FOURTH EDITION

BIOLOGICAL PERFORMANCE of MATERIALS

Fundamentals of Biocompatibility

Jonathan Black

CRC Taylor & Francis
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Preface

Biocompatibility of materials increasingly occupies the consciousness of engineers dealing with medical and biological problems. The engineer has long been accustomed to dealing with materials, limits on design. These limits, such as yield stress, endurance limit, and rupture life, are reflected in design margins tailored to the criticality of the specific application. In situations involving biological interactions as a portion of the design problem, the additional materials limit of biocompatibility must be considered.

Failure of compatibility (that is, incompatibility) is proving to be the ultimate limit to the engineering solution of many biomedical problems. As a result, it is necessary to incorporate a thorough grounding in the aspects of biocompatibility — or, as I prefer to term it more generally, biological performance of materials — into the training of bioengineers.

When this book was first conceived, in the early 1970s, no suitable textbooks dealing with broad aspects of biomedical materials or, as the field rapidly came to be called, biomaterials, were available. Today, as this field has matured into biomaterials science and engineering (BSE), many edited collections and topical monographs are available for students and workers at many different levels. However, none seems to suit the neophyte: the former are invariably written by a panel of experts and thus tend to be uneven in attempting to be comprehensive and the latter are the work of a single investigator or research group focusing on relatively narrow and parochial interests. Both of these types of books have a place and many are extremely valuable to the advanced worker, but they all fail to meet the needs of the student or the professional without a background in the field. Thus, it appears that the current work is still needed; it focuses primarily on principles of biological performance at a relatively fundamental level: interactions between living and nonliving materials whose consideration sets BSE apart as a distinct field of investigation and knowledge.

Biological Performance of Materials: Fundamentals of Biocompatibility was originally intended for use as an undergraduate text for a one-term, junior–senior-level bioengineering course on biological performance. I and others have used it in this role. However, with the assignment of selected articles as reading and study sources, it has also proven useful as the central text in undergraduate survey courses on biomaterials and on artificial organs. With additional reading material from the scientific and clinical literature and from materials science texts, it has also been used as the focus of a first-year graduate course in biomaterials for students with engineering (but not biological or medical) backgrounds and, conversely, as a supplementary text for courses on implants for nursing students with little or no

engineering training. Finally, engineers working in medical device development and evaluation in industrial as well as governmental settings have found it a useful reference book. The scarcity of reference to actual materials and specific applications has apparently made this diversity of use possible; this revision attempts to maintain the versatility of the work. Primary training in materials science and biology is useful, but not totally essential, because this book is intended for use in conjunction with undergraduate texts in materials science and biology, as needed, so as to accommodate variations in individual degrees of preparation.

We begin with an examination of the concept of "biocompatibility" and arguments for the broader concept of biological performance. Two major sections are devoted to the effect of biological systems on materials ("biodegradation" = material response) and of materials on biological systems ("biocompatibility" = host response), respectively. Selected additional readings are provided at the end of each chapter.

The reader will note an emphasis on methods for determination of biological performance, throughout and especially in Chapter 17 and Chapter 18. This reflects the centrality of material and host response in the clinical performance of medical devices and surgical implants as well as the continued need to select new and modified materials for specific applications. These questions become even more challenging and complex as increasing numbers of viable and nonviable untraditional materials come under consideration for clinical use. The practicing engineer will find this book a useful source of references, test methods, and approaches to the problem of establishing biological performance of materials. Generic materials properties are tabulated in Interpart 1; Interpart 2 is an example of diagnostic approaches to detection of clinical issues associated with biomaterials in animal models and in patients. The final four chapters deal with design, qualification, standardization, and regulation of implant materials and will be of special assistance to the professional. In response to comments on earlier editions, an extensive glossary is also included.

Due to the fundamental nature of this examination, I have elected in this revision to retain many earlier examples and studies, providing updated material and more current references only when needed. The reader is advised to make use of the online resources of the National Library of Medicine (PubMed*) to provide additional, more recent, and more specialized information.

I wish to thank the many undergraduate and graduate students and colleagues whose ideas, questions, and discussions have contributed significantly to the scope and content of this work. Special thanks are due to G.K. Smith and J.L. Woodman for their seminal contributions to Chapter 14 and Chapter 15. An appeal for corrections and suggestions was issued to readers of two listserves (BIOMAT-L and BIOMCH-L) and considerable useful feedback was received.

* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed.

In the preface to the second edition (1992), I suggested that inappropriate host response to implants and premature device failure secondary to materials degradation continue to impose unwanted limits on engineering solutions to biological and medical problems. This is still the case today. It can only be hoped that ideas and information contained in this revised work will contribute to the further improvement of biomaterials in their application to the alleviation of human disability, disorder, and disease.

Jonathan Black

Abstract

Biological Performance of Materials: Fundamentals of Biocompatibility presents an organized approach to examining and understanding the interactions between materials used in medical devices and implants and living organisms. After an introductory section addressing definitions and aspects of biological environments, the work is divided into three principal sections. These deal with material response to biological systems, host response to biomaterials, and test methods for determining biological response *in vitro* as well as in animal models and clinical settings. Interparts provide summaries of physical properties of commonly used metallic, polymeric, and ceramic biomaterials as well as a guide to understanding clinical performance of implanted biomaterials. In addition to numerous references to the literature, each chapter includes an additional bibliography; an extensive glossary completes the work. Now in its fourth edition, this work draws on Black's more than 35 years experience as a teacher, researcher, and consultant in biomaterials science and engineering.

The Author

Jonathan Black is professor emeritus of bioengineering at Clemson University in Clemson, South Carolina. He holds degrees in physics (Cornell University), engineering science (Pennsylvania State University), and metallurgy (biomaterials) (University of Pennsylvania). Before his appointment as the first occupant of the Hunter Chair of Bioengineering at Clemson in 1988, he was a member of the Department of Orthopaedic Surgery at the University of Pennsylvania for 17 years with a secondary appointment in the Department of Bioengineering. From 1992 to 1995, he was a senior visiting fellow in the IRC for biomaterials at Queen Mary and Westfield College (London), with support from an SERC fellowship.

Black has been active in research and teaching in several areas of biomaterials, with special reference to the biological performance of metallic implants and to the needs of orthopaedic clinical practice. He is the author of many articles and several textbooks, including *Biological Performance of Materials* (1981, 1992, 1999, 2005), *Orthopaedic Biomaterials in Research and Practice* (1988), and, with G. Hastings, *Handbook of Biomaterial Properties* (1998). He has a long-term interest in implant retrieval and analysis and is the author of a major 1992–1993 study of the field for the USFDA.

Black has been involved in professional activities in biomaterials for more than 30 years and is a charter fellow of biomaterials science and engineering (FBSE). He is a charter member and past president of the Society for Biomaterials (U.S.) and has been a frequent presenter and session chair at the Gordon Research Conferences on Biomaterials and an organizer of the triennial Biointeractions conference series in the United Kingdom. He has served on a number of advisory and editorial boards and was an assistant editor of the *Journal of Biomedical Materials Research* from 1978 to 1995. Black is an associate member of the American Academy of Orthopaedic Surgeons and recipient of the presidential gold medal from the British Orthopaedic Association.

In 1992, Black established and served as principal of IMN Biomaterials, a professional consultancy in biomaterials and orthopaedic engineering. He concentrated his efforts in this area after retirement from Clemson in 1993 and closed this enterprise at the end of 1998. He continues to chair the Scientific Advisory Board for Stryker Orthopaedics.

Contents

Part I

General Considerations

1

Biocompatibility: Definitions and Issues

1.1 Introduction

The issue of biocompatibility arises from recognition of the profound differences between living tissues and nonliving materials. In an historical and a practical perspective, a wide range of interactive behavior occurs between tissues and materials. In any of these interactions, beneficial and adverse effects may be observed. Thus, materials considered foods and beverages can be nutritious or non-nutritious. From another viewpoint, they can be considered toxic or nontoxic. Such judgments are relative to use or abuse rather than to an absolute scale. Although it is a central nervous system depressor, alcohol has a positive virtue as a disinhibiting stimulant and social drug in small doses. Internally, large doses are toxic, and still larger doses are lethal. However, even in toxic doses, alcohol is a useful external antiseptic.

It is desirable to extend this sort of relativism of dose and type of use to examination of the interactions between biomaterials and living systems. Biomaterials are materials of natural or man-made origin that are used to direct, supplement, or replace the functions of living tissues. When these materials evoke a minimal biological response, they have come to be termed biocompatible. As it is typically used, the term biocompatible is inappropriate and defective of content. Compatibility is strictly the quality of harmonious interaction. Thus, the label biocompatible suggests that the material described displays universally "good" or harmonious behavior in contact with tissue and body fluids. It is an absolute term without any referent.

Furthermore, the traditional ideas of biocompatibility refer essentially to the effect of the material on the biological system. Effects of biological processes on materials are rarely included in the meaning, unless the results of material changes elicit a change in biological response. The effects of the biological system on the material are usually lumped in the term biodegradation, which implies "bad" behavior — again without a referent. However, in the case of a deeply implanted suture, biodegradation may be a sought-after result.

One can protest that this is a semantic discussion without content. On the contrary, I think that the terminology used and the assumptions inherent in

that terminology tend to condition the approach taken in experiment and analysis. Thus, the most common approach to establishing the biocompatibility of a material is still to establish the absence of deleterious effects associated with its use in biological applications. Once such tests are completed, the material is regarded as qualified. I believe that the absolute nature of the language employed has led to the use of absolute, and thus inappropriate, criteria.

