Infection and Implants

I had a total knee replacement (right knee arthroplasty) in December. Without going into detail as the why, this was the long-term consequence of a youth time spent committing assault and battery on other young men, and being similarly assaulted in front of thousands of witnesses. The how was accomplished by several skilled surgeons and their colleagues at North Carolina Memorial Hospital. With this rite of passage, I join some 4.5 million other individuals in the United States; there are many in Europe as well. During the pre-op discussion, I was surprised to learn that the risk of infection from a joint arthroplasty(hip or knee) is greater than the risk of thrombosis (Since I have spent a good part of my career working on blood coagulation, I would take thrombosis as a personal insult more than a medical problem). The rate of post-surgical infection appears to be between 1-3% (1-4). Infection following arthroplasty presents a major problems for the health care system (5). In 2005 (using data from 2001-2002), Bozic and Ries (6) showed that hospital costs for revision athroplasty[a] following infection was $96,166 (US), while revision arthroplasty for aseptic loosening was $34,866 and $21,654 for primary arthroplasty. There were similar differences in outpatient costs. Despite considerable work, surgical site infection continues to be a major problem for the health care system (7,8). Considering that the number of knee replacements will markedly increase in the next several decades, this is obviously a great opportunity. The issue is not unique to the United States as it is estimated that the number of knee replacements in Scandinavia will soon exceed the number of hip replacements (9). Kurtz and collegues suggest that demand for both knee and hip arthroplasties will grow markedly by 2030 (10).

While I was associated with some work on the artificial heart program some years ago and periodically work on biocompatibility issues with respect to the blood/biomaterial interface, biomaterials are not my strong suite. Biocompatibility issues largely focus on interaction with blood and the requirement for a non-thrombogenic surface; thrombosis is not a problem with the implants used for joint arthroplasty. Orthopedic implants such as the cobalt chrome device residing in my right knee generally do not elicit a tissue response unless the process of device loosening occurs 11,12). Aseptic loosening occurs when the implant-bone bond fails in the absence of infection (13) while septic loosening occurs in the presence of an infection (14) although differentiation between the two separate etiologies is difficult (15,16).

Infection does pose a significant problem for implant success (1,5,7). The importance of bacterial adhesion to implant in septic infection of joint arthroplasty was the subject on an excellent review by the late Tony Gristina in 1987(17). The source of the bacteria can be either external or internal to the patient. The possibilty of hematogeneous infection was advanced by Stinchfield and colleagues (18) in 1980. The formation of a biofilm on biomaterial surface secondary to adhesion was discussed by Gristina and Costerton in 1985 (19). These investigators and others (20) suggest that the formation of a biofilm creates a problem for antibiotic therapy and focus should be directed at the prevention with emphasis on inhibiting the initial binding of bacterial to the implant surface. There has been interest in pre-operative screening for bacterial pathogens such as *Staphylcococcus aureus* (21,22).

Slover and coworkers (22) suggest that pre-operative screening could be cost-effective if there were a 35% reduction in revision rate. Other approaches involve the use of antibiotic-containing bone cement (23,24). Systemic and local application of antibiotic are considered useful (25-27) but antibiotic-resistance (28,29) is a problem. While the percentage of infections is low, the increasing number of total joint arthroplasties combined with the likely entry of new facilities into surgical joint replacement, it is likely that the number of infections will markedly increase during the next decade. In consideration of this hypothesis and the above information, it is apparent that new and novel approaches to the prevention of infection should be considered.

Prevention of infection has at least two approaches. The first is make sure that the implant recipient is sterile. Screening for bacteria as mentioned above is one approach; however, it is not clear that such can be fully effective (30). Pre-operative use of antibiotics can be useful but there are issue of resistance and emerging pathogens. The second approach is based on prevention of adhesion to the implant which would also include indwelling catheters.

