drugs [77].

Moore et al. [56] developed an infection-resistant vascular prosthesis by bonding amikacin to a knitted Dacron graft using a collagen-release system. All the control grafts were infected compared to only 8% of the experimental grafts. This technique provides for a controlled sustained release of antibiotic material and represents a considerable advantage over the technique of passive antibiotic soaking of a prosthesis.

Clearly, the most potentially effective strategy for the control of bacterial colonization, and subsequent biofilm formation, is the incorporation of diffusible antibacterial molecules into the polymers used in the manufacture of prosthetic devices.

Conclusion

The threat of bacterial colonization and biofilm formation poses the most important limitation on the use and development of prosthetic devices in human medicine. Data from the literature suggest that microbial adherence effected by the glycocalyx is a fundamental factor in sepsis involving biomaterials and that it may explain the resistance of such infections to host defense mechanisms and to antibiotherapy. A full appreciation of the existence and the consequences of the biofilm mode of bacterial growth is required so that we can both prevent and eliminate these protected microbial reservoirs.

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