The real issues in the use of materials in medical and surgical devices are not any more absolute than is the choice of a material for any other engineering application. The choice of materials for construction of a device or machine is made early in the design process. The properties of the candidate materials, particularly those properties that bear on the intended function of the complete assembly, then interact strongly with the design. The ultimate test of the appropriateness of the choice of materials is the performance of the completed device in its intended application. In this performance, the interaction between design choices (shape, size, linkage, etc.) and materials properties (strength, density, composition, etc.) can be seen. Chapter 21 deals with some of these points more fully.

The real issue of biocompatibility is not whether there are adverse biological reactions to a material, but whether that material performs satisfactorily (that is, in the intended fashion) in the intended biomedical application and thus can be considered a successful biomaterial. This goal should lead directly to a traditional engineering design process of considering the advantages and disadvantages inherent in the selection of a particular material for a design in a specific application. Among the factors considered must be the interaction of the material with the biological processes in its intended site of operation.

One of the consequences of this relative approach to material performance in contact with living tissues must also be the rejection of the idea that any material in any selected application can be categorically safe or unsafe. In dealing with food additives, it is possible to draw up a list of materials that are "generally regarded as safe" (GRAS).* This results from the situation in which each dye, sweetener, flavoring agent, etc. is serving the same function, no matter what the apparent application, and is consistently used in a low but relatively uniform amount or "dose." Food is always ingested and never implanted, and all food is subjected to the same succession of physiological degradation, storage, and excretion processes. By contrast, a material used successfully in one medical device, and thus considered a biomaterial, may then be used in a different form in a different location with another intended response, with an unsatisfactory result. Thus, it should be no surprise that there is no GRAS list for biomaterials.**

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* This register or list is maintained by the US-FDA's Center for Food Safety and Applied Nutrition (CFSAN) and, as of May 2005, contained 158 completed entries. See: http://www.cfsan.fda.gov/~rdb/opa-gras.html.

** However, see Section 20.4.1 for an attempt to create such a list.

1.2 Biological Performance

I adopted the term biological performance as a descriptor of materials in order to replace the historical or classical idea of biocompatibility. Biological performance and two closely related terms are defined as follows:

Biological performance: the interaction between materials and living systems

The two aspects of this performance are:

Host response: the local and systemic response, other than the intended therapeutic response, of living systems to the material

Material response: the response of the material to living systems

The generality of these terms is obvious. Their definitions have no inherent value judgments, and they do not suggest absolute qualities.

However, these terms are not sufficient for a full discussion. I have stressed the need for consideration of interactions between materials and living systems on a relative, rather than an absolute, basis. This suggests the need for a system of grading or ranking based upon the results of tests. Additional terms are needed to implement such a concept. The first three definitions are therefore supplemented with several others:

Reference (or control) material: a material that, by standard test, has been determined to elicit a reproducible, quantifiable host or material response*

Level of host (or material) response: the nature of the host (or material) response in a standard test with respect to the response obtained with a reference material

A standard test, as referred to in these two definitions, is simply any well-defined, repeatable test. The requirements for such tests are discussed in Chapter 17 and Chapter18.

Finally, I suggest that the use of the term biocompatibility be retained for historical reasons, but with a narrow and careful redefinition:

Biocompatible (-ility): biological performance in a specific application that is judged suitable to that situation

* Note that this definition carries no implication of "good" or "bad" behavior on the part of the reference material. A reference material might be a material with minimal host response (a negative reference) or an extreme host response (a positive reference). Reference materials may or may not be selected from those conventionally used for implant fabrication. The use of a material as a reference material does not qualify it as a biomaterial.

So, at the end of the consideration, when host and material responses are known and the particular device application is examined, a final value judgment can then be made that leads to the acceptance or rejection of the material for that application. Such a selection and a resulting record of adequate performance do not "qualify" a material. Rather, they increase the confidence in the use of the material as a biomaterial in that particular application and point to possible successful use in similar applications.

This last point is extremely important. The final arbiter of biocompatibility, as defined here, can only be satisfactory clinical performance, insofar as material properties affect the outcome of the treatment. Thus, if a biomaterial has been in use for a long time, it makes no sense to go back to the materials science laboratory, the tissue culture laboratory, and the animal colony in an attempt to determine its biocompatibility. The experiment has already been performed during human clinical use; what is required is careful observation to determine and interpret the outcome. This point is discussed at length in Chapter 22.

1.3 Consensus Definitions

A major attempt has been made to reach consensus concerning some definitions related to biocompatibility. A working consensus conference, sponsored by the European Society for Biomaterials, was held in 1986 to discuss these matters in an international setting (Williams 1987). Of the 13 terms that gained consensus definitions; the following are relevant to this discussion:

Biomaterial: a nonviable material used in a medical device, intended to interact with biological systems

Host response: the reaction of a living system to the presence of a material

Biocompatibility: the ability of a material to perform with an appropriate host response in a specific situation

Although they are terse, these are not bad definitions. They preserve the idea of interaction and of relative, rather than absolute, attributes. They are limited definitions in that they specifically exclude living tissues from the spectrum of biomaterials. In addition to exhibiting active physiological processes, tissues are materials with definable physical structure and properties; thus, their exclusion seems unwarranted and unwise. It is unfortunate that the conferees chose to deprecate the terms biological performance and material response because I consider them to embody concepts that lend clarity to the discussion of biocompatibility.

The success of this conference and, in particular, the widespread acceptance of biocompatibility as a relative rather than an absolute attribute of biomaterials led to the convening in 1991 of a second consensus conference, again in Chester, U.K., under the same sponsorship (Williams et al. 1992). After intensive discussion, five additional terms related to biomaterials and biological performance were agreed to by consensus:

Biomaterial: a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body

Bioactive material: a biomaterial designed to elicit or modulate biological activity

Bone bonding: the establishment, by physicochemical processes, of continuity between implant and bone matrix

Biodegradation: the breakdown of a material mediated by a biological system

Inherent thrombogenicity: thrombus formation controlled by the material surface

The definition of biomaterials clearly matured in the interval between these two conferences. The concept of bioactivity will be discussed in the next section in the context of interactivity. Biodegradation now was given a special meaning: not merely the passive response of a material to the physicochemical conditions found in living systems, but also involving actual cellular effects on the pericellular environment (see Section 2.3). Finally, the compound term inherent thrombogenicity represents the first small, solid achievement in defining the very complex interactions between blood and biomaterials (see Chapter 9 for further discussion).

However, words become part of language by the repetition of their use or they are abandoned, in the same way that paths broken through the wild may or may not become superhighways. Thus, it remains to be seen how these and other terms discussed here will be conventionally understood and used in the scientific literature.*

1.4 Discussion

The use of the definitions discussed here has gradually redirected the study of interactions between biological systems and materials. It has moved from efforts to obtain qualification and blanket assurances of safety to description and grading of biological performance based upon the careful development

* See the Glossary for additional consensus definitions.

of standard tests and the characterization of reproducible response relative to reference materials. This is a central idea that will guide considerations throughout this work.

I feel strongly that absolute qualification of an artificial or processed material in biological applications is not possible now or in the foreseeable future. It is necessary to establish minimum requirements for performance at various stages of materials development. Strategies for setting such levels are discussed in Chapter 21.

It has been suggested that no foreign material is biocompatible (old meaning) and that the best that can be expected is that the results of its use are "physiologically tolerable." This is a somewhat negative view that overlooks the essentially benign responses elicited by many materials in living systems. However, such a suggestion should attract attention to another important point. Living systems differ most from machines in respect to the constant flux and change of their components — that is, in their physiology. Biological performance, particularly host response, ought not to be defined in terms of tissue structure and pathology but primarily in terms of local, organ, and systemic physiology. Deviations from usual physiological conditions may lead to changes in the structure and function of living tissues.

The key to understanding host response and, to a lesser degree, material response, is knowledge of the participation of the material in the physiology of the host. Extrapolation of results obtained in tissue culture and animal models rests significantly on knowledge of how normal and abnormal physiological processes in these systems differ from those in humans, in health and in disease. Thus, in addition to concentrating on making relative rather than absolute determinations, care will also be taken to attend to physiology (normal and abnormal) and its interspecies variations.

Osborn (1979) attempted to take such physiological considerations into account by classifying all biomaterials as biotolerant, bioinert, or bioactive, conveying respectively the sense of negative (but tolerable) local host response, absence of local host response, and positive (desired) local host response. Slutskii and Vetra (1996) revived Osborn's approach by defining a term, reactogenicity, as the intrinsic property (or combination of properties) of a biomaterial that produces a certain tissue reaction. This approach essentially converts Osborn's categories into a continuous scale — presumably running from normal to some degree of inflammation (see Chapter 8) — because Slutskii prefers to restrict reactogenicity to the description of the intrinsic properties of "biocompatible," that is, successful biomaterials. Both of these treatments mirror an earlier approach by Steinemann (1975), in which he explicitly classified metallic implant materials, by reference to the nature of the local encapsulization response, as toxic, scar tissue, or vital. Steinemann's approach is of particular interest in that he tried, somewhat unsuccessfully, to correlate these categories with an intrinsic material property, polarization resistance (see Section 4.6), thus presaging Slutskii and Vetra.

