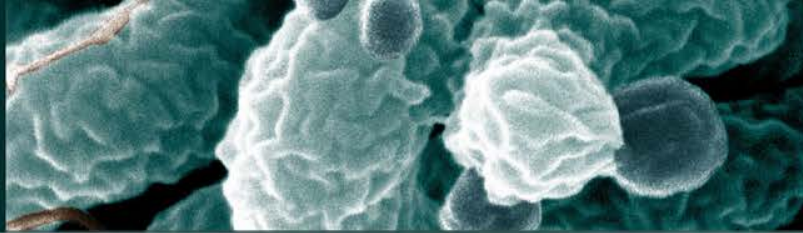




CHAPTER

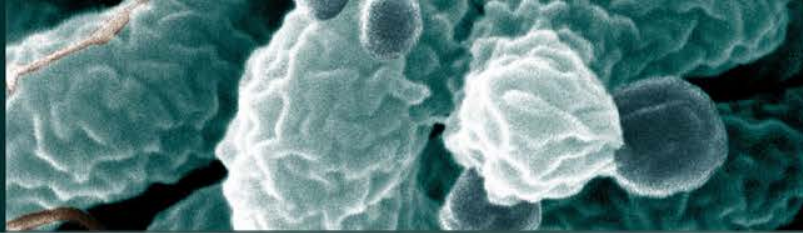
3

Degradation of Materials in the Biological Environment



3.1 INTRODUCTION

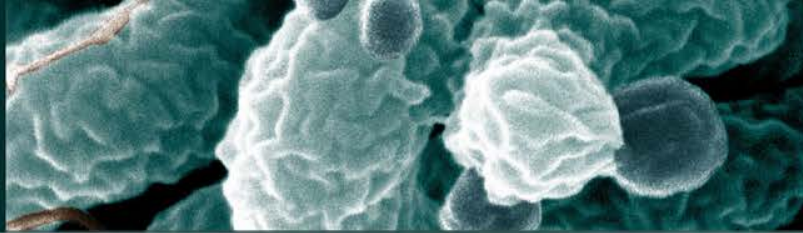
- The biological environment is **surprisingly harsh** and can lead to rapid or gradual **breakdown** of many materials. Superficially, one might think that the neutral pH, low salt content, and modest temperature of the body would constitute a mild environment. However, many specialized mechanisms are brought to bear on implants to break them down.
- These are mechanisms that have evolved over millennia specifically **to rid the living organism** of invading foreign substances and they now attack our contemporary biomaterials.
- First, consider that, along with the **continuous or cyclic stress** many biomaterials are exposed to, **abrasion and flexure** may also take place. This occurs in an **aqueous, ionic** environment that can be **electrochemically active** to metals and **plasticizing** (softening) to polymers. Then, specific biological mechanisms are invoked.
- **Proteins adsorb** to the material and **can enhance the corrosion rate** of metals. Cells secrete powerful **oxidizing agents and enzymes** that are directed at digesting the material.
- The potent degradative agents are concentrated between the cell and the material where they **act undiluted** by the surrounding aqueous.
- To understand the biological degradation of implant materials, **synergistic pathways** should be considered. For example, the cracks associated with **stress crazing** open up fresh surface area to reaction. **Swelling** and water uptake can similarly increase the number of sites for reaction.



- Degradation products can alter the local pH, stimulating further reaction.
- Hydrolysis of polymers can generate more hydrophilic species, leading to polymer swelling and entry of degrading species into the bulk of the polymer.
- Cracks might also serve as sites initiating calcification.
- Biodegradation is a term that is used in many contexts. It can be used for a reaction that occurs over minutes or over years. It can be engineered to happen at a specific time after implantation, or it can be an unexpected long-term consequence of the severity of the biological environment.
- Implant materials can solubilize, crumble, become rubbery, or become rigid with time.
- The products of degradation may be toxic to the body, or they may be designed to perform a pharmacologic function.
- Degradation is seen with metals, polymers, ceramics, and composites.
- Thus, biodegradation as a subject is broad in scope and rightfully should command considerable attention for the biomaterials scientist.
- This chapter, in three sections, introduces biodegradation issues for a number of classes of materials and provides a basis for further study on this complex but critical subject.

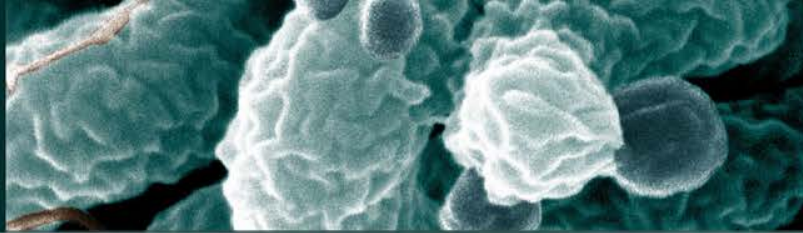
3.2 CHEMICAL AND BIOCHEMICAL DEGRADATION OF POLYMERS

- Biodegradation is the **chemical breakdown** of materials **by the action of living organisms** which leads to changes in physical properties.
- It is a concept of vast scope, ranging **from decomposition** of environmental waste involving microorganisms **to host-induced deterioration** of biomaterials in implanted medical devices.
- Yet it is a precise term, implying that **specific biological processes** are required to effect such changes.
- This chapter, while grounded in biodegradation, addresses other processes that contribute to the often **complex mechanisms of polymer degradation**. Its focus is the **unintended chemical breakdown** in the body of synthetic solid-phase polymers.

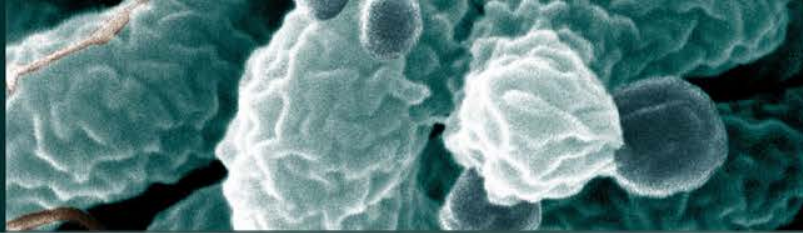


POLYMER DEGRADATION PROCESSES

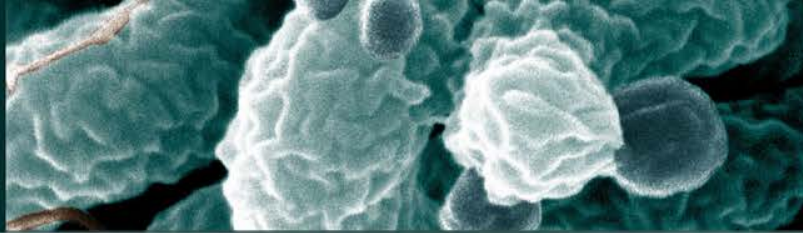
- **Polymeric components** of implantable devices are generally reliable for their **intended lifetimes**. **Careful selection** and extensive preclinical testing of the compositions, fabricated components, and devices usually establish **functionality and durability**.
- However, with chronic, indwelling devices, it is **infeasible** during qualification to match all implant conditions **in real time** for years or decades of use. The **accelerated aging, animal implants**, and statistical projections employed cannot expose all of the variables that may cause **premature deterioration** of performance. The ultimate measure of the acceptability of a material for a medical device is **its functionality** for the device's intended lifetime as ascertained in human post-implant surveillance.
- No **polymer** is totally impervious to the **chemical processes** and **mechanical action** of the body. Generally, polymeric biomaterials **degrade** because body constituents attack the biomaterials directly or through other device components, sometimes with the intervention of external factors.



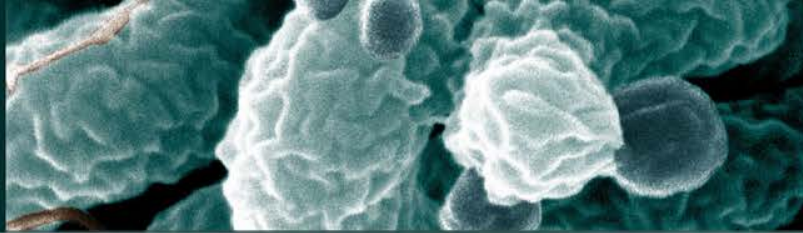
- Numerous operations are performed on a polymer from the time of its synthesis to its use in the body (*Ch.6.2: Table 1*).
- Table 2 lists mechanisms of physical and chemical deterioration, which may occur alone or in concert at various stages of a polymer's history. Moreover, a material's treatment prior to implant may predispose it to stable or unstable end-use behavior.
- A prominent example of biomaterial degradation caused by preimplant processing is the gamma irradiation sterilization of ultra-high molecular weight polyethylene used in total joint prostheses.
- The process generates free radicals within the material which react with oxygen to produce undesirable oxidation products.
- Chain oxidation and scission can occur for periods of months to years, causing loss of strength and embrittlement with limited shelf life.
- Polypropylene and polytetrafluoroethylene are also notable as polymers that are generally chemically stable in the body but can be severely degraded during processing by sterilization with ionizing radiation.



