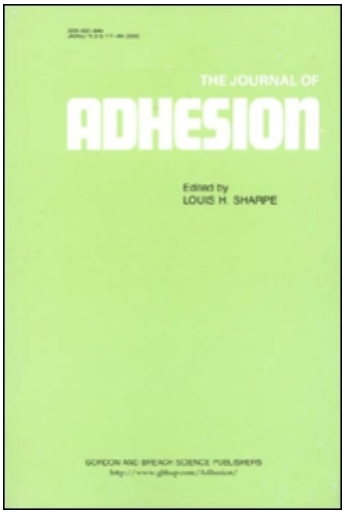

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Modification of Surfaces to Meet Bioadhesive Design Goals: A Review

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Modification of Surfaces to Meet Bioadhesive Design Goals: A Review†

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The modern range of medical devices presents contrasting requirements for adhesion in biological environments. Strong bioadhesion is desired in many circumstances to assure device retention and immobility. Minimal adhesion is absolutely essential in others, where thrombosis or bacterial adhesion would destroy the utility of the implants. A brief review is given of some analytical approaches, based in adhesion science, most useful in addressing these needs. Familiar correlating parameters, such as the critical surface tension, are surprisingly good in predicting bioadhesive outcomes such as tissue integration. The example of dental implants is given to illustrate this correlation. In every case, primary attention must be given to the qualities of the first interfacial conditioning films of bio-macromolecules deposited from the living systems. For instance, fibrinogen deposits from blood may assume different configurations on surfaces of different initial energies, and thus trigger different physiological events. Standard surface modification techniques, such as siliconization, when properly quality controlled can yield improved blood-compatible devices like substitute blood vessels and artificial heart sacs. Promising extensions to new areas of biotechnology are forecast.

KEY WORDS Adhesion; bioadhesion; dental implants; medical devices; review; surface modification.

INTRODUCTION

This brief review presents some concepts of surface modification as recently applied successfully in the field of bioadhesion. Careful

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surface preparation is necessary to assure tenacious biological adhesion where that is desired; for example, in the firm tissue and bone integration of dental and orthopedic implants.[1] Different surface conditions are required for effective function of such devices as substitute blood vessels and artificial heat sacs, where biological adhesion must be minimized.[2]

As has been presented elsewhere[3,4,5] scrupulous cleansing of all manufacturing and handling debris by a method such as radio frequency glow-discharge treatment[6,7] can be critical to the performance and success of such devices as the femoral stem artificial hip prosthesis and modern dental implants.[4,8,9,10,11] Such cleaning or surface preparation regimens, that are also capable of providing sterile appliances for immediate implantation, are even more important when it is recognized that conventional sterilization techniques (such as steam autoclaving, ethylene oxide gas sterilization) or disinfection techniques (such as immersion in alcohol or glutaraldehyde solutions) usually leave disabling residues. These surface deposits are of highly variable and usually bio-incompatable consequence on devices to be implanted in human hosts.[12,13]

DISCUSSION

Analytical approaches

Considerable advances have been made recently in the field of "osseo-integration," as defined by Swedish workers,[14,15] and in tissue integration. More than 10,000 patients have benefited for over a decade from improved dental implants used as permanent bioadhesive fixtures for the placement of load-bearing dentures. Those patients are representative of many thousands of others who cannot tolerate dentures of conventional design because of irreversible loss of their mandibular or maxillary bone structures.

Other groups, using subperiosteal dental implant designs, have evaluated fully buried implants in contact with both tissue and bone while providing a critical permucosal post extending into the nonsterile oral cavity.[8,9] Particularly promising improvements in bioadhesion have been obtained by attention to the surface conditioning of the implants before their biological placement. Prior art

results, neither desirable nor clinically tolerable, were dominated by dehiscence of the tissues from these buried implants, and associated with inflammation and infection around the permucosal posts. These results have been almost completely reversed to routinely show superior tissue bonding at all segments of the devices, when attention is properly focussed on the initial interfacial conditions.