Collectively, these approaches provide little illumination because they fail to look beyond the immediate biomaterial–tissue interface to the larger requirements of specific clinical applications. However, it is possible to extend these ideas, taking into account the development of the field of biomaterials and eliminating the undesirable use of the prefix bio- (as used by Osborn). Examining the historical development of biomaterials, I have identified four phases (or types) of biomaterials, based upon changing concepts of host response:

- Phase 1. Inert (biomaterials): implantable materials that elicit little or no host response
- Phase 2. Interactive (biomaterials): implantable materials designed to elicit specific, beneficial responses, such as ingrowth, adhesion, etc.
- Phase 3. Viable (biomaterials)*: implantable materials, incorporating or attracting live cells at implantation, that are treated by the host as normal tissue matrices and are actively resorbed and/or remodeled
- Phase 4. Replant (biomaterials)*: implantable materials consisting of native tissue cultured *in vitro* from cells obtained previously from the specific implant patient

It is now recognized that searches for type 1** materials are as pointless as the historical pursuit of the Philosopher's Stone — the talisman that would turn any base material into gold. Many biomaterials in present clinical use, such as porous structures and bioactive coatings, as well as ones in development are properly called type 2 materials. Type 3 materials are the subject of active research and commercial interest, with initial examples in limited clinical use (see Warnke et al. 2004). Advances in control and manipulation of the genetic code in mammals suggest that no intellectual barrier exists to prevent the broad future realization of type 4 materials at the tissue and organ levels. In fact, a true type 4 material (implantable, live tissue with the identical genetic code and immunological determinants of the recipient patient) represents the ultimate fulfillment of the original search for biocompatibility: implantable materials demonstrating harmonious interaction.

Medical practice today utilizes great numbers of artificial devices and implants. As long ago as 1988, by some estimates (Moss et al. 1991), as many as one in 22 Americans had at least one implant and the proportion clearly continues to increase. For any one application, a wide variety of

* In the 15 years since I conceived these definitions, the field has advanced rapidly. Thus, I now implicitly include the implantation of DNA, as plasmids or in transfected cells, in the definition of phase 3 and 4 biomaterials and similarly broaden the phase 4 definition to read "*in vitro* or *in vivo*."

** I have generally used the term *phase* to discuss the historical development and *type* to address the actual biomaterials.

similar designs exist with different degrees of efficacy. In contrast to this profusion of design, materials suitable as biomaterials continue to be scarce. Perhaps no more than a few dozen of the millions of available metal, polymer, and ceramic compositions have proven useful in medical devices and implants.

The limiting factor in the use of materials as biomaterials continues to be achieving appropriate biological performance. Better understanding of biological performance and the factors affecting it will lead to a variety of useful new materials options. This in turn will lead to substantial expansion of the role that artificial devices can play in the prevention and treatment of human disability and disease. At the end of this progression, when the technology for preparation of type 4 materials is readily, widely, and affordably available, artificial devices will be called upon to serve only as "bridges" to replantation and the field of biomaterials will emerge in its rightful place as one of the healing arts.

1.5 The Discipline of Biomaterials*

The concluding comments in the preceding section presuppose that a field of study or an intellectual discipline — biomaterials — exists. Such a field exists when a definition that includes all valid aspects and excludes all other aspects is recognized. I define the field of biomaterials thus:

> Biomaterials: the organized study of the materials properties of the tissues and organs of living organisms; the development and characterization of pharmacologically inert materials to measure, restore, and improve function in such organisms; and the interaction between viable and nonviable materials

This definition can be seen in graphic form in Figure 1.1. The bases for the field, its foundation disciplines, are the traditional intellectual fields of engineering, medicine, and the physical and biological sciences. The body of the field is the materials science approach to manufactured (artificial) and natural (or native) biomaterials (including tissues). The apex or distinguishing feature of the field is the study of biological performance of materials as defined by their host and material responses. This last area is unique to the discipline of biomaterials and leads to a further definition:

> Biomaterials science: the study and knowledge of the interaction between living and nonliving materials

* Parts of this section were previously published, in different form, in Black et al. (1992).

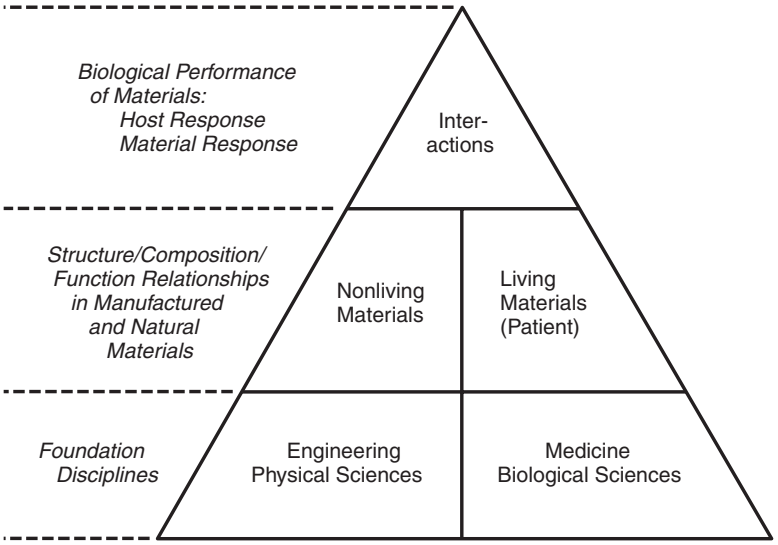

FIGURE 1.1
The structure of the discipline of biomaterials.

A complementary definition is:

> Biomaterials engineering: the application of the principles of biomaterials science and its foundation sciences to the solution of practical problems of human health, disability, and disease

Taking into account the definitions of biomaterials as objects and as a field of study, I advance three propositions about the nature of the intellectual field of biomaterials:

> Biomaterials is a materials science: the central issue is the dependence of physical properties on composition and structure.
>
> Biomaterials is an interdisciplinary science: its unique feature is consideration of the interactions between living and nonliving materials.
>
> Biomaterials is a medical science: its ultimate goal is the improvement of human health and quality of life.

Biomaterials science and engineering are evolving fields of study, investigation, and development. However, their meets and bounds are now understood well enough to assert safely that they are parts of an established discipline, the field of biomaterials.

1.6 Afterword: Paradigmatic Shift

As the field of biomaterials began to be organized as a field of research and an academic discipline in the early 1970s,* a recognizable paradigm emerged that dominated the efforts in the field (Figure 1.2). In this analysis, the central issue was seen as the interaction between implant and patient at the interface: the effect of the patient on the implant ("biodegradation" = material response) and the converse effect of the implant on the patient ("biocompatibility" = [local] host response). The principal foci of investigation of material response were fracture, wear, corrosion, and dissolution, with lesser interests in transport, storage, and excretion of degradation products. Host response was viewed primarily in a local or interface context, with emphasis on ingrowth, inflammation, fibrosis (encapsulation), and, when in chronic contact with blood, coagulation and hemolysis.

As the field began to mature and interest moved away from the apparently impossible and fruitless search for inert (type 1) materials to active pursuit and design of bioactive (type 2: interactive) materials, some trends could be noted:

- Biological models began to focus less on animals and patients and more on cells and molecules.

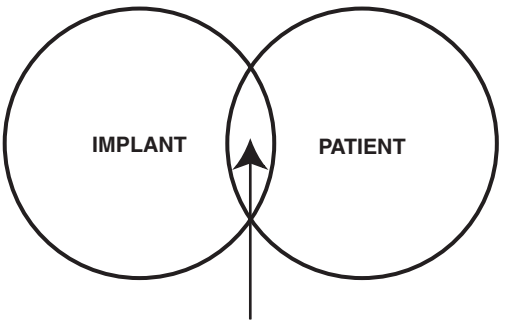

FIGURE 1.2
The old biomaterials paradigm.

* A key milestone was the organization of the Society for Biomaterials (SFB) in 1973.

- Investigations and design of materials began to emphasize three-dimensional structures over two-dimensional interfaces.
- Effects of material-living systems' interactions were increasingly examined in terms of systemic biology as well as local biological response.
- Initial efforts at replacement of absent, damaged, or diseased parts of the human body broadened into concern for diagnosis, repair, and regeneration.
- Overall, the field moved from a more applied engineering approach of providing pragmatic solutions to clinical problems to a concern for more science-based fundamental understanding of clinical problems and of potential routes to their solution.

These shifts in emphasis are contained in the modern reference to the field as "biomaterials science and engineering," rather than as "biomaterials," and are reflected in a new paradigm (Figure 1.3). Here, *material* is replaced by *matrix* and *patient* by *cell*, and a third factor, *signal*, is added. Each of these factors interacts with the other two: the cells are affected by their matrix and by bound and free signals; the signals are modified by cellular activity and by association with matrix while the matrix can be remodeled by cells, based upon its native structure and upon interaction with signaling molecules. The emphasis is now larger than merely a study of the interface between body and biomaterial, as in the old paradigm; now it is on interactions and their local, systemic, and remote consequences.

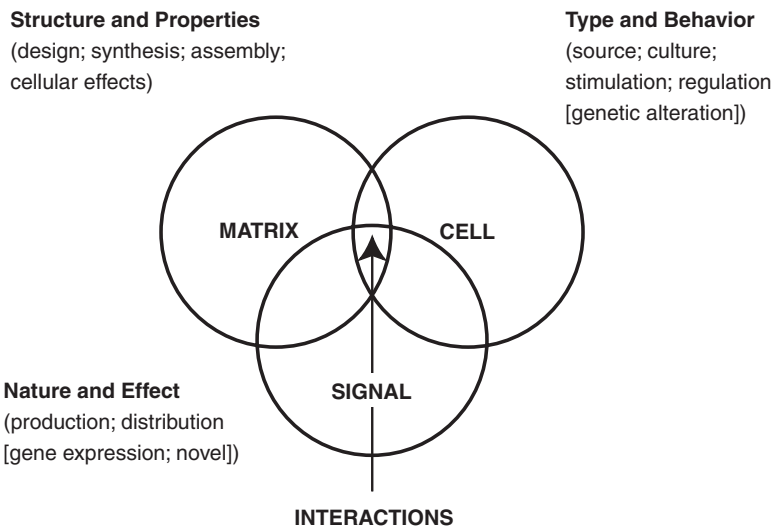

FIGURE 1.3
The emerging new biomaterials paradigm.