- **Gamma irradiation** may also cause optical changes such as **darkening of poly(methyl methacrylate) intraocular lenses**. It is crucially important, therefore, that appropriate and rigorous processing and characterization protocols be followed for all operations.
- After a device has been implanted, **adsorption and absorption** processes occur. Polymeric surfaces in contact with body fluids immediately adsorb **proteinaceous components**, and the bulk begins to absorb soluble components such as water, ions, proteins, and lipids.
- **Cellular elements** subsequently **attach** to the surfaces and **initiate chemical processes**. With **biostable components**, this complex interplay of factors is of **little functional** consequence. At equilibrium fluid absorption, there may be **some polymer plasticization**, causing dimensional and mechanical property changes.



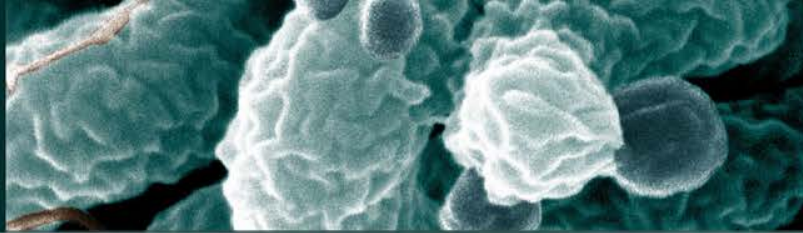
- On the surface, a **powerful acute attack** by cells and many chemical agents, including **oxidants and enzymes**, will have been substantially withstood. With the resolution of this **acute inflammatory phase**, a **fibrous capsule** will likely have formed over the device, and the rate of release of powerful chemicals from activated cells will have markedly decreased.
- For those polymers **subjected to chemical degradation** in vivo, **few** if any reports have comprehensively described the **multistep processes and interactions** that comprise each mechanism. Rather, **explant analysis** and occasionally **metabolite evaluation** are used to infer reaction pathways.
- The analysis of **chemically degraded polymers** has almost always implicated either **hydrolysis or oxidation** as an essential component of the process.



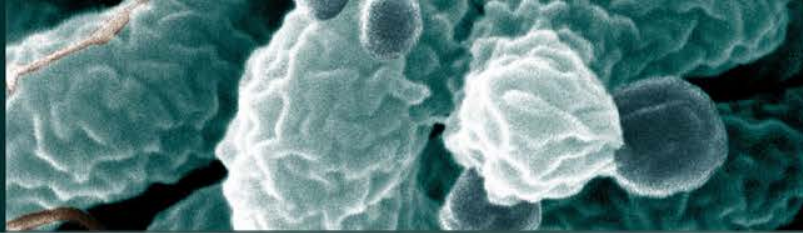
HYDROLYTIC BIODEGRADATION

Structures of Hydrolyzable Polymers

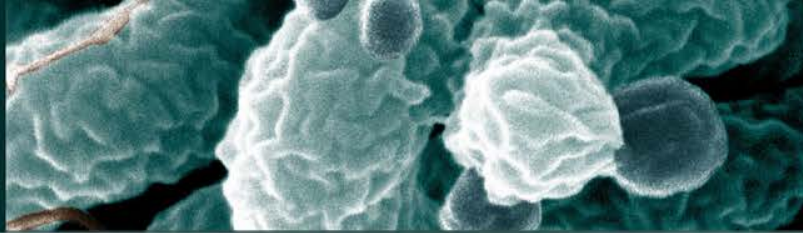
- **Hydrolysis** is the scission of susceptible molecular functional groups by reaction **with water**. It may be **catalyzed by acids, bases, salts, or enzymes**.
- It is a **single-step process** in which the **rate of chain scission** is directly proportional to the **rate of initiation of the reaction**.
- A polymer's susceptibility to hydrolysis is the **result of its chemical structure**, its **morphology**, its **dimensions**, and the body's **environment**.
- In a commonly used category of hydrolysable polymeric biomaterials, **functional groups** consist of **carbonyls bonded to hetero-chain elements** (O, N, S). Examples include **esters, amides, urethanes, and carbonates, and anhydrides**. (*Ch.6.2: Fig. 1*).



- Other polymers containing groups such as **ether, acetal, nitrile, phosphonate, sulfonate, sulfonamide or active methylenes** hydrolyze **under certain conditions** (*Ch.6.2: Fig. 1*).
- Hydrolytically susceptible groups exhibit **differing rates of degradation**, which are dependent on **the intrinsic properties** of the functional group and on other molecular and morphological characteristics.
- Among carbonyl polymers, **anhydrides** display the **highest hydrolysis rates** followed, in order, by **esters and carbonates**. Polymers containing such groups, in fact, comprise many of the **resorbable** devices.
- Other carbonyl groups such as **urethane, imide, amide and urea** can demonstrate **long-term stability** in vivo if contained in a **hydrophobic backbone** of highly crystalline morphologic structure. Groups that are normally **very stable to hydrolysis** are indicated in (*Ch.6.2: Fig. 2*).

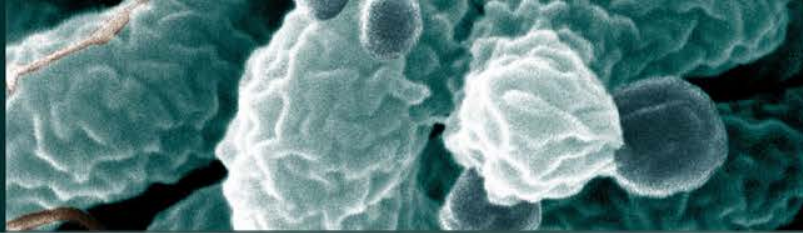


- The **rate of hydrolysis** tends to increase with a high **proportion of hydrolysable groups** in the main or side chain, other polar groups which **enhance hydrophilicity**, **low crystallinity**, **low or negligible cross-link density**, a high ratio of exposed **surface area to volume**, and, very likely, **mechanical stress**.
- **Porous** hydrolysable structures undergo especially **rapid** property loss because of their large surface area.
- Factors that tend **to suppress hydrolysis** rate include **hydrophobic moieties** (e.g., hydrocarbon or fluorocarbon), **cross-linking**, **high crystallinity** due to chain order, thermal annealing or orientation, **low stress**, and **compact shape**.
- While the **molecular weight** of linear polymers per se may **not have a great effect** on degradation rate, physical property losses may be **retarded** for a given number of **chain cleavage** events with relatively high-molecular-weight polymers. Property loss caused by chain cleavage is more pronounced in polymers with **weak intermolecular bonding forces**.

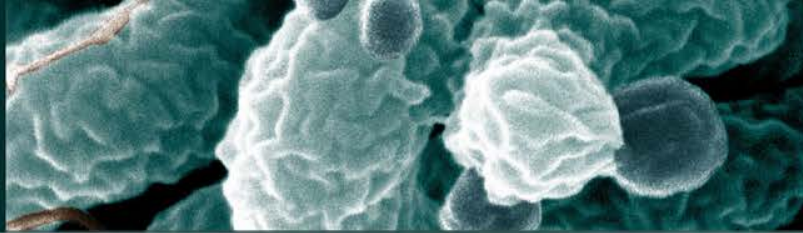


Host-Induced Hydrolytic Processes

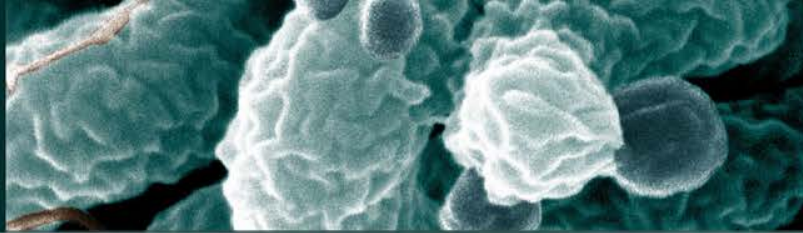
- The body is normally a highly controlled reaction medium. Through **homeostasis**, the normal environment of most implants is maintained at **isothermal (37°C), neutral (pH7.4), aseptic, and photoprotected aqueous steady state**.
- By in vitro standards, these conditions may appear **mild**. However, **complex interactions** of humoral and cellular components of body fluids involving activators, receptors, inhibitors, etc., produce **aggressive responses** to any foreign bodies through the processes of adhesion, chemical reaction, and particulate transport.
- Several scenarios leading to hydrolysis in the host can be considered. Whatever the scenario, **hydrolysis** can only occur at a site other than the surface of a polymer mass after **water of permeation** reaches that site.
- First, essentially **neutral water** is capable of hydrolyzing certain polymers (e.g., polyglycolic acid) at a significant rate. However, this simple mechanism is unlikely to be significant in polymer compositions selected for long-term in vivo biostability. Next, **ion-catalyzed hydrolysis** offers a likely scenario in body fluids.



