THE NEW NEW BIOMATERIALS

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I. What Happened to Inert Biomaterials?

In the beginning, there were metals and materials scientists. Plastics, polymers, and soft materials came later and then came the chemical engineers. The artificial heart program had a few (Artificial Heart Program Conference, 1969) but it was the artificial kidney program and the interest in new membranes that really started things off. Merrill at Massachusetts Institute of Technology (Merrill *et al*., 1966) was a pioneer as was Leonard and Gregor (Friedman *et al*., 1970) at Columbia and Hoffman at the University of Washington. Now almost every chemical engineering department has someone working on biomaterials or there is a bioengineering department nearby with chemical engineers on faculty. Several illustrations of this activity are apparent in this volume.

In the beginning the emphasis was on biocompatibility. Inertness was the key. We had our lists of no's (Table I) and the paradigm was focused on finding, synthesizing or surface modifying materials to make them fit these negative commandments. Interestingly, a large part of the early involvement of chemical engineers was to make materials that were not inert. Heparin immobilization was a hot topic in the late sixties and early seventies and the whole purpose was to make a surface that would actively interact with blood and prevent clotting. "Anti-thrombogenicity" was the keyword.

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TABLE I

Commandments for inert biomaterials
No toxicity
No hemolysis
No pyrogens (endotoxin)
No protein or cell consumption
No thrombosis (and no emboli)
No inflammation
No infection
No immune response
No complement activation
No carcinogenicity and mutagenicity

Now with tissue engineering, regenerative medicine and combination products, active materials are the topic of interest of biomaterials specialists.

Some active materials are carriers for drugs (drug delivery systems), some have immobilized peptides to enable cell adhesion or migration, some are degradable by hydrolysis or by specific enzyme action. Some contain bioactive agents (e.g., heparin, thrombomodulin) to prevent coagulation or platelet activation while others incorporate bioactive groups to enhance osteoconduction. Many include polyethylene oxide to retard protein adsorption and this is perhaps the closest we have come to a kind of inertness.

The advent of these materials has challenged the regulatory authorities since the materials are no longer being used simply for medical devices. Some include drugs and some include cells or biologicals. It was once sufficient to show that the material had no effect (i.e., it was inert) and then to get the blessing of the regulatory authorities. Now, it is the presence of an effect and a significant one at that, that needs to be regulated. The FDA has established an Office of Combination Products (http://www.fda.gov/oc/combination/) to deal with these products and every indication suggests that it is not long before these products are the norm. It is now not so simple to argue that the next generation of medical devices "does not achieve any of its primary intended purposes through chemical action within or on the body of man" as it is given in part of the FDA definition of a medical device.

II. Biocompatibility of Modern Biomaterials

When biomaterials were inert it was simple to think of biomaterials in terms of the absence of inflammation or the absence of thrombi. Now, with

these newer combination materials we think of biocompatibility in more complex and subtle terms. The "appropriate host response" associated with the definition of biocompatibility has much more subtlety and complexity than we had hitherto considered. Blood compatibility may require some limited platelet adhesion and activation to passivate a material rather than the complete absence of adherent platelet deposits, especially if we want to limit embolization. What we now really mean by blood compatibility has been described in more detail elsewhere (Sefton *et al.*, 2000).

We now recognize that blood compatibility is more complex than it was because we have to consider more than just platelets and coagulation factors and we have to consider the interactions among all the components of blood, including neutrophils, monocytes, and complement. This has led to the conclusion that thrombogenicity is really a special case of inflammation. That modern hematologists disregard Factor XII and the intrinsic coagulation system and focus on tissue factor (Jesty *et al.*, 1995) and that tissue factor is expressed on activated monocytes (Gorbet *et al.*, 2001) highlights further this linking of thrombogenicity and inflammation.