The foci of interest have also shifted:

- Matrix: here interest still closely resembles traditional materials scientists' concerns for the relationships between structure and properties; however, rather than mere selection and adaptation of materials, the activities tend to involve prospective design, synthesis, and assembly and investigation of cellular effects on the resulting material.
- Cells: replacing earlier attention centered on the biological response (of tissues) at the interface, the studies now address the cells, which can interact with the matrix as well as local and systemic signals. The focus is on cell source, *in vitro* culture, stimulation, and regulation, as well as the possibility of transient or permanent genetic alteration.
- Signals: the final member of the triad is a class of molecules of biological and synthetic origins that can affect cellular behavior, especially insofar as cell–matrix interactions are concerned. Here, the focus of interest is on characterization, production, and distribution of known and novel molecular sequences and molecules and on the possibility of their production *in situ* through genetic expression.

An obvious early exemplar of this new or modern paradigm is the type 3 or biohybrid biomaterial: a matrix capable of being remodeled by implanted or attracted cells, cells cultured *in vitro* or recruited upon implantation, and signals to regulate cell–matrix and construct–host interactions. This paradigm makes it clear that the newly emerging bioengineering fields of genetic, cellular, and tissue engineering are, in fact, not new but simply logical extensions of the historic and maturing field of biomaterials science and engineering.

Thus, as a basic science field, as an engineering field allied to clinical medicine, and as a class of materials, biomaterials continues to grow and diversify. The new paradigm questions our earlier assertions of knowledge and suggests that biomaterials science and engineering will continue to be an exciting and viable field for the foreseeable future.

References

Black, J., Shalaby, S.W. and LaBerge, M., Biomaterials education: an academic viewpoint, *J. Appl. Biomater.*, 3, 231, 1992.

Moss, A.J. et al., Use of selected medical device implants in the United States, 1988, *Advance Data No. 191*, February 26, 1991, Centers for Disease Control, National Center for Health Statistics, Washington, D.C.

Osborn, J.F., Biomaterials and their use in implants, *Schw. Mschr. Zahnheilk.*, 89, 1138, 1979.

Slutskii, L.I. and Vetra, J.J., Letter to the editor: biocompatibility and reactogenicity of materials: a semantic and logical analysis of definitions and their practical significance, *Cells Mater.*, 6, 137, 1996.

Steinemann, S., [Corrosion, compatibility, and mechanical properties of metallic implants] (Ger.), *Fortschr. Kiefer Gesichtschir.*, 19, 50, 1975, discussed in Steinemann, S., Introduction, in Winter, G.D., Leray, J.L., de Groot, K.(Eds), *Evaluation of Biomaterials*, John Wiley & Sons, Chichester, U.K., 1, 1980.

Warnke, P.H. et al., Growth and transplantation of a custom vascularised bone graft in a man, *Lancet*, 364, 766, 2004.

Williams, D.F. (Ed.), *Definitions in Biomaterials: Proceedings of a Consensus Conference of the European Society for Biomaterials*, Chester, England, March 3–5, 1986. Elsevier, Amsterdam, 1987.

Williams, D.F., Black, J. and Doherty, P.J., Second consensus conference on definitions in biomaterials, in Doherty, P.J. et al. (Eds.), *Biomaterial–Tissue Interfaces. Advances in Biomaterials* Vol. 10, Elsevier, Amsterdam, 525, 1992.

Bibliography

Bush, R.B., Biomaterials: an introduction for librarians, *Sci. Technol. Lib.*, 15(4), 3, 1996.

Feldman, D.S. et al., A biocompatibility hierarchy: justification for biomaterial enhanced regeneration, in Wise, D.L., Trantolo, D.J., Altobelli, D.E. et al. (Eds.), *Encyclopedic Handbook of Biomaterials and Bioengineering, Part A: Materials,* Vol. 1, Marcel Dekker, New York, 223, 1995.

Peppas, N.A. and Langer, R., New challenges in biomaterials, *Science*, 264, 25 March 1994, 1715.

2

Introduction to the Biological Environment

2.1 General Considerations

The central idea developed in the previous chapter is that biological performance should be defined in terms of interaction between materials and their operational setting, the biological environment. This is not qualitatively different from the normal consideration given to the material aspects of performance and durability during any engineering design process. However, two relative quantitative aspects set biological performance apart and create the need for an independent study of material and host responses:

- High demand: the biological environment, especially internal to living systems, is a remarkably aggressive one, resembling tropical marine conditions. It is a milieu of high chemical activity combined with a highly variable spectrum of combined mechanical stresses.
- Invariant conditions: despite its aggressive aspects, the biological environment displays an extraordinary quality of constancy in physical conditions and composition. Complex control systems exist to maintain that constancy; thus, deviations from established conditions attendant to the presence of materials may be expected to incite restoring responses.

The latter portions of this work deal with many aspects of this peculiar environment during examination of typical material and host responses. At this point, it is advisable to examine general points that will serve as guides for discussion.

2.2 Comparison of External and Internal Conditions

The aggressive aspects of the biological environment may be understood if the differences between conditions external and internal to living systems

are examined. Externally, the familiar aspects of the physical world can be found. Most materials are inorganic and are partially or fully oxidized. Although physical processes are interrelated, there is an absence of active environmental control systems. Time constants for change are long, determined by processes of chemical reaction and diffusion, and driven by sources that supply energy primarily through radiation, conduction, and convection. A wide variety of atomic species are present. Structure and chemical content vary greatly and little evidence of compositional or structural optimization can be found.

By contrast, the internal environment arises from a system in which materials (molecules and tissues) are largely organic and are partially or fully reduced. Most changes are mediated by active, energy-requiring control systems. In many cases, multiple parallel systems with different time constants and extensive intersystem interactions control a single transformation or process. Time constants are orders of magnitude shorter than for most inorganic reactions due to mediation by specialized organic catalysts (enzymes) and the derivation of energy from chemical sources through coupled reactions. Although a great variety of chemical content and structure exists, arrangements and combinations of a few elements — primarily carbon, oxygen, hydrogen, and nitrogen — comprise the vast majority of this complexity. Elements that are present are generally utilized and structures display a parsimonious efficiency, providing an overall impression of design optimization.

Whatever one's views on the origin and development of biological systems, one must be impressed by the complexity of these systems and their economy of action. They obtain their objectives by excluding, through accident, design, or active process, materials that are unnecessary or harmful to the function of their individual processes. These phenomena act to exclude all materials other than healthy, autologous (belonging to the same organism) tissue. Furthermore, the systems interact locally as well as on a regional and global (whole organism) scale. Thus, a constant aspect of the biological environment is that the introduction of a foreign material will elicit a host response, which may have local, systemic, and remote aspects.

2.3 Problems in Definition of the Biological Environment

Until now, I have referred to "a" biological environment. However, a variety of sets of conditions is associated with life processes, and it is difficult to define the actual environment in which a material or device is called upon to function. More will be said about this later. The difficulty arises from a lack of detailed knowledge of *in vivo* conditions and the local variations that can occur in the face of overall maintenance of conditions, termed homeostasis, necessary for life. Also, there is ambiguity in defining the region that

is coupled with an implant. Implants in isolated locations can interact with the rest of the system through diffusion of ions and fluids, circulation of blood, and drainage of the lymphatics. Even the definition of absolute volumes of material in communication with an implant is difficult. As Chapter 15 will show, the volume of water in which an implant is immersed in the human body may be taken as 10^{-15}, 8.4, or 1000 l, depending upon the details of consideration.

A last general point has to do with the maintenance of homeostasis. In a particular location, temperature, pH, pO_2, equivalent electrical potential, hydrostatic and osmotic pressure, and tissue/fluid composition are closely controlled. However, the observation of such active control should not lead to unwarranted conclusions concerning its adaptability. The control systems most in evidence are those that control for the usual situation and small deviations. Superimposed upon these are "emergency" protection systems, such as coagulation, inflammation, and nonspecific immune response. These initiate programmed deviations that attempt to restore normal conditions locally, as long as systemic integrity is maintained. Taking a control systems viewpoint, one can foresee challenges that can overwhelm the restorative capabilities of local and systemic control. Only challenges that occur within the "design" spectrum of the system can be expected to elicit satisfactory responses, except by chance. Thus, when viewing host response, it is wise to recognize the limited environmental variations that occur in the absence of outside intrusion. It is also prudent to consider the qualitative and quantitative differences between chance intrusion and deliberate functional implantation of biomaterials.

Materials must be tested *in vitro* before implantation, even in animals. It is desirable to attempt, in large or small part, to replicate the operating environment that the material may encounter after implantation. Here it is useful to distinguish among four classes of exposure environments:

- Physiological: chemical (inorganic) and thermal conditions controlled to normative mammalian values for the intended application
- Biophysiological: physiological conditions with the addition of appropriate types and concentrations of initially nondenatured (active) cell products (serum proteins, enzymes, etc.)
- Biological: biophysiological conditions with the addition of appropriate viable, active cells
- Pericellular (circumcellular): a special case of "biological": the conditions in the immediate vicinity of appropriate, viable, active cells

I term these "classes" of environments because the exact value of parameters within each depends upon the specific details of the location within tissue or organ and, in the case of materials (rather than device) testing, upon the design details and functional goals of the device.