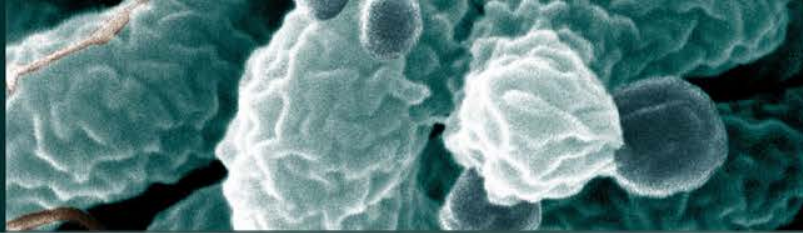
- Extracellular fluids contain ions such as: H^+ , OH^- , Na^+ , Cl^- , HCO^- , K^+ , Mg^{2+} , and $SO_2,4^-$.
- Organic acids, proteins, lipids, lipoproteins, etc. also circulate as soluble or colloidal components.
- It has been shown that certain ions (e.g., $PO_3,4^-$) are effective hydrolysis catalysts, enhancing, for example, reaction rates of polyesters by several orders of magnitude.
- Ion catalysis may be a surface effect or a combined surface-bulk effect, depending on the hydrophilicity of the polymer.
- Very hydrophobic polymers (e.g., those containing $< 2\%$ water of saturation) absorb negligible concentrations of ions.
- Hydrogels, on the other hand, which can absorb large amounts of water ($>15\%$ by weight) are essentially “sieves,” allowing significant levels of ions to be absorbed with consequent bulk hydrolysis via acid, base, or salt catalysis.
- Localized pH changes in the vicinity of the implanted device, which usually occur during acute inflammation or infection, can cause catalytic rate enhancement of hydrolysis.



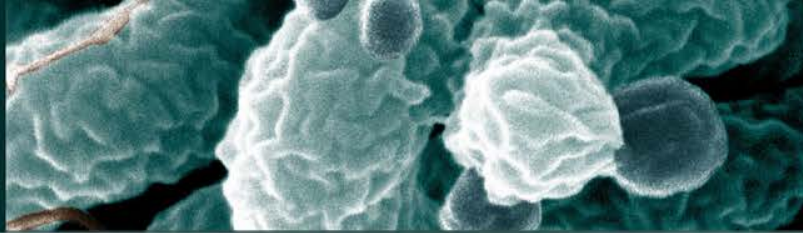
- Organic components, such as **lipoproteins**, circulating in the bloodstream or in extracellular fluid, appear to be capable of **transporting catalytic inorganic ions** into the polymer bulk by poorly defined mechanisms.
- **Enzymes** generally **serve a classic catalytic function**, altering reaction rate (via ion or charge transfer) without being consumed by **modifying activation energy** but not thermodynamic equilibrium.
- While **enzymes** function in extracellular fluids, they are **most effectively transferred onto target substrates** by direct cell contact (e.g., during **phagocytosis**).
- **Hydrolytic enzymes** or hydrolases (e.g., proteases, esterases, lipases, glycosidases) are named for the **molecular structures** they affect. They are **cell-derived proteins** which act as **highly specific catalysts** for the scission of water-labile functional groups.
- Enzymes contain **molecular chain structures and develop conformations** that allow “**recognition**” of chain sequences (receptors) on biopolymers. **Complexes** form between segments of **the enzyme and the biopolymer** substrate which result in **enhanced bond cleavage** rates. Lacking the recognition sequences of susceptible natural polymers, **most synthetic polymers** are **more resistant** to enzymatic degradation.



- Nevertheless, comparative studies have shown **some enhancement of hydrolysis** rates by enzymes, particularly with **synthetic polyesters and polyamides**.
- Apparently **the enzymes** can recognize and interact with structural segments of the polymers, or more accurately, of the **polymers coated with serum proteins, to initiate their catalytic action** in vivo.
- **Enzymes** with demonstrated effects on hydrolysis rates can be **quite selective** in the presence of **several hydrolysable functional groups**.
- For example, **polyether urethane ureas and polyester urethane ureas** exposed to **hydrolytic enzymes** (an esterase, cholesterol esterase, and a protease, elastase) were observed for rate and site of hydrolysis.
- **Enzyme catalysis** was clearly observed for the **ester groups** while the **hydrolytically susceptible urea, urethane, and ether groups** did **not show** significant hydrolysis as indicated by release of radiolabeled degradation products.



- Many enzymes exert **predominantly a surface effect** because of their great molecular size, which prevents absorption.
- **Even hydrogels** [e.g., poly(acrylamide)], which are capable of absorbing certain proteins, have **molecular weight cutoffs** for absorption well below those of such enzymes.
- However, as the **degrading surface** becomes roughened or fragmented, enzymatic action may be enhanced as a result of **increased surface area** if the substrates remain accessible to phagocytic cells that contain the active enzymes.
- Implanted devices that are **in continuous motion** relative to neighboring tissue can **provoke inflammation, stimulating enzyme release**.

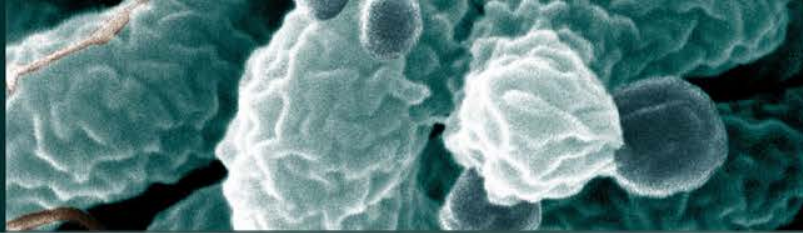


Hydrolysis: Preclinical and Clinical Experience

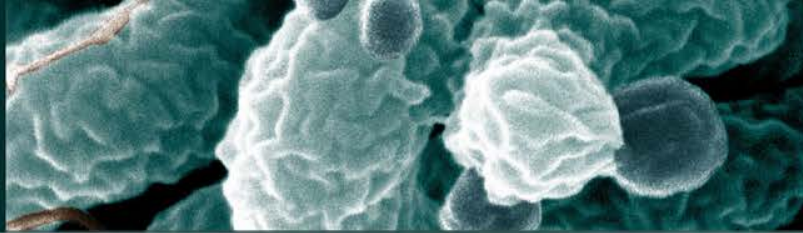
- A discussion of **in vivo responses** of **several prominent polymer** compositions known to be susceptible to hydrolysis follows.

Polyesters

- Poly (ethylene terephthalate) (PET), in woven, velour, or knitted fiber configurations, remains a primary choice of cardiovascular surgeons for large-diameter vascular prostheses, arterial patches, valve sewing rings, etc.
- It is a strong, flexible polymer, stabilized by high crystallinity as a result of chain rigidity and orientation and is often considered to be **biostable**.
- Yet, over several decades, there have been numerous reports of **long-term degeneration** of devices in vivo, owing to breakage of fibers and device dilation.
- Proposed causes have been **structural defects**, **processing techniques**, handling procedures, and hydrolytic degradation. Systematic studies of PET implants in healthy dogs have shown **slow degradation rates**, which were estimated to be equivalent to those in humans.

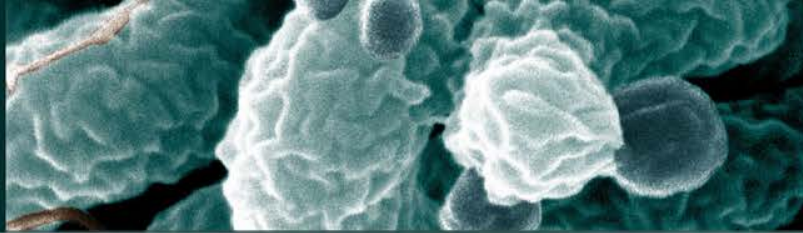


- For **woven patches** implanted subcutaneously, a mean **total absorption time** by the body of **30 ± 7 years**, with **50% deterioration of fiber strength in 10 ± 2 years** was projected.
- In infected dogs, however, where **localized pH dropped** to as low as 4.8, degradation was **enhanced exponentially**, with complete loss of properties within **a few months**.
- **Human implant** retrieval studies have shown significant evidence of **graft infection**. Besides the obvious pathological consequences of infections, the **enhanced risk of polymer degradation** is a cause for concern.
- **Aliphatic polyesters** are most often intended for use as **biodegradable polymers**, with poly(caprolactone), for example, undergoing a significant decrease in molecular weight as indicated by **a drop of 80-90% in relative viscosity within 120 weeks** of implant.