The crucial learning experiences came from a series of studies that placed implants of various surface qualities into the subdermal fascial zones of New Zealand white rabbits. Harvesting of these specimens and their surrounding tissue capsules was followed by a protocol for analysis that allowed, for the first time, inspection of the actual interfacial events from both the metallic side of the joint and the side provided by the investing biological tissue. In this model, it was discovered that implantation times as short as ten to twenty days were sufficiently long to discriminate convincingly between two different states of adhesion: (1) cases of tenacious biological coupling to properly prepared metallic implants, and (2) those cases—unfortunately more representative of conventional dental and orthopedic implants—in which biological adhesion was poor to negligible (with consequent nonfunctional results).

Multiple, interfacial biophysical analytical methods (internal reflection infrared spectroscopy,[16] ellipsometry,[17] contact potential determination,[18] contact angle measurement,[19] scanning electron microscopy, energy dispersive X-ray analysis, and glancing angle X-ray diffraction) were applied in sequence to the identical thin deposits of biological matter still in place on the relevant implanted substrata. These methods provided sufficient characterization of the crucial interfacial conditioning layers to strongly implicate the adsorbed configuration of the first deposited biological macromolecules as the determining factor in the success or failure of variously treated implants.

It was, obviously, important to carry the actual implant materials (such as those of the cobalt–chromium alloy family favored for orthopedic and dental implants in many cases) through these implantation trials concurrently. Test objects that lend themselves more readily to analytical procedures are not yet widely accepted by the biomedical device development community. Biologists are not generally willing to accept arguments that criteria like surface energy, for example, are sufficient to accurately predict biological

responses to diverse implanted materials. Nevertheless, the growing experimental data base now available does support the conclusion that, independently of the bulk composition of various implants of polymeric or metallic character, their outermost atomic constitutions (as assayed by classical surface chemical/physical criteria) are the determining parameters. The evidence is particularly strong with regard to the configuration and subsequent bio-attachments of the first spontaneously deposited biological conditioning films.

The critical surface tension, related to the outermost atomic constitution of most materials now available to the biotechnology community—ranging from the very low surface energy fluorocarbons to the intrinsically high surface energy, clean metals and ceramics—has proven to be an excellent correlating parameter.[20,21,22,23] For example, when implants having critical surface tensions in the low 20's dynes/cm, as usually results from contaminating films of oils, greases, or silicones employed in various fabrication and packaging steps, are placed into living tissue, the tissue response is almost universally that of "walling off" the implant. The host surrounds the implant with a scar-like capsule, exhibiting no adhesion to the foreign material. There can be no immobilization, therefore, of that implant at its placement site. In the zone around the amorphous, scar-like capsule is usually connective tissue of poor cellularity. A disorganized fibrous matrix forms, usually showing poor mechanical strength not leading to permanent retention of implants of this low-surface-energy character. In those circumstances where some tissue adhesion to the implant has been noted, it was easily dislodged from the original implant surface as well as delaminated in layers from itself by even gentle mechanical force.

In striking contrast, materials of identical bulk composition but prepared to exhibit higher surface energies—usually with a dominant proportion of polar surface binding sites exposed, as well—evoke minimum capsule formation. They become, instead, tightly integrated through only a very thin, strongly bound layer of biomacromolecules to aggressively dividing, organizing connective tissue. The host tissue response securely binds such implants in place and provides the desired anchorage in the placement sites. An insufficiently explored feature of this improvement in surface-modulated response of the adjacent host tissue is its propagation,

for many cell layers, into the adjacent surrounding tissue zones. The spreading cells seem to stimulate mitogenic activity that increases adjacent cell density two- to threefold over that surrounding lower energy materials. To the inexperienced examiner of histologic sections of such tissues, this desirably enhanced cellularity and aggressive proliferative activity might be mistaken as an induction of malignancy. Obviously, such high surface energy materials brought into contact with epidermal tissues (of known greater susceptibility to neoplastic or pre-neoplastic transformation) might increase the malignant potential. This may, indeed, be a causative factor yet incompletely investigated in such circumstances as asbestosis, mucosal carcinoma, or cervical cancer where synthetic materials (*e.g.*, in the latter case, the "tail strings" of intrauterine contraceptive devices) are in long-term contact with sensitive tissues.