In vitro testing is usually carried out under physiological or biophysiological conditions only. The problems associated with *in vitro* testing and its comparison to *in vivo* conditions will be discussed further in Chapter 17 and Chapter 18. In this chapter, "biological environment" is taken to mean, most generally, the combination of conditions that an implanted material will encounter acutely and chronically in actual service: the combination of biological and pericellular conditions, as well as the instantaneous requirements placed upon the design and function of the device in which it is incorporated. The combination of these intrinsic and extrinsic environmental effects with the overall patient requirements during the proposed period of implantation produces what is properly termed the implant life history: the total combination of requirements that the biomaterial must meet to be successful in a specific application.

2.4 Elements of the Biological Environment

The human body is generally considered in terms of a standard or reference configuration: this is the 70-kg man.* This standard has the macroscopic parameters given in Table 2.1. Wide individual variations from these parameters exist. Age, type and level of activity, disease state, national origin, and genetic factors will also affect the absolute values. Furthermore, the values given here, as in the following tables in this chapter, are mean normative values for a male Anglo–Saxon individual aged in his mid-30s. They represent an average expectation and do not account for any variations within physiological limits. It is common to describe such variations under the overall term "biological variation." The physicochemical and mechanical conditions encountered in the body can also be defined (Table 2.2).

When the effects of release of material from the implant into the body are considered, it is necessary to know the starting or nominal inorganic chemical composition of the body. Although the concentrations of major elements have been known for some time, those of trace elements, present in very low concentrations, are just beginning to be appreciated fully. Table 2.3 presents nominal or reference mean values; see Chapter 15 for a more detailed discussion.

Taken together, these parameters define the intrinsic physicochemical and mechanical parameters appropriate to generic biological environments. Exact dimensional and functional details of a particular anatomical site may be required when designing tests for particular materials or devices. In another area, more detailed information is desirable. Blood is a delicate and pervasive

* It is usual practice to speak of the standard man rather than the standard human. Recent comments in the lay literature concerning the focus of federal funding for biomedical research have drawn attention, once again, to important differences between men and women. Thus, the values in Table 2.1 should be taken as guidelines; other sources, such as Lentner (1981), should be addressed for values applicable to gender-specific applications for northern hemisphere Anglo–Saxon subjects.

TABLE 2.1

Macroscopic Parameters of the Reference Human[a]

Weight: 70 kg	**Height (medium frame): 1.80 m**
Surface area: 1.88 m²	**Volume: 0.065 m³**
Composition:	**Density:**
Water: 60% (42 l)	Fat: 0.9 g/cm³
Solid: 40% (28 kg)	Whole body: 1.07 g/cm³
Distribution of tissue types (as percentages of body weight)	
Muscle:	43
Bone:	30
Internal organs:	
Heart:	0.4
Liver:	2
Kidneys (2):	0.5
Spleen:	0.2
Lungs:	1.6
Brain:	2.3
Viscera:	5.6
Skin:	7
Blood:	7.2 (5 l)
Basal metabolic rate: 37/kcal.m²/h	

[a]Values given for a male individual in his mid-30s.

Source: Lentner, C. (Ed.), *Geigy Scientific Tables,* Ciba–Geigy, Basle, 1981.

tissue. It is essential to understand its makeup and normal values, especially for applications involving blood contact on a chronic basis. Information describing the composition and cellular distribution of blood is given in Table 2.4.

It is difficult to obtain engineering properties of biological materials for use in design processes. With a group of contributors, Black and Hastings (1998) took a major step by attempting to collate reliable properties of normal human tissues and fluids. However, effects of age and disease processes on engineering properties of tissues are still not well reported. Reference should be made to contemporary literature or individual experimental studies may need to be undertaken to obtain design data for specific applications.

Beginning with the information given in Table 2.1 to Table 2.4 and from other sources, it is possible to develop a picture of the thermal, mechanical, and chemical environment that an implant will encounter when it is implanted in a specific anatomical site. Some of the material responses during implant service life will be described in Chapter 3 to Chapter 7 of this work. This defined environment may be changed acutely and chronically by the presence of an implant.* Chapter 8 to Chapter 15 deal with some

* Although it is possible to define four types of "biological" environments, it should be appreciated that the fourth — the pericellular environment — is the least known and understood. On this scale of consideration, it is clear that cellular events produce dynamic and continuing changes (Konttinen et al. 2005). These are difficult to measure and to replicate *in vitro*. In the general case, there can probably be no substitute for *in vivo* studies in intact animals to examine host–material interactions at this level.

TABLE 2.2

Physicochemical and Mechanical Conditions in Humans

	Value	Location
pH	1.0	Gastric contents
	4.5–6.0	Urine
	6.8	Intracellular
	7.0	Interstitial
	7.15–7.35	Blood
pO_2 (mmHg)	2–40	Interstitial
	12	Intramedullary
	40	Venous
	100	Arterial
	160	Atmospheric
pCO_2 (mmHg)	40	Alveolar
	2	Atmospheric
Temperature (°C)	37	Normal core
	20–42.5	Deviations in disease
	28	Normal skin
	0–45	Skin at extremities

Mechanical	Stress (MPa)	Tissues
	0–0.4	Cancellous bone
	0.08–0.1	Across aortic valve (ventricular diastole)
	0.12–0.16	Across mitral valve (ventricular systole)
	0–4	Cortical bone
	4	Muscle (peak stress)
	40	Tendon (peak stress)
	80	Ligament (peak stress)

Stress Cycles (per year)	Activity
3×10^5	Peristalsis
3×10^6	Swallowing
$0.5–4 \times 10^7$	Heart contraction
$0.1–1 \times 10^6$	Finger joint motion
$1–2 \times 10^6$	Walking

variations in the biological environment that arise, locally and systemically, as a result of implantation — that is, the host response.

2.5 Implant Life History

The thermal, mechanical, and chemical parameters described in previous sections are sufficient to predict, in general, the acute or instantaneous biological environment encountered by an implant. These acute values differ little from patient to patient; differences have only small effects on acute host and material responses. Phenotypic and genotypic biological differences that

TABLE 2.3

Inorganic Composition of the Human Body

		Total Body Burden	Conc. (aver.)
Basic elements[a]	Oxygen	43,000 g	61.4%
	Carbon	16,000 g	22.9%
	Hydrogen	7,000 g	10.0%
	Nitrogen	1,800 g	2.6%
	Total	67,800 g	96.9%
Physiological elements[a]	Calcium	1000 g	1.43%
	Phosphorus	780 g	1.11%
	Potassium	140 g	0.20%
	Sulfur	140 g	0.20%
	Sodium	100 g	0.14%
	Chlorine	95 g	0.14%
	Total	2255 g	3.22%
Trace elements[a]	Magnesium	19 g	271 ppm
	Iron	4.2 g	61.4 ppm
	Zinc	2.3 g	33 ppm
	Iodine	130 mg	1.9 ppm
	Copper	72 mg	1.0 ppm
	Aluminum	61 mg	0.9 ppm
	Vanadium	18 mg	260 ppb
	Selenium	<13 mg	<190 ppb
	Manganese	12 mg	170 ppb
	Nickel	10 mg	140 ppb
	Molybdenum	<9.5 mg	<136 ppb
	Titanium	9 mg	130 ppb
	Chromium	<6.6 mg	<94 ppb
	Cobalt	<1.5 mg	<21 ppb
	Total	<25.84 g	<0.37%

[a] Total of body burdens exceeds 70,000 g and 100% due to variety of primary sources and experimental error in individual values.

Source: Data from Lentner, C. (Ed.), *Geigy Scientific Tables*, Ciba–Geigy, Basle, 1981.

affect chronic host response to materials do exist. These may only be discernible by clinical testing of a specific patient; analyses of body fluids and tissues are probably inadequate for a full understanding of individual differences. It is unfortunate that technology for determination of the functional behavior of implants and implant–patient interactions is weak compared with that available to biological scientists for the study of natural organs *in situ*.

Beyond these obvious similarities and possible individual biological differences, the demands and expectations of individuals vary considerably. A total hip replacement prosthesis for a 40-year-old head of a family presents

TABLE 2.4

Components and Composition of Human Blood

Blood			
Packed cell volume	**38.5%**		
Serum volume	**61.5%**		
Serum composition (mean values)			
Cations	**mEq/l**	**Anions**	**mEq/l**
Sodium	142	Chlorine	101
Potassium	4	Bicarbonate	27
Calcium	5	Phosphate	2
Magnesium	2	Sulfate	1
Total	153	Organic acids	6
		Proteins	16
		Total	153

Other elements		
Iron	0.75–1.75	mg/l (ppm)
Nickel	1.0–5.0	μg/l (ppb)
Titanium	3.3	μg/l
Aluminum	2.0	μg/l
Copper	0.8–1.4	μg/l
Chromium	0.3	μg/l
Manganese	0.4–1.0	μg/l
Vanadium	<0.2	μg/l
Cobalt	0.15	μg/l

Serum proteins	
Total	65–80 g/ l
Distribution (%):	
Albumin	61.5
Globulins (total)	34.5
α	8.2
β	10.3
δ	12.6
Fibrinogen	4.0

Cellular Distribution Type	**Blood Concentration**	**Typical Dimension (μm)**
Erythrocyte	4–5.6 × 10^6/μl	8–9
Platelet	1.5–3 × 10^5/μl	2–4
Leukocyte	2.8–11.2 × 10^3/μl	—

Leukocyte Distribution Type	**(%)**	**Typical Dimension (μm)**
Neutrophils	59	10–15
Eosinophils	2.4	10–15
Basophils	0.6	10–15
Monocytes	6.5	12–20
Lymphocytes	31	7–18

Sources: Data from Lentner, C. (Ed.), *Geigy Scientific Tables*, Ciba–Geigy, Basle, 1981, and author's research.