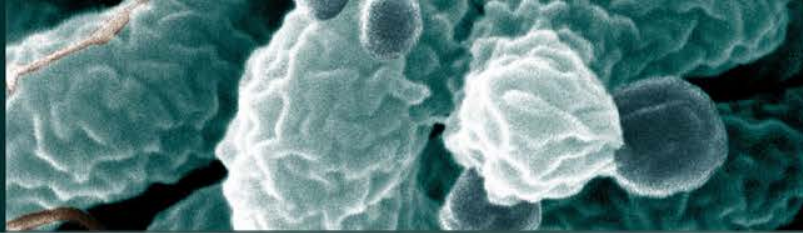


Poly(ester urethanes)

- The earliest reported implants of polyurethanes, dating back to the 1950s, were **cross-linked, aromatic poly(ester urethane) foam** compositions.
- Their use in plastic and orthopedic reconstructive surgery initially yielded **promising results**.
- Acute inflammation was low.
- Tissue ingrowth promoted **thin fibrous capsules**.
- However, **within months they were degraded** and fragmented, producing untoward **chronic effects**.
- Foci of **initial degradation** are generally considered to be the **polyadipate ester** soft segments which undergo **hydrolysis** (*Ch.6.2: Fig. 3*).
- By comparison, corresponding poly(**ether** urethanes) are **very resistant to hydrolysis**, although more susceptible to oxidation (see the section on oxidative biodegradation).

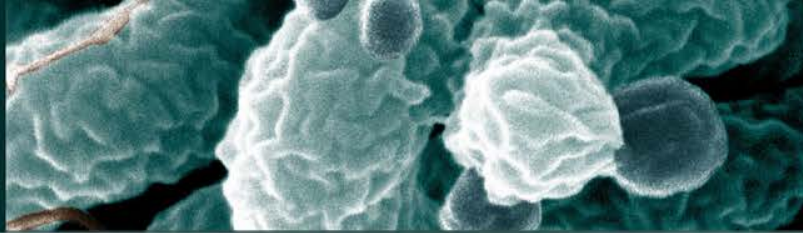


- Whether such **hydrolytically degraded poly(ester urethanes)** subsequently produce meaningful levels of **aromatic amines (suspected carcinogens)** by hydrolysis of urethane functions in vivo is currently an unresolved subject of considerable debate.
- It is noteworthy that poly(ester urethane) foam-**coated silicone mammary implants** have survived as commercial products for decades, despite their known tendency to degrade.
- Apparently, **the type of fibrous capsules** formed on devices containing degradable foam were **avored** by some clinicians **over** those caused by **smooth-walled silicone** implants.
- In large device, **unstabilized tissue ingrowth**, the **frictional effects of sliding** may cause **increased capsule thickness** and **contraction along with extensive chronic inflammation**.

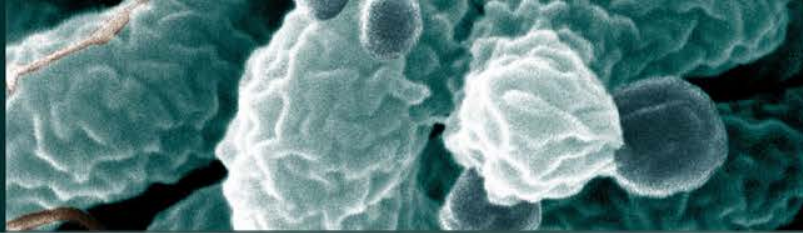


Polyamides

- **Nylon 6** (polycaprolactam) and **nylon 6,6** (poly(hexamethylene adipic amide)) contain a hydrolysable amide connecting group, **as do proteins**.
- These synthetic polymers can **absorb 9-11% water**, by weight, at saturation. It is predictable, then, that they **degrade by ion-catalyzed surface and bulk hydrolysts** (Fig.1).
- In addition, hydrolysis due to **enzymatic catalysis** leads to **surface erosion**. Quantitatively, nylon 6.6 lost **25% of its tensile strength after 89 days**, and **83% after 726 days** in dogs.
- An example of polyamide degradation of particular consequence involved the in vivo fragmentation of the **nylon 6 tail string** of a **intrauterine contraceptive device**. This string consisted of a nylon 6-sheath around nylon 6 multifilaments.
- The combination of **fluid absorption (>10%)** and **hydrolysis** was claimed to produce **environmental stress cracking**.
- The **cracked coating** allegedly provided **a pathway for bacteria** to travel from the vagina into the uterus, resulting in **significant pelvic inflammatory disease**.

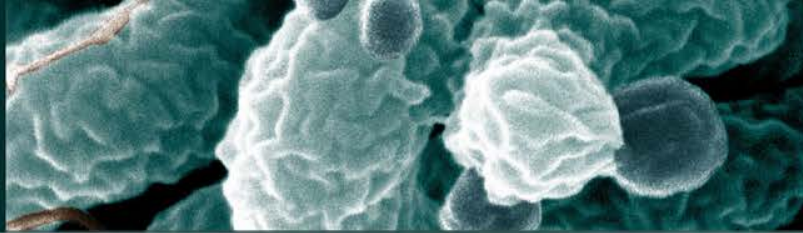


- Degradation of a poly(arylamide) intended for orthopedic use (the fiber-reinforced polyamide from m-xylylene diamine and adipic acid) was also shown in a rabbit implant study,
- [Although the material provoked a foreign-body reaction comparable to a polyethylene control, surface pitting associated with resolving macrophages was noted at 4 weeks and became more pronounced by 12 weeks. This result was not predicted since polyarylamides are very resistant to solvents and heat.]
- Polyamides with long aliphatic hydrocarbon chain segments [e.g., poly(dodecanamide)] are more hydrolytically stable than shorter chain nylons and correspondingly degrade slower in vivo.



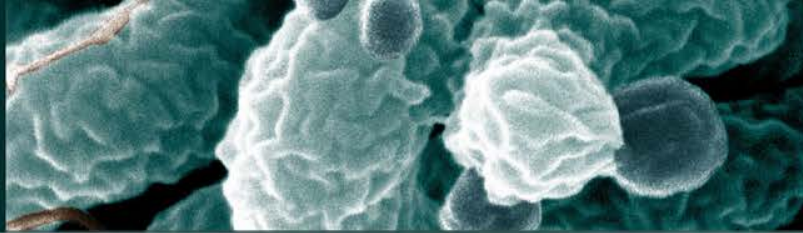
Poly(alkyl cyanoacrylates)

- This class of polymers used as **tissue adhesives** is noteworthy as a rare case in which carbon-carbon bonds are cleaved by hydrolysis (*Ch.6.2: Fig. 1*).
- This occurs because the **methylene (-CH₂-) hydrogen** in the polymer is highly activated inductively by **electron-withdrawing neighboring groups**. Formation of the polymer adhesive from monomers is base catalyzed, with adsorbed water on the **adherend being basic** enough to initiate the reaction.
- **Catalysts** for equilibrium reactions **affect the reverse**, as well as the forward reaction. Therefore, **water** associated with tissue can induce **polycyanoacrylate hydrolysis** by a “reverse Knoevenagel” reaction (*Ch.6.2: Fig. 1*).
- More **basic conditions** and (as suggested by in vitro cell culture or implant studies) **enzymatic processes** are much **more effective**.
- In chick embryo liver culture (a rich source of a variety of enzymes), methyl cyanoacrylate **degraded much faster** than in cell culture medium alone.
- In animal implants, poly(methyl cyanoacrylate) was extensively **degraded within 4-6 months**.
- **Higher alkyl** (e.g., butyl) homologs **degraded slower** than the methyl homolog and were **less cytotoxic**. -> **safe length ?**

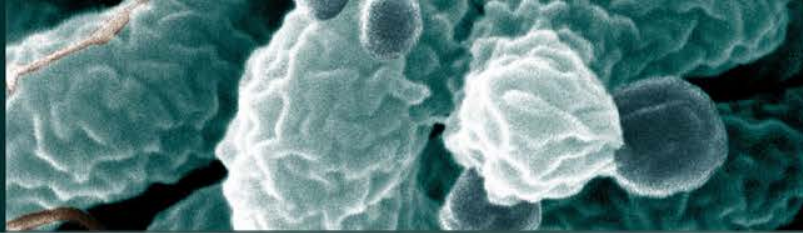


Polymers Containing Hydrolyzable Pendant Groups

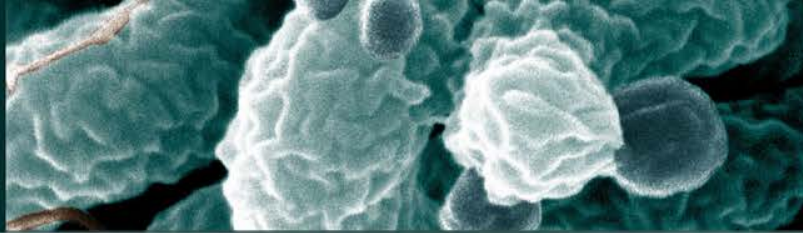
- Certain polymers intended for long-term implantation consist of **biostable main-chain sequences** and **hydrolysable pendant groups**.
- **Poly(methyl methacrylate)** (PMMA) used in bone cements and intraocular lenses is an example of a hydrophobic polymer with a stable hydrocarbon main chain and **hydrolysable ester side groups**.
- It has been proven, **over decades** of use, to provide reliable, stable service.
- Another polymer system with a hydrocarbon backbone, **poly(methylacrylate-co-2-hydroxyethyl acrylate)** also contains hydrolysable ester side groups. This polymer, which forms **hydrogels** in an aqueous environment, has been used as a “**scleral buckling**” device for retinal detachment surgery. Basically, the dry polymer, shaped as a band or ring, placed as a “**belt**” around the sclera, expands through hydration to create an indentation in the zone of the retinal detachment **to reestablish retinal contact**.
- The device is left in place as a **permanent implant** for “**exoplant**” as it is sometimes called because it is external to the sclera. This hydrogel device, introduced into clinical practice in the 1980s, apparently performed satisfactorily **for years** as an approved product.