It will be a surprise to most investigators that the usually applied methods of electropolishing and acid passivation of metallic implants do not, in fact, remove the organic contamination at their outermost faces. Metals treated by such methods are not substantially more bioadhesive than the simply mechanical polished versions.[5,13]

In all instances, the crucial conditioning event once the biological milieu has been entered, is the spontaneous deposition of usually glycoproteinaceous macromolecules from the fluids at the implant site. This event transduces the controllable surface properties of the modern materials of biotechnology to the living biological strata with which they must interact in the manner desired by the device designer. Before describing the molecular details so far investigated in this regard, a brief example of the human application of the principles already described is useful.

Clinical applications

Many unfortunate persons lose their teeth to disease or traumatic accidents, and subsequently lose the bone in which those teeth were set. They face a difficult future of poor nutrition and social discomfort due to their disfiguring injuries. Dental implants, particularly of the custom made subperiosteal type, lend themselves well to correction of these defects; they depend absolutely for their

success on tenacious integration with the tissue into which they are placed. The implants must display an ability to sustain significant mechanical, thermal, and biological stresses in the oral cavity. Applying the glow-discharge treatment technique to such custom fabricated implants of cobalt–chromium alloy (Vitallium) and storing the appliances in boiled, distilled water (to preserve their high-surface-energy state and sterility) prior to implantation, has proven to be a serviceable method of surface preparation. In the course of studies to qualify the simple, underwater method for preservation and storage, it was discovered that inadvertent transfer of non-noble, usually ferrous metals to the appliances had often occurred during their fabrication. Various polishing and finishing tools used in the dental laboratory transferred corrosion-susceptible components that had previously gone unobserved on dental implant devices, because no prior surface preparations required their storage under water. Elimination of this source of inadvertent metallic contamination was accomplished in a straightforward manner by reserving the dental laboratory tools to be used on corrosion-resistant alloys to those alloys, exclusively.

The critical event observed, when these properly prepared dental implants are first placed into the surgical site in the oral cavity, is uniform coating of the metal with a thin, tenaciously adherent film of blood from that site. It is at this stage that the adhesive potential of the high surface energy implant is first expressed in the strong binding and denaturation of the usually fibrinogen-dominated blood protein layer. Subsequent remodeling of that film by the healing adjacent tissues (after the implant is covered over by the oral flap) then proceeds in a manner that allows excellent cellular adhesion and immobilization in the host. After many weeks of such healing time, the implants are then ready to receive denture placements which restore both chewing and aesthetic qualities to the patients fortunate enough to have this modern therapy offered to them. X-ray documentation of the continued acceptance of these implants, without inducing further bone resorption in the jaw, continues to endorse this approach as a significant improvement in what was once a not very successful therapeutic modality.

We are coming closer to the prescription given by Dr. John Autian regarding biomedical devices: "When used as intended, they should behave as intended."[24]

Interfacial conditioning films

In many cases, the best natural models come from unlikely sources. For example, as recently described, the external surfaces of porpoises and killer whales are dominated by living parakeratotic epidermal layers with surrounding glycoproteinaceous exudates that provide excellent models for intraoral mucosa.[25] Other natural mucosal surfaces of the human body are also similar. From the perspective of surface properties analysts, these films also mimic the naturally nonadhesive glycoproteinaceous veil surfacing the endothelial lining of healthy blood vessels. When any of these protective interfacial films are breached (as in damage to the endothelial lining of arteries *via* atherosclerosis, for instance) adverse biological consequences from increased surface interactions and attachments are the norm. Thrombosis, for example, is a natural sequela of disruption of the closely packed endothelial lining of blood vessels. Bacterial adhesion and infection is often the result of abrasion of the inside of one's cheek.