TABLE 2.5

Implant Life History

Implant: anterior cruciate ligament replacement
Type: permanent
Patient indications:
Post-traumatic replacement, age: 35–48
(est. mean life expectancy: 40 years)
pH = 7 ± 0.3
pO_2 = <40 mmHg
pCO_2 = <40 mmHg
25°C ≤ T ≤ 37°C
Mechanical conditions[a]
Strain (range of maximum): 5–10%
Loads: (moderate activity level, including recreational jogging)

Activity	Peak Load (N)	Cycles/Year	Total Cycles
Stairs:			
Ascending	67	4.2×10^4	1.7×10^6
Descending	133	3.5×10^4	1.4×10^6
Ramp walking:			
Ascending	107	3.7×10^3	1.5×10^5
Descending	485	3.7×10^3	1.5×10^5
Sitting and rising	173	7.6×10^4	3.0×10^6
Undifferentiated	<210	9.1×10^5	3.6×10^7
Level walking	210	2.5×10^6	1.0×10^8
Jogging	630	6.4×10^5	2.6×10^7
Jolting	700	1.8×10^3	7.3×10^5
Totals		4.2×10^6	2.9×10^8

[a] Adapted from Table III in Chen, E.H. and Black, J., *J. Biomed. Mater. Res.*, 14, 567, 1980.

a quite different engineering problem from such a device for an 80-year-old nursing home resident. Accounting for these functional differences completes the description of the service environment; the full picture thus formed is termed, as previously defined, the implant life history.

Implant life histories vary considerably from application to application and, of necessity, involve a high degree of engineering estimation. Within given target (patient) groups, the choice and intensity of work and leisure activities will vary widely (e.g., Schmalzried et al. 2000). As a result, implant life histories can only be regarded as predictive guides in the development, evaluation, and study of implantable biomaterials.

Table 2.5 gives an example of an implant life history, in this case for a permanent anterior cruciate ligament replacement. The supposed patient presents an example of an individual with moderate demands: presumably a full-time worker with evening and/or weekend physical recreational interests. If this individual were disabled in some manner or employed in a setting with unusual physical demands, such as mining or construction, or took part in other more demanding physical activities, such as wind surfing, mountain climbing, or parachute jumping, these facts should be noted and

the physical consequences accounted for, in terms of different estimated peak loads and numbers of repetitions.

Asymmetry may also be a factor. Whether it is intrinsic or acquired, "handedness" is a possible source of laterality in physical properties of tissues, such as bone (Dane et al. 2001), subject to dynamic remodeling (see Chapter 10). Less controversial and more obvious are the visible effects of repetitive asymmetric physical activities, such as certain sports (soft- and hard-ball pitching, golf, archery, etc.) or work tasks (using a sledge hammer, painting, etc.). In some individual cases, laterality in tissue properties or material response (Joshi et al. 2001) is observed without any obvious source.

Within a particular application, the selection of particular materials and designs incorporating them has come to be termed demand matching. Demand matching cannot account for changes in a patient's life postimplantation, but it can be used to guide selection of technologies preimplantation. In the best of all possible words, one would try to design the longest lived, most durable materials that evoked optimum responses. However, present concerns about the cost of medical care and the way in which biomaterials and biomedical devices contribute to these costs result in cost containment, or more properly cost minimization, as a stimulus for "good enough" provided devices (and their constituent biomaterials) — that is, that will meet the patient's needs and expectations without excessive cost.

There is no general agreement on what patient features contribute to demand and how these features should be balanced in deriving a predictive formula. Demand matching tends to be individualized for the medical practitioner and to depend upon subjective as well as objective measures. Of the objective measures available, age (as measured by life expectancy) and gender (as a predictor of body weight and activity level) are the most widely accepted.

The mean U.S. life expectancy as a function of age is shown graphically in Figure 2.1 (NCHS 2002). Life expectancy now declines nearly linearly from early childhood (~6 months of age) to around age 50. Thereafter, however, the curve has a positive upward bend. Thus, mean life expectancy at age 60 is 21.6 years and, by age 70, it has declined by only 7.2 years to 14.4 years. Table 2.6 shows the clear effect of gender and national origin on life expectancy. It should be remembered that these data are averages.* Therefore, although mean life expectancy of U.S. residents at 75 is 11.3 years, only 24 of every 1000 that turn 75 will die before their next birthday.

In an example of demand matching (Black 1997), I have discussed selection of alternate bearing technologies in implants for total hip replacement arthroplasty; patient age at surgery, as well as other, less well defined demand components, has been taken into account.

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* It is interesting to note that U.S. life expectancy at birth continues to increase, although it rose by more than 50% (49.2 to 76.9 years) during the 20th century. Thus, although Figure 2.1 and Table 2.6 reflect data only to age 100, U.S. life insurance underwriters have recently begun to use tables that extend to 110 years of life.

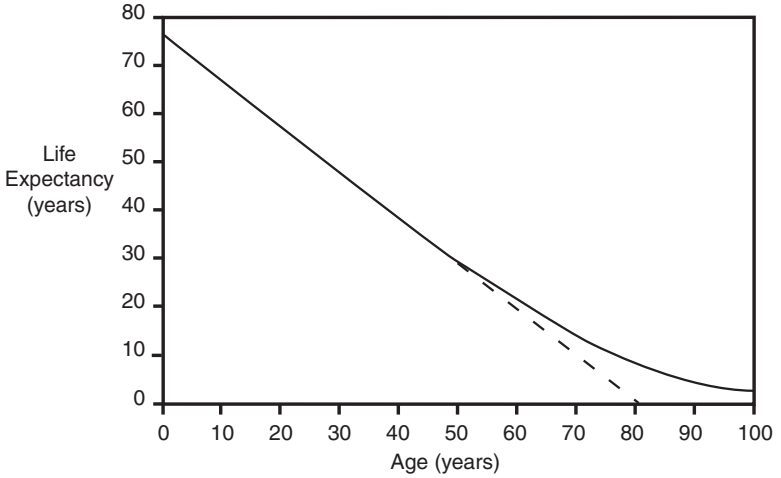

FIGURE 2.1
Average U.S. life expectancy 2000 mean (average of male and female, all national origins). (National Center for Health Statistics (NCHS), *National Vital Statistics Reports*, 51(3), 29, 2002.)

TABLE 2.6

U.S. Life Expectancy (Years)[a]

		All Races		White		Black	
Age	**Total Persons**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0	76.9	74.1	79.5	74.8	80.0	68.2	74.9
20	57.8	55.2	60.3	55.7	60.7	49.9	56.3
35	43.6	41.3	45.8	41.7	46.1	36.6	42.1
50	30.0	27.9	31.8	28.2	32.0	24.2	28.9
65	17.9	16.3	19.2	16.3	19.2	14.2	17.4
70	14.4	13.0	15.5	13.0	15.5	11.7	14.1
75	11.3	10.1	12.1	10.3	12.1	9.4	11.2
80	8.6	7.6	9.1	7.6	9.1	7.3	8.6
85	6.3	5.6	6.7	5.5	6.6	5.7	6.5
90	4.7	4.1	4.8	4.0	4.7	4.5	4.8
100	2.6	2.4	2.7	2.2	2.4	2.9	2.7

[a] Year 2000.

Source: National Center for Health Statistics (NCHS), *National Vital Statistics Reports*, 51(3), 29, 2002.

2.6 Preimplantation Handling Effects

One tends to think of the biological environment as that into which the implant passes after manufacture and storage. This assumption overlooks two intermediate processes common to all implant applications. In the first place, the implant may become contaminated, accidentally or as a side effect of planned processing and handling during manufacture, storage, and insertion. It is usually assumed that the implant surface is a pure, clean one with the composition of the bulk material. The truth may be far different. Organic films introduced during manufacture or by inadvertent handling may persist. Oxidation or other attack may occur during preoperative storage. Materials may be picked up from packaging used for storage or during sterilization. Contaminants may be transferred from surgical instruments.

For this reason, experimental studies of biological performance should include surface characterization of actual implant specimens selected from the full group fabricated in a particular study in the condition just before surgical insertion. Furthermore, care should be taken when materials are incorporated into devices for clinical trials and use, to see that the surface conditions are the same as those found during earlier developmental studies.

Second, all implants must be cleaned and sterilized before use; the manufacturer may supply some in sterile, double-wrapped packages, but others must be sterilized in the laboratory or hospital before use. The common forms of sterilization used in implant practice are:

- Cold solution
- Dry heat
- Moist heat (steam)
- Gas
- Gas plasma
- Gamma irradiation

Some typical sterilization parameters for each of these common methods are listed in Table 2.7. The particular method and parameters used must be suited to the individual implant type to provide maximum safety with minimum cost and implant degradation. Newer methods include electron beam irradiation and radio frequency plasma gas sterilization (Chau et al. 1996; Feldman and Hui 1997), which have the virtue of cleaning implant surfaces as well as sterilizing them.