- However, in the 1990s, reports of **long-term complications** of these hydrogel scleral buckles **began to surface**. The hydrogel structures resumed **swelling**, sometimes **with fragmentation**, after maintaining stable dimensions for years.
- One report described a difficult explanation 13 years after implantation. **Pressures** applied to the eye by this swelling have led **to blindness** and loss of the eyeball. Hydrogel scleral buckles are **no longer used** in retinal surgery.
- Very **little speculation** has been provided in published articles about the mechanism of failure of acrylate scleral buckling devices other than that **chemical degradation has occurred**.
- I suggest that a likely mechanism involves **hydrolysis** of the ester side groups enhanced by the **hydrophilic nature** of the polymer (as contrasted to hydrophobic polymers such as PMMA).
- Hydrolysis of **either of the two acrylate esters** in the polymer chain provides **an acrylic acid moiety**. Linear poly(acrylic acid) is fully **water soluble** and each hydrolytic event renders the polymer **more hydrophilic** and subject to **enhanced swelling**.
- This process is **slow but inexorable** in the case of the scleral buckling device.



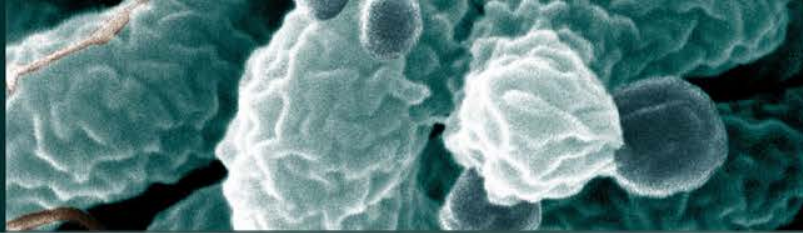
- The valuable lesson is that devices **with intrinsically susceptible groups** can eventually degrade by predictable mechanisms.
- This may take longer than is required for pivotal preclinical qualification studies (typically **2-year animal implants**).
- If **late degradation is suspected**, therefore, **accelerated aging studies** should be performed in vitro with correlations made to in vivo studies.
- Such efforts give **valuable**, if not completely trust-worthy, information. (See this chapter, “Polymer Degradation Processes” section.)



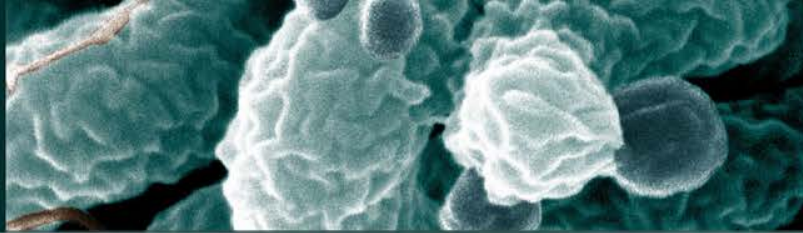
OXIDATIVE BIODEGRADATION

Oxidation Reaction Mechanisms and Polymer Structures

- While much is **known** about **the structures and reaction products** of polymers susceptible to oxidative biodegradation, confirmation of the **individual reaction steps** has **not yet** been demonstrated analytically.
- Still, mechanistic inferences are possible from extensive knowledge of physiological oxidation processes and polymer oxidation in vitro. The **polymer oxidation processes** to be discussed may be consistent with a **hemolytic chain reaction** or a **heterolytic mechanism**.
- Species such as carbonyl, hydroxyl, and chain scission products are detectable. **Classic initiation, propagation, and termination events** for hemolysis and ionic heterolytic processes are detailed in *Ch.6.2: Fig.4*.
- Except for the nature of susceptible functional groups, the principles of polymer degradation resistance stated in the section on the **structures of hydrolyzabled polymers** are valid for **predicting relative oxidation resistance of polymers**.

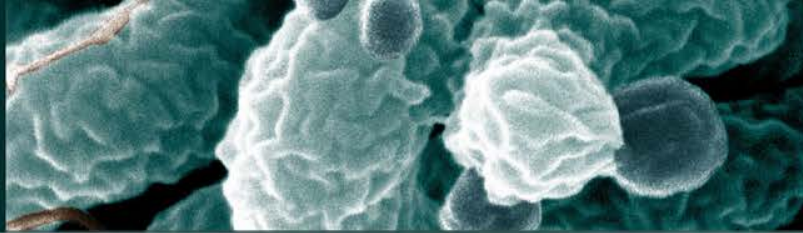


- **Sites** favored for initial oxidative attack, consistent with a hemolytic or heterolytic pathway, are those that allow abstraction of an atom or ion and provide **resonance stabilization** of the **resultant radical or ion**.
- Figure 5 provides a selection of **readily oxidized groups** and the atom at which initial attack occurs.
- In Fig. 6, examples of **radical and ion stabilization** by resonance in ether and branched hydrocarbon structures are provided.
- **Peroxy, carbonyl, and other radical intermediates** are stabilized by similar resonance delocalization of electrons from the elements C, O, H, or N.
- **Two general categories** of oxidative biodegradation, based on the source of initiation of the process, are direct oxidation by **the host and device** or **external environment** mediated oxidation.

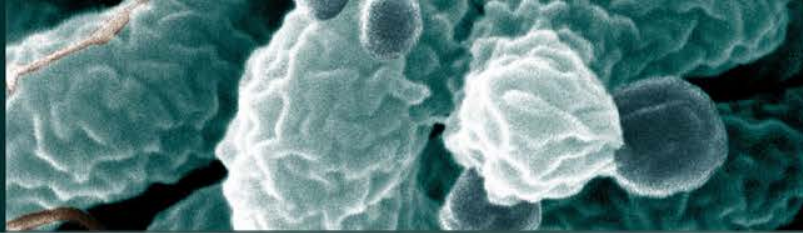


Direct Oxidation by Host

- In these circumstances, **host-generated molecular species** effect or potentiate oxidative processes directly on the polymer. Current thinking, based on solid analytical evidence, is that such reactive molecules are derived **from activated phagocytic cells** responding to the injury and **the properties of the foreign body** at the implant site.
- **These cells**, which originate in the bone marrow and populate the circulatory system and connective tissues, are manifest as **two types**, the **neutrophils** (polymorphonuclear leukocytes, PMNs) and the **monocytes**.
- The latter can differentiate into **macrophage** and **foreign body giant cell (FBGC)** phenotypes.
- Much work is **under way to elucidate** the sequence of events leading to **phagocytic oxidation** of biomaterials.
- Certain important **processes of wound healing** in the presence of **biologically derived foreign bodies** such as bacteria and parasites, are showing some **relevance to biomaterial implants**.



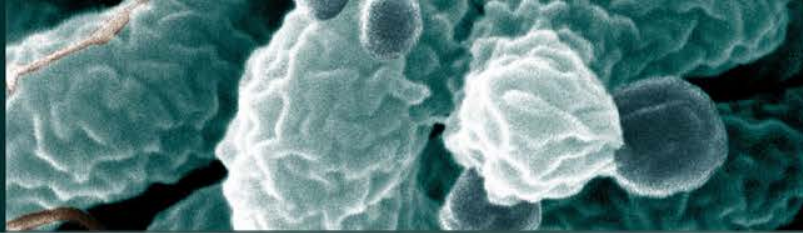
- **Neutrophils**, responding to chemical mediators at the wound site, mount a **powerful but transient chemical attack** within the first few days of injury.
- Chemically **susceptible biomaterials** may be affected if they are in **close apposition to the wound site**.
- **Activated macrophages** subsequently multiply and **subside within days** at a benign wound site or **in weeks** if stimulants such as toxins or particulates are released at the site.
- Their fusion products, **foreign body giant cells**, can **survive for months to years on the implant surface**.
- **Macrophages** also remain **resident in collagenous capsules** for extended periods.
- While we recognize that the **mechanism** of cellular attack and oxidation of biomaterials is as yet unconfirmed, the following discussion attempts to provide **logical biological pathways** to **powerful oxidants** capable of producing known degradation products.
- Both **PMNs and macrophages** metabolize oxygen to **form a superoxide anion** (O_2^-). This intermediate can undergo transformation to more powerful oxidants on conceivably can **initiate hemolytic reactions** on the polymer.