It is in the understanding of the properties of macromolecular layers at interfaces that the classical approaches and techniques of adhesion science can have their greatest value. For instance, with regard to understanding the initial events in blood contact with foreign solid materials, the techniques of streaming potential measurements, voltage clamping and surface analysis have all been combined to realize that the adsorbed configuration of (usually, preferentially deposited) blood proteins is a strong function of the surface properties of the original solid materials exposed. Particularly important studies were performed by a group at the National Bureau of Standards.[26] Using the methods of infrared spectroscopy and ellipsometry, they showed the adsorbed amounts of specific blood proteins to be nearly identical on materials as different from one another as platinum, quartz, carbon, and polyethylene. In contrast, the extension of the adsorbed molecules out into the solution phase (and, therefore, their degree of retained native or solution-like structure) was considerably different. The higher surface energy materials like platinum and quartz had the flatter, more denatured configurations, more capable of inducing tenacious attachments of arriving cellular elements. The lower surface energy materials, like polyethylene, support cellular deposits much less securely.

The most important protein involved in blood contact phenomena is fibrinogen; the accepted configuration for this molecule[27,28,29] is sketched in Figure 1.

Figure 2 provides a cartoon of how these originally highly hydrated molecules may adsorb at the blood/gas interface or at solid surfaces exposed to blood, developed by combining the available data on adsorbed amounts, film thicknesses, wettabilities, contact potentials, and zeta potentials.

When adsorbed to highly polar, high-surface energy materials like glass, metals or metal oxides, these molecules tend to attain a

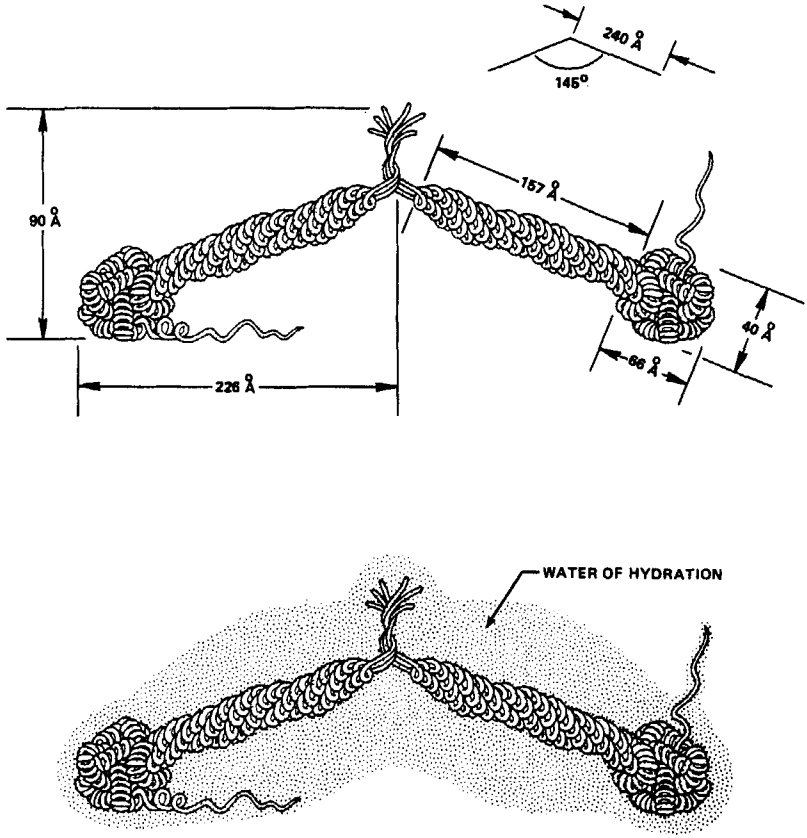

FIGURE 1 Molecular model of the blood protein, fibrinogen (drawn from data in Refs 27, 28, 29 and others).