There has been major effort over the last fifty years to make artificial materials[b] more acceptable for *in vivo* use . I was involved in early work on the development of the artificial heart where the main problem was thrombogenicity. The current discussion is focused on infection secondary to joint replacement surgery where the implant material can serve as a nidus for bacterial colonization and subject biofilm formation. Alteration of the implant surface by application of "coatings" has been an attractive approach to the prevention of bacterial adherence. Recent work in this area has included antibiotic coatings (31), antimicrobial peptides (32,33), poly (ethylene glycol)/poly (ethylene oxide) (34-36), immobilized lysozyme (37) and nanostructural modification of the implant surface (38-40). A study of the of nisin (Nisaplin®) to prevent the growth of bacteria on surfaces in the food industry has also been reported (41). The reader is directed to several reviews in this area which may be useful (42-46).

Plasma proteins have been shown to influence the bacterial adherence to implant materials. The term plasma proteins is used advisedly since with many proteins, the bulk of such proteins are in the extravascular space and thus available for interaction with implant surfaces. Vaudaux and workers (47,48) observed that fibronectin promoted adherence while serum inhibited adherence. The presence of fibronectin in the extravacular space is well documented (49,50). Fibronectin has also been observed to enhance adherence of *Staphylococcus aureus* and *Staphylococcus epidermidis* to polyvinal chloride and heparin-boned polyurethane catheters (51). There have been a number of subsequent studies demonstrating the promotion of bacterial adherence to surfaces by fibronectin (52-55). As noted above, Vaudaux and coworkers (47,48) observed that pretreatment of surfaces with serum inhibited bacterial adherence. Some 10% of plasma proteins are removed during the formation including major amounts of fibrinogen and fibronectin. Inhibition of bacterial adherence by serum has been confirmed and extended by other investigators (56-59). There have been efforts to determine if a specific factor or specific factors in serum is responsible for the inhibition of bacterial adherence. There is some evidence to support a role for albumin[c] (60-65). There was an observation suggesting that lactoferrin increased total binding of *Psuedomonas aeruginosa* to contact lenses but there was a decrease in the binding of viable organisms (61). One laboratory showed that apotransferrin inhibited adherence (66,67); such inhibition would be based on iron limitation (68,69). Another group (70) recently

identified a low-molecular weight component in serum which inhibited biofilm formation with *Staphylococcus aureus*. This group raised the issue that biofilm forms on intravenous catheters questioning the value of the serum observation and suggesting that the formation of biofilm resulted from intravascular dynamics. It observed that I have spent a fair amount of effort trying to educate individuals on the difference between plasma and serum (71,72).

The most consistent results for plasma proteins blocked bacterial adherence have been obtained with IgG (58,59,73-75). There is also early work on the effect of secretory IgA on bacterial adherence to tissue (76-78) and hydroxyapatite surfaces (79). There is also literature on the topical use of IgG which essential increases local concentration of therapeutic product (80-83). However, it is fair to say that the interest in this area has been modest. The late Tony Gristina and colleagues did execute several patents (c.f. reference 84 and references therein) for the concentrated delivery of passive immunotherapy but I have not been able to determine if this information is being used for product development. There appears to be an opportunity for the use of hyperimmune globulins on the surfaces of implanted devices. There is obviously considerable work to be done but there is a clear path to successful development .

[a]I discovered that the term revision is used to describe the surgical procedure required to correct problems with the initial arthroplasty. I will never revise another manuscript under less-than-sterile conditions.

[b]The term biomaterial covers a broad range of products including metals, plastics, and processed tissue (such as porcine heart valves) which are used for a variety of "permanent" or temporary purposes including stents, indwelling catheters, artificial joints, and dental implants.

[c] Much of the earlier work on albumin has not been included. Suffice to say that there are studies where albumin inhibits adherence, promotes adherence, or has no effect. Results can vary according to biomaterial surface studies and bacterial strain. Several recent studes have been cited in the current work.

Given that my more-or-less naive status is established, I offer the following two assumptions regarding solutions to the implant infection problem.

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