The process of sterilization, if overlooked, may affect perception of the material and the host response. It is possible for some sterilization processes, such as irradiation, to change material properties, particularly of polymers,

TABLE 2.7

Methods and Typical Parameters of Sterilization

Method	Temperature	Time	Notes
Cold solution	RT	1–3 h	Commercial solutions; usually include formaldehyde or gluteraldehyde
Dry heat	160–175°C (max.)	0.5–2 h	Time/temperature vary inversely
Moist heat	120–130°C (max.)	2–15 min	Time/temperature vary inversely
Gas	RT — 55°C	1–24 h	Gas is usually ethylene oxide, 400–1200 mg/l; 48-h degassing required
Plasma discharge	45–55°C	1–2 h	RF discharge (var. frequencies) in <0.5 torr gas; hydrogen peroxide or peracetic acid most common
Irradiation	RT	2–24 h	^{60}Co gamma irradiation, 10–40 kGy dose; time/dose rate vary inversely

immediately (Nuutinen et al. 2002) and/or during subsequent preimplantation storage (Edidin et al. 2002). This might be interpreted, in error, as a material response effect if it is detected after implantation, or it might produce changes in host response secondary to the changes in the materials' properties (Stanford et al. 1994). It is also possible for traces of liquid or gaseous sterilants to be carried into the implant site, thus modifying the host response. Finally, sterilization of an unclean implant may render it sterile but not clean or pyrogen free (Gorbet and Sefton 2005), thus affecting the host response (see Section 8.2.2). Therefore, in any examination of material and host responses to implanted materials, it is necessary to pay close attention to actual surface conditions and sterilization effects as a prologue to exposure to the biological environment.

References

Black, J., Prospects for alternate bearing surfaces in total replacement arthroplasty of the hip, in *Performance of the Wear-Couple BIOLOX Forte in Hip Arthroplasty*, Puhl, W. (Ed.), Enke Verlag, Stuttgart, 1997, 2.

Black, J. and Hastings, G.W. (Eds.), *Handbook of Biomaterial Properties*, Part 1, Chapman & Hall, London, 1998.

Chau, T.T. et al., Microwave plasmas for low-temperature dry sterilization, *Biomaterials*, 17, 1273, 1996.

Chen, E.H. and Black, J., Materials design analysis of the prosthetic anterior cruciate ligament, *J. Biomed. Mater. Res.*, 14, 567, 1980.

Dane, S. et al., Differences between right- and left-femoral bone mineral densities in right- and left-handed men and women, *Int. J. Neurosci.*, 111(3–4), 187, 2001.

Edidin, A.A. et al., Accelerated aging studies of UHMWPE. I. Effect of resin, processing, and radiation environment on resistance to mechanical degradation, *J. Biomed. Mater. Res.*, 61(2), 312, 2002.

Feldman, L.A. and Hui, H.K., Compatibility of medical devices and materials with low-temperature hydrogen peroxide gas plasma, *Med. Dev. Diagn. Ind.*, 19(12), 57, 1997.

Gorbet, M.B. and Sefton, M.V., Endotoxin: The uninvited guest, *Biomaterials*, 26, 6811, 2005.

Joshi, A., Ilchmann, T. and Markovic, L., Socket wear in bilateral simultaneous total hip arthroplasty, *J. Arthrop.*, 16(1), 117, 2001.

Konttinen, Y.T. et al., The microenvironment around total hip replacement prostheses, *Clin. Orthop. Rel. Res.*, 430, 28, 2005.

Lentner, C. (Ed.), *Geigy Scientific Tables,* Ciba–Geigy, Basle, 1981.

National Center for Health Statistics (NCHS), *National Vital Statistics Reports*, 51(3), 29, 2002.

Nuutinen, J.P. et al., Effect of gamma, ethylene oxide, electron beam, and plasma sterilization on the behavior of SR-PLLA fibers *in vitro*, *J. Biomater. Sci. Polym. Ed.*, 13(12), 1325, 2002.

Schmalzried, T.P. et al., Wear is a function of use, not time, *Clin. Orthop. Rel. Res.*, 381, 36, 2000.

Stanford, C.M., Keller, J.C. and Solursh, M., Bone cell expression on titanium surfaces is altered by sterilization treatments, *J. Dent. Res.*, 73(5), 1061, 1994.

Bibliography

Altman, P.L. and Dittmer, D.S. (Eds.), *Biological Handbooks: Blood and Other Body Fluids*, 1961; *Biology Data Book*, 1964. Federation of American Societies for Experimental Biology (FASEB), Bethesda, MD.

Åstrand, P.-O. et al., *Textbook of Work Physiology: Physiological Bases of Exercise*, 4th ed., Human Kinetics Pub., Champaign, IL, 2003.

Baier, R.E. et al., Radiofrequency gas plasma (glow discharge) disinfection of dental operative instruments, including handpieces, *J. Oral Implantol.*, 18(3), 236, 1992.

Block, S.S. (Ed.), *Disinfection, Sterilization and Preservation*, 5th ed., Lippincott, Williams & Wilkins, Philadelphia, 2000.

Cooney, D.O., *Biomedical Engineering Principles*, Marcel Dekker, New York, 1976.

Ganong, W.F., *Review of Medical Physiology*, 21st ed., McGraw–Hill, New York, 2003.

Gaughran, E.R.L. and Kereluk, K. (Eds.), *Sterilization of Medical Products*, Johnson & Johnson, New Brunswick, NJ, 1977.

Kurtz, S.M. et al., Advances in the processing, sterilization, and crosslinking of ultra-high molecular weight polyethylene for total joint arthroplasty, *Biomaterials*, 20, 1659, 1999.

LeVeau, B. (Ed.), *Williams and Lissner: Biomechanics of Human Motion,* 2nd ed., W.B. Saunders, Philadelphia, 1977.

Matthews, I.P., Gibson, C. and Samuel A.H., Sterilization of implantable devices, *Clin. Mater.*, 15, 191, 1994.

Nair, P.D., Currently practiced sterilization methods — some inadvertent consequences, *J. Biomater. Appl.*, 10, 121, 1955.

Nordin, M., Frankel, V.H. and Frankel, V.H., *Basic Biomechanics of the Skeletal System*, 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2001.

Northrip, J.W., *Introduction to Biomechanic Analysis of Sport*, 2nd ed., Wm. C. Brown, Dubuque, IA, 1979.

Snyder, W.S. (Ed.), *Report of the Task Group on Reference Man*, International Commission on Radiological Protection, No. 23, Pergamon, Oxford, 1975.
Staff, Plastics Design Library (Eds.), *The Effect of Sterilization Methods on Plastics and Elastomers*. W.A. Morris, Inc. (for Plastics Design Library), Norwich, NY, 1994.
Wise, D.L. et al. (Eds.), *Encyclopedic Handbook of Biomaterials and Bioengineering, Part B: Applications.* (Vols. 1, 2), Marcel Dekker, New York, 1995.

References

Contents

General Considerations

Black, J., Shalaby, S.W. and LaBerge, M., Biomaterials education: an academic viewpoint, J. Appl. Biomater., 3, 231, 1992.

Moss, A.J. et al., Use of selected medical device implants in the United States, 1988, Advance Data No. 191 , February 26, 1991, Centers for Disease Control, National Center for Health Statistics, Washington, D.C.

Osborn, J.F., Biomaterials and their use in implants, Schw. Mschr. Zahnheilk ., 89, 1138, 1979.

Slutskii, L.I. and Vetra, J.J., Letter to the editor: biocompatibility and reactogenicity of materials: a semantic and logical analysis of definitions and their practical significance, Cells Mater. , 6, 137, 1996.

Steinemann, S., [Corrosion, compatibility, and mechanical properties of metallic implants] (Ger.), Fortschr. Kiefer Gesichtschir ., 19, 50, 1975, discussed in Steinemann, S., Introduction, in Winter, G.D., Leray, J.L., de Groot, K.(Eds), Evaluation of Biomaterials , John Wiley & Sons, Chichester, U.K., 1, 1980.

Warnke, P.H. et al., Growth and transplantation of a custom vascularised bone graft in a man, Lancet , 364, 766, 2004.

Williams, D.F. (Ed.), Definitions in Biomaterials: Proceedings of a Consensus Conference of the European Society for Biomaterials , Chester, England, March 3-5, 1986. Elsevier, Amsterdam, 1987.

Williams, D.F., Black, J. and Doherty, P.J., Second consensus conference on definitions in biomaterials, in Doherty, P.J. et al. (Eds.), Biomaterial-Tissue Interfaces. Advances in Biomaterials Vol. 10, Elsevier, Amsterdam, 525, 1992.

Bush, R.B., Biomaterials: an introduction for librarians, Sci. Technol. Lib. , 15(4), 3, 1996.

Feldman, D.S. et al., A biocompatibility hierarchy: justification for biomaterial enhanced regeneration, in Wise, D.L., Trantolo, D.J., Altobelli, D.E. et al. (Eds.), Encyclopedic Handbook of Biomaterials and Bioengineering, Part A: Materials, Vol. 1, Marcel Dekker, New York, 223, 1995.

Peppas, N.A. and Langer, R., New challenges in biomaterials, Science, 264, 25 March 1994, 1715. 17

2

Introduction to the Biological Environment

2.1 General Considerations

The central idea developed in the previous chapter is that biological perfor

mance should be defined in terms of interaction between materials and their

operational setting, the biological environment. This is not qualitatively dif

ferent from the normal consideration given to the material aspects of per

formance and durability during any engineering design process. However,

two relative quantitative aspects set biological performance apart and create

the need for an independent study of material and host responses:

- High demand: the biological environment, especially internal to living systems, is a remarkably aggressive one, resembling tropical marine conditions. It is a milieu of high chemical activity combined with a highly variable spectrum of combined mechanical stresses.