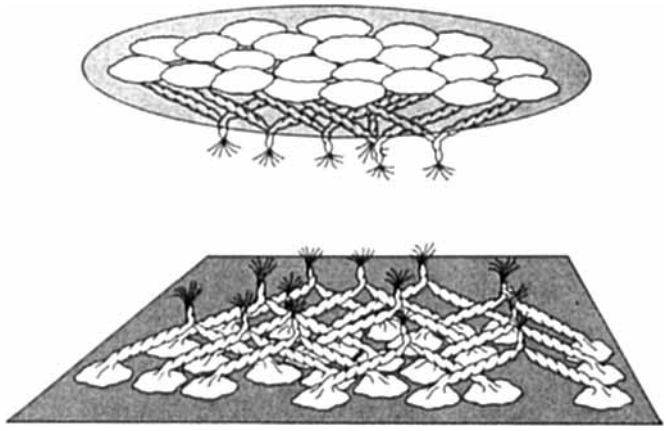

FIGURE 2 Cartoon of the probable adsorbed configurations of interfacial films of fibrinogen. Above: at the gas/liquid interface. Below: at the solid/liquid interface.

flatter, dehydrated configuration. The shape change upon adsorption also can induce significant strain in the more sensitive central (*E*-knot) portion of the molecule. Subsequent aggregation or polymerization with other molecules can occur as a result of this surface binding event, without requiring the normal enzymatic (thrombin) induction of the fibrinogen–monomer-to-fibrin–polymer conversion. During film growth or thickening of this incompletely polymerized fibrinogen layer, platelet attachment is noted to be quite strong.[30] Platelet adhesion is tenacious and consequential, in that the first adherent platelets are subject to pseudopodal spreading, degranulation and increased aggregation with their arriving neighbors to induce thrombogenic deposits.[22,31,32]

Conversely, fibrinogen tends to deposit spontaneously in more native form, but in the same amounts over the same times, on substrata expressing only noninteracting surface sites (such as those exhibited by closely packed methyl groups or having available only weak, dispersive or van der Waal's force fields). The molecules adhere less tenaciously, extend in a more hydrated state (curiously, from a usually more hydrophobic surface) in a more solution-like fashion into the liquid phase. They do not undergo so significant a distortion as to encourage their ready transformation into fibrin-like polymers. Platelets arriving at such more native fibrinogen-coated

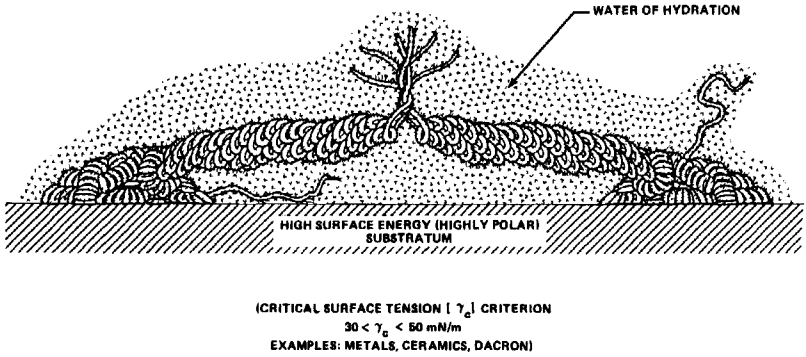

FIGURE 3 Adsorbed configuration of fibrinogen at a high-energy, highly polar solid surface.

boundaries do adhere but seldom elaborate pseudopods or exude their granular contents. They are readily detached or re-entrained into the flowing blood without becoming the sites for thrombotic deposits.

