Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

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Version of record first published: 24 Sep 2006

To cite this article: Anthony P. Prezyna M.D (2000): Adverse Biologic Reactions to Polymers, Metals and Other Prosthetic Materials, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 354:1, 239-242

To link to this article: http://dx.doi.org/10.1080/10587250008023617

Mol. Cryst. and Liq. Cryst., 2000, Vol. 354, pp. 239-242
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Adverse Biologic Reactions to Polymers, Metals and Other Prosthetic Materials

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Adverse reactions to implants have provided a framework to evaluate the suitability of polymers, metals, ceramics and composites for applications in tissue or organ repair or replacement. The lessons learned emphasize the need to marry the implant to the structural, functional and temporal requirements of the host. Implant failure and adverse host reactions have effects that may be local, regional or systemic. Loss of structural integrity follows corrosion or stress leading to fracture, fragmentation or leaching. Local mobilization of host reactions may produce inflammation, sepsis, coagulopathy, fibrosis and lytic effects. Rarely, neoplasia supervenes . Remote effects include toxicity, altered immune status, allergy or the systemic effects of implant failure or fragmentation, coagulopathy or sepsis. The most serious litigious consequences have implicated putative autoimmune phenomena still mired in controversy. Finally implants should anticipate possible interference with the use of diagnostic or therapeutic modalities.

INTRODUCTION

In recent years, the alleviation of bodily structural and functional defects has been greatly facilitated with implants of innovative exogenous materials. Chiefly represented have been members of families of polymers, metals, ceramics and composites. These implants have repaired or replaced faulty structures, most notably in the cardiovascular, osseoskeletal and ocular lens tissues. Recently the ability to miniaturize devices has led to increasing efforts at vessel wall repair, to improve perception of sight, hearing, smell and taste at the sensory level and to facilitate nerve repair. On a grander scale, replacement of extremities with both sensor and force capability by ionic polymer metal composite muscles is in test phase. The promising field of tissue engineering offers the hope of allowing living grafts to replace damaged tissue using exogenous materials as scaffolding, most notably polymers. Furthermore, an understanding of the remarkable interplay of growth factors is preparing the way for utilization of polymers to permit their timely release and effect more rapid and secure success in such applications. Thus,

major directions in bioengineering are altering to goals which facilitate tissue replacement with endogenous sources using stem cells, tissue culture or other forms of native tissue with reinforcing exogenous materials. The latter can be engineered to effect structural support as needed and also timely release of growth and other factors that provide an optimal environment. Our focus here is on summarizing concisely salient features of implant failure and their effect on the host. .

THE IMPLANT COMPONENT

Implants are made of polymers, metals, ceramics and composites and ideally are the most appropriate substance for the intended use. They come in liquid, solid and gel forms and are appropriated for permanent or temporary placement. They serve for structural replacement or repair, as conduits, biosensors, therapeutic drug carriers, support systems for heart-lung machines and dialysis units, scaffolds for tissue and organ grafts and for cosmesis. The implant itself can be the source of problems directly or indirectly. It may undergo swelling or leaching wherein there is transfer of material across the implant-tissue interface by diffusion with altered behavior of materials. Additionally, stress and strain lead to implant failure. The sum total of adverse events that follow may have local, regional or systemic complications. The implant should minimize possible sequelae due to therapeutic measures as exemplified, for example, in a lens haptic meltdown induced by a laser due to wavelength incompatibility. Nor should it seriously impede the application of common diagnostic tools.

TOPICAL AND REGIONAL EFFECTS

Topically the implant can deform, break or fragment. A major category of fragmentation pathology in association with joint replacement has been so called "particulate disease". It has been chiefly associated with the use of polymerized methylmethacrylate as a glue to hold the hip prosthesis. Over time this polymer may debond and extensively fragment. Host reaction with mobilization of macrophages leads to release of chemical mediators such as prostaglandins, collagenases and interleukin-1. Host tissues respond with osteolytic effects, ischemic necrosis and connective tissue alterations with subsequent instability of the implant. Similarly, polypropylene, used as a cartilage substitute in the prosthesis, may lead to particulate disease. More rarely, chrome-cobalt and titanium alloy have been implicated . Again mediator release from macrophages is believed to be the chief cause of the problem. Epiphenomena of hemorrhage, infection, inflammation and fibrosis may also be complicating factors. Finally, malignant growths occasionally follow in a few years, notably near the osseous implant . Lytic effects within the bone may simulate neoplasia on x-ray. An additional problem is tumefactive enlargement of regional lymph nodes due to the migration and storage of particulate debris. In a cardiovascular setting dealing with a blood interface, thrombosis can disable the prosthetic function by occlusion or deformity