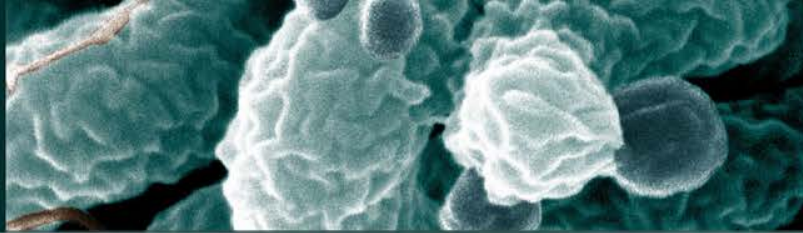
- **Superoxide dismutase (SOD)**, a ubiquitous peroxidase enzyme, can catalyze **the conversion of superoxide to hydrogen peroxide**, which in the presence of myeloperoxidase (MPO) derived from PMNs, is converted to **hypochlorous acid (HOCl)**.
- A potent biomaterial oxidant in its own right, **hypochlorite** can oxidize free amine functionality (e.g., in **proteins**) to **chloramines** that can perform as **long-lived sources** of chlorine oxidant.
- Hypochlorite can oxidize other substituted nitrogen functional groups (**amides, ureas, urethanes, etc.**) with potential chain cleavage of these groups.
- The following paragraphs describe potential cooperative reactions involving acquired peroxidase and free ferrous ions.
- Macrophages contain essentially no MPO, so their hydrogen peroxide is not normally converted to HOCl. However, PMN-derived **MPO can bind securely to foreign body surfaces**, and serve as **a catalyst reservoir** for macrophage or FBGC-derived HOCl production.



- If **free ferrous ion**, which is normally present in negligible quantities in the host, is released to the implant site by hemolysis or other injury, it can catalyze the formation of the powerfully **oxidizing hydroxyl radical** via the Haber-Weiss cycle.
- In a more general sense, the MPO may come from within or outside of the cell.
- Figure 8 shows radical and ionic intermediates of HOCl that may initiate biomaterial oxidation.
- Figure 9 is a diagram showing a **leukocyte phagocytic process** that employs endogenous MPO catalysis of HOCl formation.
- The foregoing discussion of sources of **direct oxidation** focused primarily **on acute implant periods** in which **bursts of PMN activity** followed by macrophage activity normally resolve within weeks.
- However, since the **foreign body subsequently remains** implanted, a sustained if futile attempt to phagocytose an implanted device provides a **prolonged release of chemicals** onto the biomaterial.

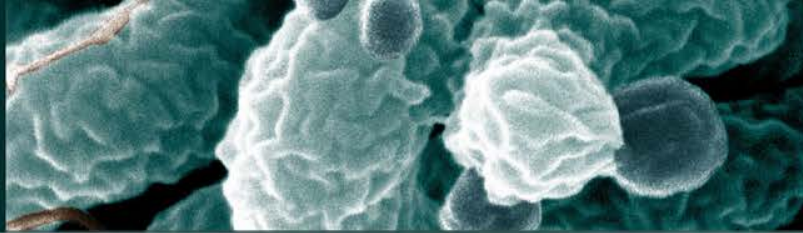


- This phenomenon, called **exocytosis**, occurs **over months to possibly years** and results primarily from **the macrophage-FBGC line**. It can contribute to **long-term chemical degradation of the polymer**.
- The **oxidation processes** induced by phagocytes are the result of oxidants produced by **general foreign body responses**, **not** direct receptor-ligand catalysis **by oxidase enzymes**.
- Attempts to degrade oxidatively susceptible polymers by direct contact with **oxidase enzymes** have produced **short-range or limited effects**.
- **Macrophages** mediate other processes, such as **fibrous capsule formation** around the device. Their **release of cellular regulatory factors** stimulates **fibroblasts to populate the implant site** and produce the **collagenous sheath**.
- Any knowledge of the effects of factors such as **fibroblasts or fibrous capsules** on rates and **mechanisms of polymer degradation** is, at this time, extremely **rudimentary**.

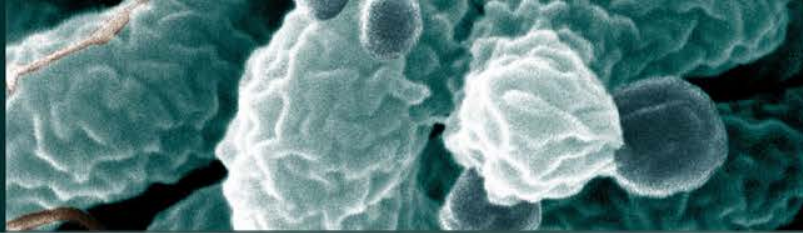


Stress Cracking

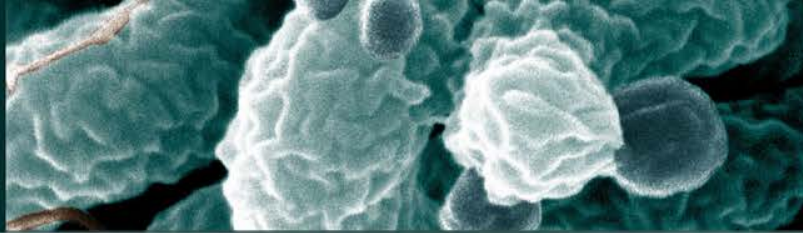
- An **important** category of **host-induced biodegradation with an oxidative** component is **stress cracking** as manifest in poly(ether urethane) elastomers.
- It differs from **classic environmental stress cracking** (ESC), which involves a susceptible material at a **critical level of stress** in a medium which may permeant but does not dissolve the polymer.
- **Classic ESC** is **not** accompanied by significant **chemical degradation**. Instead, stress cracking of polyurethanes is characterized by **surface attack** of the polymer and by **chemical changes** induced by relatively specific in vivo or in vitro oxidizing conditions.
- **Conditions relevant to stress cracking** of certain poly(ether urethane) compositions are stated in *Ch.6.2: Table 3*.
- Recent information on the stress cracking of poly(ether urethanes) and poly(ether urethane ureas) (*Ch.6.2: Fig. 3*) has provided insights which may be valid for these and other **compositions that can be oxidized**.
- **Poly(ether urethanes)**, which are resistant to hydrolysis in vivo, are **used as** connectors, insulators, tines, and adhesives for cardiac pacemakers and neurological stimulators.



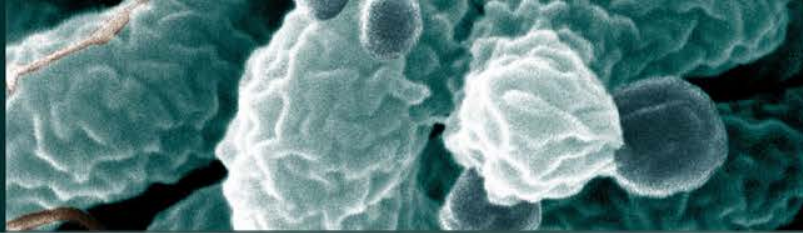
- They have performed with high **reliability in chronic** clinical applications since 1975. Certain poly(ether urethane) pacing leads have displayed **surface cracks** in their insulation after residence times in vivo of months to years. These cracks are directly related in **frequency and the ether (soft segment) content** of the polyurethane.
- Morphologically, **the cracks** display **regular patterns** predominately **normal to the force vectors** with very **rough walls**, occasionally with “**tie fibers**” bridging the gaps, indicative of **ductile** rather than brittle fracture.
- Infrared analysis indicates that oxidation does **not take place detectably in the bulk**, but only on the **surface** where extensive **loss of ether functionality(1110cm⁻¹)** and enhanced absorption in the **hydroxyl and carbonyl** regions are observed.
- Possible mechanisms for the oxidative degradation of ethers are presented in *Ch.6.2: Fig 15*.



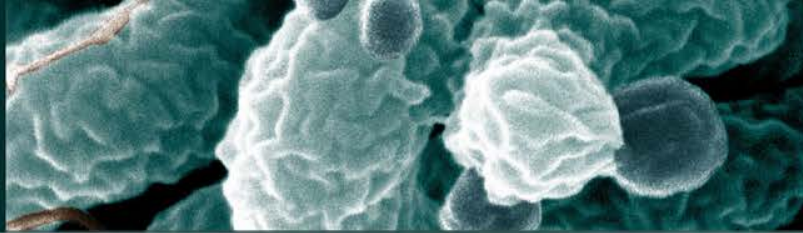
- The participation of **molecular oxygen** in the **degradation mechanism** is supported by studies which showed that poly(ether urethane urea) degradation in vitro correlate with **oxygen diffusion into the polymer bulk** after surface oxidation was initiated by hydrogen peroxide/cobalt chloride.
- In a seminal study, Zhao et al. placed **polyurethane tubing** in cages permeable to fluids and cells **under strain** (therefore under high initial stress, which was subject to subsequent stress relaxation) and implanted them in rats.
- In certain cases, anti-inflammatory steroids or cytotoxic polymers were coimplanted in the cages.
- Implants of **up to 15 weeks** were retrieved. The only prestressed samples to crack were those that did not reside in the cages with the coimplants.
- The authors concluded that **adherent cells caused the stress cracking**, and cell necrosis or deactivation inhibited crack induction.
- Subsequently, **viable phagocytic cells** were implicated as a cause of crack initiation in vivo. By **removing adherent foreign body giant cells** after implantation of a curved poly(ether urethane urea) film in a wire cage for **up to 10 weeks**, exposed “footprints” showed **localized surface cracking** on the order of several microns deep and wide.
- **Adjacent areas** of polymer which were **devoid of attached cells** were **not cracked**.