Figures 3 and 4 provide illustrations of these two differently adsorbed states for molecules occupying about the same surface areas in the model assumed. Similar arguments have been presented regarding differential degrees of protein distortion or "denaturation," with different bioadhesive consequences, for materials placed into all biological milieus.[33,34,35]

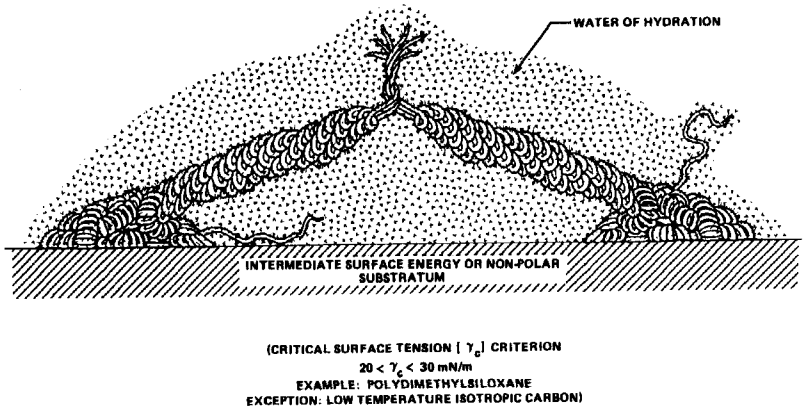

FIGURE 4 Retention of more native molecular conformation for fibrinogen adsorbed at a nonpolar, intermediate energy surface.

Surface quality control

As noted earlier, one very convenient indicator of the passive protein binding state (that is, the surface state minimizing subsequent configuration changes in depositing macromolecules such as glycoproteins) is the critical surface tension. With properly applied (not always the case in biochemical experiments) siliconizing coatings, biochemists and cell culturists routinely passivate their glassware, pipettes, and needles to minimize loss of sensitive bioadhesive preparations to the walls of their experimental equipment. A critical surface tension value of about 22 dynes/cm is always expressed when the coatings are confluent and effective.

Obviously, empirical evidence of the efficacy of this type of treatment is available from literally millions of such inadvertently designed experiments. It is one of the purposes of this review to point out that improved knowledge and deliberate use of surface modifications can have dramatic and beneficial effects in many biotechnological processes: fermentation, culture of anchorage-dependent cells, separations of proteins and cells of differing types, pasteurization of food and dairy products, minimizing of biological fouling, preventing encrustation of ship bottoms and pipe lines with mineralizing biological slimes, and preventing formation of dental plaques and thrombotic deposits on new biomedical devices. It should not be surprising that the smooth, elastomeric sacs of the successful artificial hearts already used in humans have been deliberately controlled to exhibit low-surface energy, nonretentive properties towards sensitive blood components for these reasons.[36,37]

The next generation of substitute blood vessels grafts will almost certainly include very small diameter versions of these same synthetic elastomers that display surface properties minimizing coagulation and thrombosis. At present, these surface properties are imparted mainly to stabilized tissue tubes having their origin in such previously discarded sources as the human umbilical cord.[38,39] At birth, each human child is separated from a structure (averaging 2 feet in length) that contains a valveless, branchless, muscular vein and two smaller spiraling arteries that have hitherto been wasted by incineration with the placental afterbirth. Now, a major use has been found for these structurally excellent tubes after treatment by

modern techniques including fixation, stabilization, and surface properties conversion.[40] These substitute arteries are now placed in over 100,000 humans world-wide with limb-saving and life-saving results.[41] The biosynthetic vessels carry blood successfully over cell-free, stabilized, basement membrane/internal elastic lamina surfaces that—as originally presented by nature—are amongst the most cell adhesive and thrombogenic surfaces known. After all, they evolved to meet the needs of instant hemostasis when normal vascular wall integrity is breached.