as well as induce life-threatening systemic effects due to embolization of blood clot. The cascade of events possible is well illustrated in the history of the heart valve poppet, a spherical object of a silicone elastomer encased in a rigid cage. Imbibition of blood-derived lipids produces swelling resulting either in jamming within the cage or wear with fragmentation and particle seeding of remote organs. Rarely actual escape of the ball from its cage leads to occlusion of a major vessel but more commonly blood clot formation at the valve site has been responsible. At nonvascular sites, intraluminal devices may obstruct with crystalline or proteinaceous debris or the ingrowth of host tissues.

SYSTEMIC OR REMOTE EFFECTS

Remote or systemic effects may follow leaching of components of implants or relate to implant complications of thrombosis and embolism, fragmentation and migration of implant components or sepsis. Leaching defines the diffusion of material from the implant abetted by either blood flow, by repeat frictional wear or contact with the tissue environment. It leads to progressive weakening of structure but also plays a role in adverse reactions to polymers, metals, ceramics and with composites. Leached components may induce toxicity, produce allergic and autoimmune phenomena and incite inflammation. Toxicity arising from leaching of metals is a very complicated subject and higher tissue concentrations adjoining implants (metallosis) do not usually equate with serious toxicity. Considerations of rates of absorption and excretion are paramount. Metalloenzymes participate in the body economy but transgression of the normal equilibrium or introduction of abnormal species may be detrimental. For example, iron and cobalt excesses have provided target tissues with diseases as hemochromatosis and cardiomyopathy. A dramatic recent example in Europe centered on multiple cases of disabling encephelopathy with aluminium release from a composite used to seal skull defects in otoneurosurgery (1) . The composite is a reactant of calcium aluminium fluorosilicate with polyalkenoid acid . Contact with the central nervous system fluid was implicated in the marked elevation of CNS fluid aluminium levels as well as its accumulation in lysosomes of the frontal cerebral cortex. Probably more common than toxicity has been the role of metal induced allergic reactions notably to nickel and less often to cobalt or chrome. Dental and orthopedic devices responsible have been removed with rapid remission of symptoms in putative cases. Carcinogenesis in animal settings has been ascribed to chromium, nickel, cobalt, iron and titanium by Sundermann (2). Leaching or leaking of the polymer family of silicones in breast cosmetic implants has been the base for the largest litigious consequences in the field of implants. In this regard a subset of women have presented with signs and symptoms of a systemic nature ascribed to atypical immune reactions. This category of individuals have presented with arthritic or sclerodermatous manifestations. Kossovsky and Freiman have proposed a model of silicone immunogenicity akin to the classic vaccine model(3). They have suggested that freed silicone (by rupture or bleed) in contact with native

macromolecules induces denaturation of the latter permitting them to act as autoantigens (adjuvant effect). Antibodies to fibronectin , collagen type 1 and DNA have been detected in some but not all of those affected. Munson et al have described immune cell aberrations to silicones in experimental situations with resulting reduced responsiveness to natural killer cell members of the T cell family of lymphocytes. These cells play an important role in defense against cancer as well as against viral and mycotic infection. The controversy over silicone pathogenesis still persists with a recent decision (1998) by an expert panel discounting the significance of the evidence garnered . Sepsis associated with bacterial or fungal invasion at the implant site can occur anywhere but is particularly menacing when in association with the vascular tree. Thus an infected heart valve because of direct access to the vascular stream and the dynamic forces of heart contraction has not uncommonly lead to systemic sepsis or disabling sequelae of infected thrombemboli.

CONCLUSIONS

Implants of exogenous materials have served to greatly enhance deficiencies of structure and function of tissues and organs. Deficiencies of implant design and structure abetted by adverse host reactions continue to challenge the bioengineer. The lessons of the past in mind and with new directions and broader perspectives in view, the bioengineer must be keenly aware of the potential for mishap and the consequences. The observer interested in a comprehensive treatment of this subject is directed to J. Black and his work (4).

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