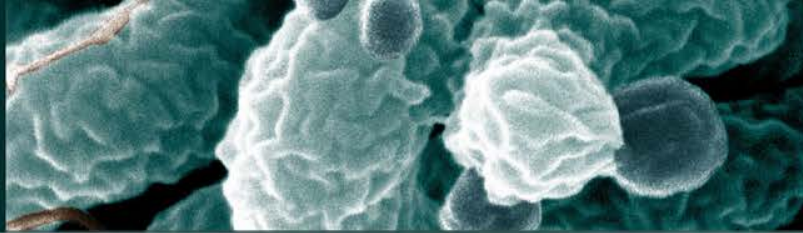
- Owing to relatively **low stresses** in the implanted film, **deep crack** propagation was **not** observed.
- In vitro studies of strained and unstrained poly(ether urethane) films **using oxidants, enzymes**, etc., have sought to **duplicate in vivo stress cracking**.
- Although some surface chemical degradation with products similar to those seen **in vivo** was demonstrated, **stress crack morphology** was **not closely matched in vitro** until recently, in two studies.
- A test which involves **immersing** stressed poly(ether urethane) tubing **in a medium of glass wool, hydrogen peroxide, and cobalt chloride** produces **cracks** which **duplicate those produced in vivo** but with rate acceleration of **up to seven times**.
- These investigators also showed that **human plasma proteins**, particularly alpha₂-macroglobulin and ceruloplasmin, enhance **in vitro stress cracking** by oxidants in patterns **morphologically similar** to those observed **in vivo**.
- The potential of **macrophages** to contribute to stress cracking of poly(ether urethanes) was verified in a recent in vitro study which succeeded in **potentiating** macrophage **oxidative effects** with **ferrous chloride** and **inhibiting** them with the **antiinflammatory steroid dexamethasone**.



- In another study, comparable **crack patterns** were produced when specimens of stressed tubing in rats were compared with those **incubated with PMNs in culture**.
- Moreover, this study revealed a difference in **chemical degradation products** with time of implant which correlated with products **from oxidants generated** primarily by **PMNs (HOCl)** and **macrophages (ONOO-)**.
- **Early** implant times, **activated PMNs**, and **HOCl** caused preferential **decrease** in the **urethane oxygen stretch peak** while **longer** implant times and **ONOO-** caused selective **loss of the aliphatic ether stretch peak** (by infrared spectroscopy).
- Taken together, the foregoing observations are consistent with **a two-step mechanism** for stress cracking in vivo.
- This hypothesis, as yet unproven, is under investigation. In the **first step**, **surface oxidation** induces very **shallow, brittle micro-cracks**.
- The **second step** involves **propagation of the cracks** in which **specific body fluid components** act on the formed cracks to **enhance their depth and width** without inducing major detectable bulk chemical reactions.



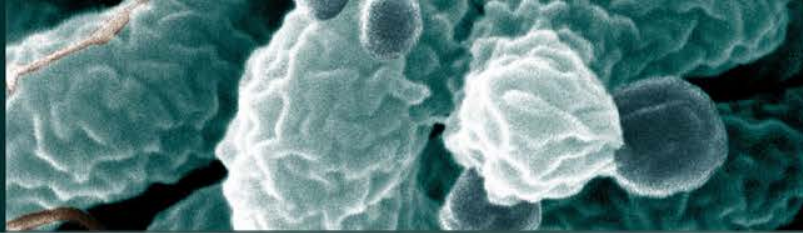
- Should this hypothesis prove correct the term “**oxidation initiated stress cracking**” would be reasonably descriptive.
- The above description of stress cracking has generally considered **static stress** such as that formed during the cooling of molten parts or the assembly of components.
- **Dynamic stresses and strains** such as those occurring during the **operation of** diaphragm or bladder heart pumps or artificial joints can cause related **cracking in areas of high flex.**
- The **cracking** has been purported to **increase with time of device operation** but to display only **minor surface chemical changes.**
- This type of stress cracking has been **controlled** by **reducing residual stress, isolating the polymer from cell contact, protecting the polymer from stress cracking media, or using stress crack-resistant polymers** (e.g., in the case of urethanes, ether-free) and **use of antioxidants** such as hindered phenols (e.g., vitamin E, Monsanto Santowhite powder).
- Stress cracking is next compared with another type of degradation, metal ion-induced oxidation.



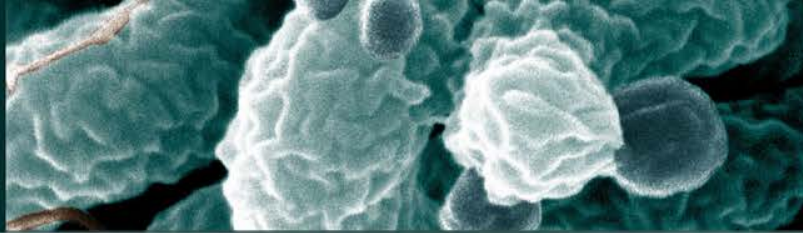
Device- or Environment-Mediated Oxidation

Metal ion-induced Oxidation

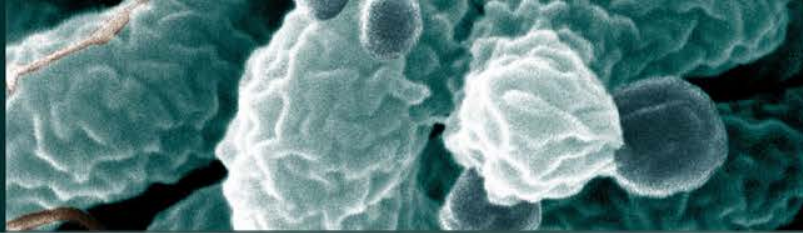
- A **process of oxidative degradation** that has, thus far, only been reported clinically for poly(ether urethane) pacemaker leads, requires, as does **stress cracking**, a very specific set of conditions.
- The enabling **variables and fracture morphology** are **quite different** from stress cracking, although oxidative degradation products area similar.
- Biodegradation of implanted devices through **stress cracking** always occurs on polymer **surfaces** exposed to cells and provides characteristic **rough walled fissures** (indicative of **ductile fracture**) oriented **perpendicular to the stress vector** (Ch.6.2: Figs.11-14).
- **Metal ion-induced oxidation** initiates on the enclosed **inner surfaces** of pacing lead insulation **near corroded metallic** components and their entrapped corrosion products. **Smooth crack** walls and microscopically **random crack** orientation is indicative of **brittle fracture** (Ch.6.2: Figs.16, 17).
- Macroscopically, crack patterns that **track metal component** configurations may be present (Ch.6.2: Fig. 18).



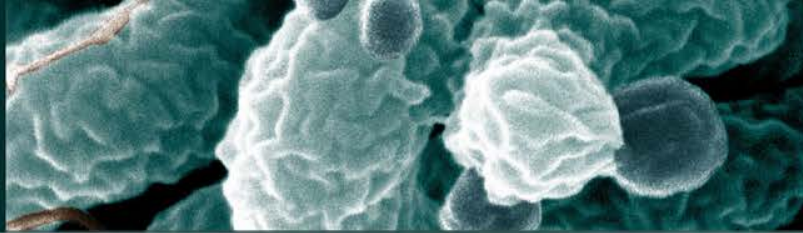
- Degradation products which may be found **deeper in the bulk** than with stress cracking are again indicative of brittle fracture.
- This phenomenon called metal ion-induced oxidation has been confirmed by in vitro studies in which **polyether urethanes** were aged in metal ion solutions of different standard oxidation potentials.
- **Above an oxidation potential of about +0.77**, chemical degradation was **severe**. **Below** that oxidation potential, changes in the polymer that are characteristic of **simple plasticization** were seen.
- This technique also showed that metal ion-induced oxidation was **proportional to the ether content** of the polyurethane.
- The effect of various metals on oxidation in vivo and in vivo HAS also been studied. **Different metallic components** of pacing lead conductors were sealed in poly(ether urethane) lead tubing and immersed in **3% hydrogen peroxide** at 37°C for up to 6 months or **implanted in rabbits** for up to 2 years.
- Both techniques resulted in **corroded metals** and **degraded tubing lumen surfaces** under certain conditions **within 30 days**. In particular, the in vivo interaction of body fluids with cobalt and its alloys resulted in **oxidative cracking** of the polymer.
- The metal ion-induced oxidation process clearly involves **corrosion of metallic elements** to their ions and **subsequent oxidation** of the polymer.