The hallmark of successful substitute blood vessels of this sort is a lumenal wall critical surface tension in the mid 20's dynes/cm; that closely simulates the original surface qualities displayed by the intact endothelial lining of living blood vessels.[42,43] Because of its delicacy, endothelium cannot yet be maintained or regrown in vessels harvested as abruptly and preserved for long-term storage as are the Biografts so far produced. Over implantation times now ranging to ten years, these grafts have shown excellent continued patency. They maintain low-surface-energy, blood flow surface qualities while allowing integration with the external tissues because of a higher surface energy, synthetic fiber mesh (usually Dacron) that does induce greater protein denaturation and cell adhesive activity. As expected for a tanned biological material in long-term contact with the blood of people suffering from systemic atherosclerosis, over a decade of implantation significant lipid deposition and resulting plasticization of the stabilized blood vessel wall does occur. Thus, with time some of these implants fail by aneurysm formation.[44] Research intensity must remain high with regard to development of truly synthetic, biodegradation-resistant materials capable of displaying the same long-term thromboresistance in even smaller diameters.

Illustrations of biological resurfacing of the umbilical cord vein implants by benignly deposited plasma protein, together with the persistence of desirable nonadhesive surface character, have been presented elsewhere.[40,45,46] The patency statistics are nearly as good as those for living saphenous veins transferred from one limb to the other, in spite of the increasing concerns about aneursymal failure of these structures.[41,44]

As already mentioned, the critical inner sacs of artificial hearts and left ventricular assist devices must—over a long term—maintain

passive surface conditions to prevent blood coagulation and thrombosis. This result has been achieved by attention to such classical adhesion parameters as the critical surface tension. A major area of continuing concern, particularly as these devices are applied in younger patients, is the tendency towards mineral deposition (predominantly calcium hydroxyapatite) on the flexing surfaces of the elastomeric materials (segmented polyether type polyurethanes) now preferred for these applications.[47,48] Anticoagulants such as sodium warfarin (Coumadin) can apparently, through their interference with the vitamin K-mediated calcium metabolism, minimize this risk of calcification of artificial hearts and other plastics placed in contact with blood or tissue. A more physical–chemically based solution to this problem is certainly preferred.

Natural fluids like blood and milk are, in fact, considerably supersaturated with mineral-forming elements.[49] One wonders whether material surfaces can ever be so benign towards depositing proteins that the chelated calcium and phosphate moieties will not be displaced into the adjacent solution and precipitate in almost all circumstances over the long term. A common observation in pasteurizers is that milkstone will form in periods as short as 8 hours at temperatures of about 70°C.[50] This suggests that such inverse-solubility calcium salts might form because of local heat buildup, and be controllable in biomedical implants by eliminating thermal buildup at the points of maximum flex.

Such facile control of mineralization may not be possible with yet more complicated biomedical processing devices as the artificial pancreas.[51] In these devices, semipermeable tubes are employed through which nutritive blood elements are carried while insulin-secreting cells are cultured on the exterior faces; exchange of insulin to the flowing blood for nutrients required for the living pancreatic cells is the steady-state goal. The combination of plasma protein deposition and apparent release of bound calcium and phosphate, coupled with the ultrafiltration of the mineral solution to the exterior face of these fibers, can cause a dramatic precipitation and deposition of calcium hydroxyapatitic crystals.

Considerable improvements might be made by modification of the surface properties of the ultrafiltration tubing to the less denaturing critical surface tension range between 20 and 30 dynes/cm. This approach is being actively explored at present.

CONCLUSION

The application of basic principles of adhesion to new biotechnologies is not limited to biomedical or dental devices or even to fermentation, pasteurization, or purification systems. The entire aqueous world that supports biological life, especially including such large volume reservoirs as the world's oceans, lakes and depots of ground water, also must variously exhibit either tenacious biological adhesion or no biological adhesion to engineering materials placed therein for technological purposes. It has been a pleasing and useful discovery that nature was extremely conservative in evolving similar mechanisms for bioadhesion in all aqueous environments. Using the expanding knowledge base available from the physical–chemical approaches described here, significant improvements in interfacing man-made materials with such natural systems—without again risking the sad, past consequences of overuse of biocides, poisons and other toxicants—are predicted for the near term.

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