Medical Device Development: Some Biomaterials Principles Confirmed

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Statement of Purpose: The 2007 "Technology Innovation and Development Award," granted to me, is a tribute to the work of many colleagues on a variety of projects, spanning 31 years. Their acknowledgement comes during my talk. My theme is that, as teams, we learned, but did not necessarily discover, certain biomaterials principles during our product R&D which provided scientific and operational guidance that can have broad applicability. Some of these principles follow.

Programs and Principles: Joining Medtronic, my first medical device company, to form their Polymer Department in 1976, I discovered that they only had two thermoplastic [poly (phenylene oxide/styrene); polyethylene] and three thermoset (epoxy; silicone, polyurethane) polymers qualified for implant. Our first task was to submit for Tripartite biocompatibility testing (now ISO), a series of polymers to bring the "arsenal" of qualified polymers to over two dozen thermoplastics and thermosets. This resulted in some devices that contained polymers [e.g., fluorocarbon (drug reservoir), copolyamide (catheter component)] which were, to our knowledge, introduced as implants for the first time. In combination with the qualified metals and ceramics, we confirmed the Principle: If a material is stable, devoid of toxic extractables, and of a size, shape and surface texture that are tolerable as an implant, it will pass the test protocol for biocompatibility.

The first product line developed entirely by our group at Medtronic was a series of sensing, stimulating, and drug releasing skin electrodes based on poly (2-acrylamido-2-methylpropane sulfonic acid) and other hydrogel-forming compositions. These were the first synthetic, solid, conductive hydrogel adhesives and are in use today. They are exceptionally adherent to the skin and even to internal tissues, and led us to the confirmation of two more Principles**:** Individuals' skin varies widely in adherence to pressure sensitive adhesives, even when "defatted" with surfactants or solvents; the best pressure sensitive tissue adhesive hydrogels are highly anionic or cationic.

Our team at Medtronic was privileged to participate in the development of the first lithium battery-powered heart pacemakers produced at Medtronic. We were asked to develop polymeric components for the first, second and third generations. Although we missed the design freeze deadline for the first product, we achieved about eight innovative components by generation three, despite advice that it was too late after missing the first deadline. Several of these components (e.g., the injection molded pacemaker connector) remain integral to current devices, over 25 years after their invention. Principle Learned: Persistence pays. Needed innovations are embraced when ready, even if delayed. We also learned that some of the materials implemented in implantable devices, e.g., poly (ether urethane) pacing lead insulation, biodegraded under certain circumstances. Most polyurethane device components performed with full competence for their intended lifetimes, but mechanical stress or exposure to strong oxidants, such as metal ion corrosion products, caused degradation of ether groups. Crazing or cracking occurred, sometimes to device failure. Our investigations of polymers with oxidizable and hydrolysable groups led us to confirm the Principles: The body degrades susceptible groups proportional to concentration, but acceptable performance is achievable by proper device design and use. We learned of the importance of realistic preclinical testing which required model development.

At my next biomaterials-based device company, Focal Inc., we developed implantable hydrogel coatings, first to prevent surgical adhesions, subsequently, as surgical sealants. Our PEG [poly (oxyethylene)]-based coatings prevented adhesions in small animals but our gynecologic clinical trial failed. . Our "disconnect" analysis revealed that the coatings, did not adhere in the larger spaces of the human pelvic cavity and migrated away. We then developed coatings with adherence to tissue unsurpassed in non-covalent bonding compositions using a primer/topcoat application technique which led to the first surgical sealant approved by the FDA. It sealed lung air leaks. Principles validated from these experiences included: Again, realistic (large) animal studies are required to predict human outcomes; classical coatings theory (rigid, penetrating primer/flexible topcoat) is valid for adherence to tissue as well as other adherends.

In my current company, Genzyme, Inc., we continue to develop hydrogels as implantable devices and drug delivery systems. For example, modified hyaluronan comprises devices such as adhesion barriers, dermal fillers, and visco-supplements for knee pain. For drug delivery, we are addressing conditions ranging from pain to cancer. From synthetic and modified natural hydrogel-forming polymers, Principles confirmed include: Hydrogel coatings enhance healing of internal and dermal tissues; while cells do not adhere well to hydrogels, they like to migrate to confluence under hydrogels; they resorb with inflammation, but benign resolution.

Final Principles: Few careers are potentially as rewarding as those that provide life-saving and -enhancing medical products to patients. A Biomaterials R&D career is one of service to the patient, first, but also to our colleagues in device design and development who need our expertise and output. The latter group has provided my greatest opportunities for value-generating projects. Even if the project "fails," knowledge gained has future potential. Product-oriented, multi-disciplinary collaborations have been the most rewarding and successful for me. I offer sincere thanks to all my colleagues.

References: For products described, refer to AJ Coury patents: U.S. 4,226,244 (1980) to U.S. 7,008,635 (2006); *Biodegradation reference: "Chemical and Biochemical Degradation of Polymers," A. Coury, Biomaterials Science; An Introduction to Materials in Medicine, B. Ratner, et al, Eds., 2nd Edition, Academic Press., San Diego, CA, 2004.