More fundamentally though the performance of these new biomaterials is challenging the entire concept of biocompatibility. A scaffold that promotes cell invasion may contain many of the attributes that in another context would lead to inflammation. Some constructs rely on a limited degree of inflammation to generate the enzymes that will cause the desired remodeling of the construct. Other uses of a biomaterial (e.g., as a vaccine adjuvant) is based on generating a local inflammatory response in order to boost the immune response, while immune responses to tissue constructs is an important, yet largely overlooked, element of the host response (Babensee *et al.*, 1998). Some new angiogenic biomaterials (Gorbet *et al.*, 2003) are designed to control the functional diversity of the monocyte (Riches, 1995), enabling a pro-angiogenic phenotype to emerge as the dominant functional form of these cells. The result is monocyte activation, but "good" activation: producing the blood vessels associated with granulation tissue but without the undesirable cytokines and other inflammatory mediators and proliferating fibroblasts. These new biomaterials are leading us to ask whether inflammation is bad or whether a little bit of inflammation can be a good thing?

Biomaterials are solid drugs. Rather than thinking of biomaterials as an inert contributor, my laboratory has taken to thinking about biomaterials as agonists of a biological response, much like drugs. However, biomaterials are solids and interact with cells and tissues through an interface, making the study of biomaterials more difficult than that of drugs, which are one-dimensional compared to the three-dimensional

biomaterial. The biological responses we are interested in range from protein adsorption and platelet activation but extend to angiogenesis, matrix metalloproteinase secretion, immune recognition, and a wide variety of other biological phenomena. We can make use of the wealth of information, reagents, and assays that are available on these phenomena, but it is necessary to adapt them for the complexities of the interfaces and the differences between drugs and biologically active materials (Table II).

The differences in Table II are intended as broad generalities and readers can easily come up with exceptions or questions about what is meant by a biologically active material. For example, is the action of a drug delivery device always "local" or is a nanoparticle "large" and a DNA drug "small." Thus these characteristics must be interpreted and ringed with qualifiers to be strictly correct.

TABLE II

Biologically active materials	Drugs
Large, 3D objects	Small, 1D molecules
Immobile	Diffusible
Action is local	Action may be systemic, with side-effects a critical concern
Subject to foreign body reaction, coagulation, complement activation, etc.	Inflammation rarely a consideration
Interact across a cell membrane although endocytosis may occur	Act through a cell surface receptor or intracellularly
Limited surface area and ligand density	Even at nanomolar levels, there are many, many ligands (excess ligands?)
Action is often nonspecific	Specificity is key element
Protein adsorption influences cell response through altered ligand or receptor presentation or changes to microenvironment	No equivalent concept, although cell microenvironment affects drug action
Metabolism rarely relevant	Metabolized after an effect or to actually generate the effect
Effect is chronic	Effect is generally short-lived (half-life is a critical parameter)
Effect is generally permanent—pharmacokinetics and bioavailability are not normally considered	Effect is generally not permanent—pharmacokinetics and bioavailability are important
Can be engineered to be degradable and eliminated but many are not	Drug elimination is critical element of design

One of the more troubling characteristics is that of "specificity." Certainly a material that contains an immobilized growth factor or enzyme, contains much of the specificity of the immobilized agent. However, here I am thinking more about the biomaterial that has bioactivity (e.g., angiogenesis or osteoconduction), but without the obvious therapeutic agent within it. Here, the effect appears to be more nonspecific than that seen with drugs. This has been controversial, especially when presented in the form that many materials act the same (with occasional and important exceptions) resulting in questioning the importance of surface chemistry differences among materials (Sefton *et al*., 2001a). The implications of this with respect to hemocompatibility testing has also been discussed in reference Sefton *et al*., (2001b). The absence of substantive differences in platelet and leukocyte activation among many materials (Sefton *et al*., 2001a) suggests that the mechanism of these responses is fundamentally nonspecific in character.

The host response central to biocompatibility is to a 3D object, the chemistry of which does not appear to be terribly important. One way of thinking about this is that the biology does not really care if one changes the chemistry of a surface from one kind of nonspecific surface to another. Only when specificity is introduced through some sort of deliberate design can the biology "appreciate" what is happening. Hence it is little surprising that biomaterials specialists in 2003 speak of understanding the mechanism of biological response as much as they may tout a novel biomaterial. There is an extensive biological literature that we have only started to appreciate and exploit. The prospects for further basic research in biomaterials is correspondingly strong.

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