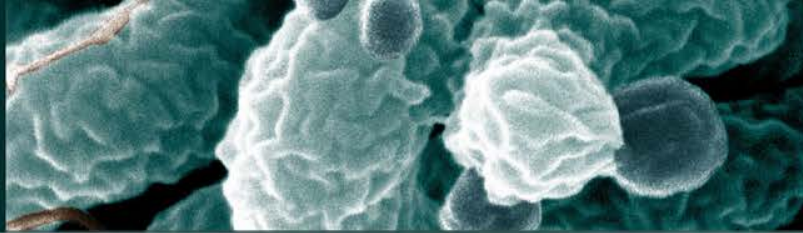
- In operating devices, the **metal ion** may be formed by solvation, galvanic or electrolytic corrosion, or chemical or biochemical oxidation (*Ch.6.2: Fig. 19*).
- In turn, these metal ions develop **oxidation potentials** that may well be enhanced in body fluids over their **standard half-cell potentials**.
- As strong oxidants, they produce intermediates or attack the polymer to **initiate the chain reaction** (*Ch.6.2: Fig. 20*).
- Metal ion-induced oxidation is therefore the result of a highly **complex interaction** of the device, the polymer, and the body.
- Should metal ion-induced oxidation be a possibility in an implanted device, several approaches are available **to control this problem**. They are not universally applicable, however, and should be incorporated only if functionality and biocompatibility are retained.
- Potentially useful techniques include using **corrosion-resistant metals**, “flushing” corrosive ions away from electrolyte solutions, incorporating **appropriate antioxidants**, and using **oxidation-resistant polymers** if available.
- Recently, **polyurethane elastomers** with enhanced oxidation stability have been developed. They are segmented, **ether- and ester-free polymers** with unconventional soft segments, including, for example, **hydrogenated polybutadiene, polydimethyl-siloxane, polycarbonate, and dimerized fat acid derivatives**.



- In implant tests, they have shown **reduced tendency** to stress crack, and some of them have shown high resistance to metal ion oxidants in vitro.
- **Early attempts** to stabilize polyurethanes by **laminating** more biostable polymers (such as silicone rubbers) to tissue-facing surfaces have met with **limited success in dynamic applications** due to delamination tendencies.
- More **recent approaches** to stabilizing polyurethanes to oxidative attack in situ have involved the use of **surface modifying macromolecules** (SMMs) and **surface modifying end groups** (SMEs).
- SMMs, typically **fluorocarbon-based polymers**, are blended with the polyurethanes during processing and migrate to the surface prior to implantation. SMEs are moieties (typically **polysiloxane**) bonded to polyurethane as end groups.
- The covalently modified polyurethanes may be used in bulk or as additives to conventional polyurethanes. Both approaches have provided enhanced in vivo stability for polyurethane implants; however, the **long-term effects** of these treatments are **not, as yet**, known.
- SMMs have been covalently modified with **bioactive agents** such as antioxidants to provide **further degradation resistance**. All of the “barrier” strategies to protecting polyurethanes described above appear to have validity, at least for protecting polyurethanes **in the short term**.

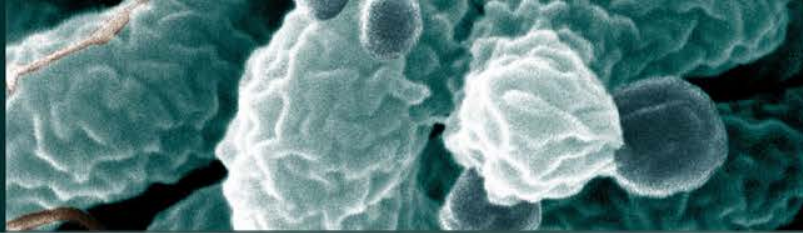


- The **long-term** (multiyear) benefits of these approaches remain to be seen in light of issues such as **surface dynamics**, **interfacial interactions**, and **coating durability**.
- A caveat relevant to the opening paragraphs of this chapter is that all of these polyurethane modifications, while potentially providing enhanced resistance to biodegradation, still allow susceptibility to attack by biological components, often at slow rates.
- With **poly(carbonate urethanes)**, for example, **superior oxidation resistance** has been observed in several studies. However, in aqueous media in vitro and in vivo, **slow degradation** attributable to **simple hydrolysis** was also detected.
- The **body fluid environment** provides a relatively **stable long-term hydrolytic medium**, generally less subject to “respiratory bursts” that strongly enhance oxidative processes. Although phagocytic processes may also produce **hydrolytic enzymes**, their effects on synthetic polymers are **specific and limited**. **Hydrolysis**, therefore, may be expected **to take place continuously** with poly(carbonate urethane) integrity susceptible to a combination of mechanical stress and vigorous oxidizing conditions.
- Studies of up to 3 years’ implantation have indicated detectable hydrolysis. Only **long-term** implant studies (e.g., **5 years or greater**) would **confirm** the acceptability of poly(carbonate urethanes) or, for that matter, other new polymers having potentially susceptible groups.



Oxidative Degradation Induced by External Environment

- Under very limited circumstances, the body can transmit **electromagnetic radiation** that may affect the integrity of implanted polymers.
- For example, the **cornea and vitreous humor of the eye** as well as **superficial skin layers** allow the **passage of long-wave (320-400 nanometer) “ultraviolet A” radiation**. Absorption of ultraviolet radiation causes electron excitation that can lead to **photo-oxidative degradation**.
- This process has been suggested in the breakdown of **polypropylene** components of **intraocular lenses**. In **maxillofacial** **exo- and very likely endo-protheses**, **elastomers** may undergo undesirable changes **in color** and **physical properties** as a consequence of exposure to natural sunlight-frequency radiation.
- Photo-oxidation mechanisms involving the urethane function of **aromatic poly(ether- or poly(ester urethanes)** are shown in *Ch.6.2: Fig. 21*.
- **Antioxidants and ultraviolet absorbers** provide limited protection for these materials.

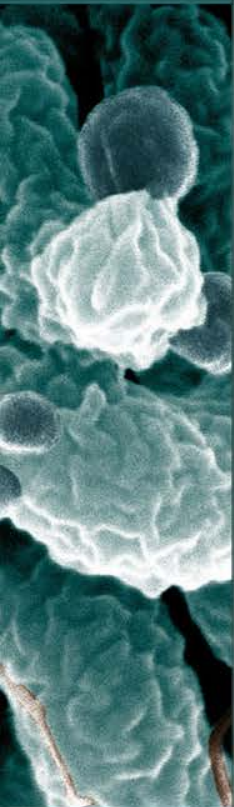


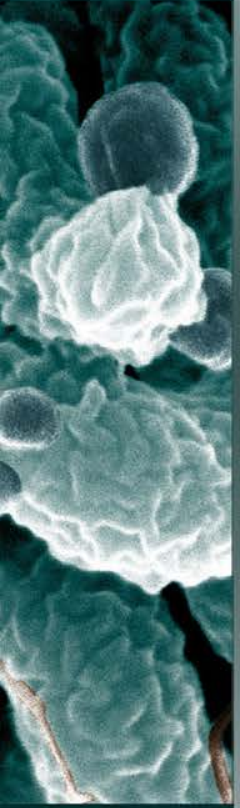
CONCLUSION

- Polymers that are carefully chosen for use in implanted devices generally serve effectively for their **intended lifetimes** if they are properly processed and device-**material-host interactions** are adequately addressed.
- In certain limited circumstances, **unintended hydrolytic or oxidative biodegradation** occurs. This may be induced by direct attack **by the host** or via the intermediacy of the device or the **outside environment**.
- With **susceptible polymers**, protective measures can be taken to ensure extended efficacy, although new, biodegradation **resistant polymer** which are on the horizon may require less protection.
- Knowledge of **biodegradation mechanisms** and the employment of **appropriate countermeasures** will promote the continued growth **in compositions** and uses of polymers as implantable biomaterials.

QUESTIONS

1. The two major mechanisms of chemical degradation of polymers in vivo are hydrolysis and oxidation. Given the following polymers, indicate whether they are susceptible to hydrolysis, oxidation or both processes. If they would be highly resistant to both processes, so indicate.
 - Poly(carbonate urethane)
 - Poly(ether urethane)
 - Poly(ester urethane)
 - Aromatic polyester, poly(ethylene terephthalate)
 - Polypropylene
 - Polyethylene(linear)
 - Polytetrafluoroethylene
 - Polydimethylsiloxane
2. What are some common polymer functional groups susceptible to hydrolysis?



- 
3. In the past, investigators have fabricated heart valves from “aromatic polyurethanes” Which contain polyether, urethane, and urea functional groups. These devices were intended to last for several years in use, but have generally failed to perform for those periods.
 - What physical and chemical forces are acting on the heart valves in vivo?
 - What are the most likely mechanisms (physical and chemical) of degradation leading to failure of these devices: State at least three mechanisms.
 4. As a materials scientist, you have experience with polyurethanes as biomaterials. Among the readily available commercial elastomers, they demonstrate the best combination of physical properties, but are susceptible to biodegradation, mostly through their polyether or polyester soft segments. You are charged with designing a biostable elastomer (polyurethane or otherwise).
 - Choose an approach to produce a chemically stable elastomer that retains reasonable physical properties for at least 3 years.
 - Describe 5 tests/analyses (in vitro/in vivo) which may be used to characterize this elastomer and confirm its potential stability.