- Invariant conditions: despite its aggressive aspects, the biological environment displays an extraordinary quality of constancy in physical conditions and composition. Complex control systems exist to maintain that constancy; thus, deviations from established conditions attendant to the presence of materials may be expected to incite restoring responses.

The latter portions of this work deal with many aspects of this peculiar

environment during examination of typical material and host responses. At

this point, it is advisable to examine general points that will serve as guides

for discussion.

2.2 Comparison of External and Internal Conditions

The aggressive aspects of the biological environment may be understood if

the differences between conditions external and internal to living systems

are examined. Externally, the familiar aspects of the physical world can be

found. Most materials are inorganic and are partially or fully oxidized.

Although physical processes are interrelated, there is an absence of active

environmental control systems. Time constants for change are long, deter

mined by processes of chemical reaction and diffusion, and driven by sources

that supply energy primarily through radiation, conduction, and convection.

A wide variety of atomic species are present. Structure and chemical content

vary greatly and little evidence of compositional or structural optimization

can be found.

By contrast, the internal environment arises from a system in which mate

rials (molecules and tissues) are largely organic and are partially or fully

reduced. Most changes are mediated by active, energy-requiring control

systems. In many cases, multiple parallel systems with different time con

stants and extensive intersystem interactions control a single transformation

or process. Time constants are orders of magnitude shorter than for most

inorganic reactions due to mediation by specialized organic catalysts

(enzymes) and the derivation of energy from chemical sources through cou

pled reactions. Although a great variety of chemical content and structure

exists, arrangements and combinations of a few elements — primarily car

bon, oxygen, hydrogen, and nitrogen — comprise the vast majority of this

complexity. Elements that are present are generally utilized and structures

display a parsimonious efficiency, providing an overall impression of design

optimization.

Whatever one’s views on the origin and development of biological sys

tems, one must be impressed by the complexity of these systems and their

economy of action. They obtain their objectives by excluding, through acci

dent, design, or active process, materials that are unnecessary or harmful to

the function of their individual processes. These phenomena act to exclude

all materials other than healthy, autologous (belonging to the same organism)

tissue. Furthermore, the systems interact locally as well as on a regional and

global (whole organism) scale. Thus, a constant aspect of the biological

environment is that the introduction of a foreign material will elicit a host

response, which may have local, systemic, and remote aspects.

2.3 Problems in Definition of the Biological Environment

Until now, I have referred to “a” biological environment. However, a variety

of sets of conditions is associated with life processes, and it is difficult to

define the actual environment in which a material or device is called upon

to function. More will be said about this later. The difficulty arises from a

lack of detailed knowledge of in vivo conditions and the local variations that

can occur in the face of overall maintenance of conditions, termed homeo

stasis, necessary for life. Also, there is ambiguity in defining the region that

is coupled with an implant. Implants in isolated locations can interact with

the rest of the system through diffusion of ions and fluids, circulation of

blood, and drainage of the lymphatics. Even the definition of absolute vol

umes of material in communication with an implant is difficult. As Chapter

15 will show, the volume of water in which an implant is immersed in the

human body may be taken as 10^{-15}, 8.4, or 1000 l, depending upon the details

of consideration.

A last general point has to do with the maintenance of homeostasis. In a

particular location, temperature, pH, pO 2 , equivalent electrical potential,

hydrostatic and osmotic pressure, and tissue/fluid composition are closely

controlled. However, the observation of such active control should not lead

to unwarranted conclusions concerning its adaptability. The control systems

most in evidence are those that control for the usual situation and small

deviations. Superimposed upon these are “emergency” protection systems,

such as coagulation, inflammation, and nonspecific immune response. These

initiate programmed deviations that attempt to restore normal conditions

locally, as long as systemic integrity is maintained. Taking a control systems

viewpoint, one can foresee challenges that can overwhelm the restorative

capabilities of local and systemic control. Only challenges that occur within

the “design” spectrum of the system can be expected to elicit satisfactory

responses, except by chance. Thus, when viewing host response, it is wise

to recognize the limited environmental variations that occur in the absence

of outside intrusion. It is also prudent to consider the qualitative and quan

titative differences between chance intrusion and deliberate functional

implantation of biomaterials.

Materials must be tested in vitro before implantation, even in animals. It

is desirable to attempt, in large or small part, to replicate the operating

environment that the material may encounter after implantation. Here it is

useful to distinguish among four classes of exposure environments:

• Physiological: chemical (inorganic) and thermal conditions controlled to normative mammalian values for the intended application

• Biophysiological: physiological conditions with the addition of appropriate types and concentrations of initially nondenatured (active) cell products (serum proteins, enzymes, etc.)

• Biological: biophysiological conditions with the addition of appropriate viable, active cells

• Pericellular (circumcellular): a special case of “biological”: the conditions in the immediate vicinity of appropriate, viable, active cells

I term these “classes” of environments because the exact value of parameters

within each depends upon the specific details of the location within tissue

or organ and, in the case of materials (rather than device) testing, upon the

design details and functional goals of the device.

In vitro testing is usually carried out under physiological or biophysiological

conditions only. The problems associated with in vitro testing and its compar

ison to in vivo conditions will be discussed further in Chapter 17 and Chapter

18. In this chapter, “biological environment” is taken to mean, most generally,

the combination of conditions that an implanted material will encounter acutely

and chronically in actual service: the combination of biological and pericellular

conditions, as well as the instantaneous requirements placed upon the design

and function of the device in which it is incorporated. The combination of these

intrinsic and extrinsic environmental effects with the overall patient require

ments during the proposed period of implantation produces what is properly

termed the implant life history: the total combination of requirements that the

biomaterial must meet to be successful in a specific application.

2.4 Elements of the Biological Environment

The human body is generally considered in terms of a standard or reference

configuration: this is the 70-kg man.* This standard has the macroscopic

parameters given in Table 2.1. Wide individual variations from these param

eters exist. Age, type and level of activity, disease state, national origin, and

genetic factors will also affect the absolute values. Furthermore, the values

given here, as in the following tables in this chapter, are mean normative

values for a male Anglo-Saxon individual aged in his mid-30s. They repre

sent an average expectation and do not account for any variations within

physiological limits. It is common to describe such variations under the

overall term “biological variation.” The physicochemical and mechanical

conditions encountered in the body can also be defined (Table 2.2).

When the effects of release of material from the implant into the body are

considered, it is necessary to know the starting or nominal inorganic chemical

composition of the body. Although the concentrations of major elements have

been known for some time, those of trace elements, present in very low con

centrations, are just beginning to be appreciated fully. Table 2.3 presents nom

inal or reference mean values; see Chapter 15 for a more detailed discussion.

Taken together, these parameters define the intrinsic physicochemical and

mechanical parameters appropriate to generic biological environments. Exact

dimensional and functional details of a particular anatomical site may be

required when designing tests for particular materials or devices. In another

area, more detailed information is desirable. Blood is a delicate and pervasive

* It is usual practice to speak of the standard man rather

than the standard human. Recent com

ments in the lay literature concerning the focus of federal funding for biomedical research have

drawn attention, once again, to important differences between men and women. Thus, the val

ues in Table 2.1 should be taken as guidelines; other sources, such as Lentner (1981), should be

addressed for values applicable to gender-specific applications for northern hemisphere

Anglo-Saxon subjects.

tissue. It is essential to understand its makeup and normal values, especially

for applications involving blood contact on a chronic basis. Information describ

ing the composition and cellular distribution of blood is given in Table 2.4.

It is difficult to obtain engineering properties of biological materials for

use in design processes. With a group of contributors, Black and Hastings

(1998) took a major step by attempting to collate reliable properties of normal

human tissues and fluids. However, effects of age and disease processes on

engineering properties of tissues are still not well reported. Reference should

be made to contemporary literature or individual experimental studies may

need to be undertaken to obtain design data for specific applications.

Beginning with the information given in Table 2.1 to Table 2.4 and from

other sources, it is possible to develop a picture of the

thermal, mechanical,

and chemical environment that an implant will encounter when it is

implanted in a specific anatomical site. Some of the material responses dur

ing implant service life will be described in Chapter 3 to Chapter 7 of this

work. This defined environment may be changed acutely and chronically

by the presence of an implant.* Chapter 8 to Chapter 15 deal with some TABLE 2.1 Macroscopic Parameters of the Reference Human a Weight: 70 kg Height (medium frame): 1.80 m Surface area: 1.88 m 2 Volume: 0.065 m 3 Composition: Density: Water: 60% (42 l) Fat: 0.9 g/cm 3 Solid: 40% (28 kg) Whole body: 1.07 g/cm 3 Distribution of tissue types (as percentages of body weight) Muscle: 43 Bone: 30 Internal organs: Heart: 0.4 Liver: 2 Kidneys (2): 0.5 Spleen: 0.2 Lungs: 1.6 Brain: 2.3 Viscera: 5.6 Skin: 7 Blood: 7.2 (5 l) Basal metabolic rate: 37/kcal.m 2 /h a Values given for a male individual in his mid-30s. Source: Lentner, C. (Ed.), Geigy Scientific Tables, Ciba-Geigy, Basle, 1981.

* Although it is possible to define four types of "biological" environments, it should be appreci

ated that the fourth — the pericellular environment — is the least known and understood. On

this scale of consideration, it is clear that cellular events produce dynamic and continuing

changes (Konttinen et al. 2005). These are difficult to measure and to replicate in vitro. In the gen

eral case, there can probably be no substitute for in vivo studies in intact animals to examine

host-material interactions at this level.

variations in the biological environment that arise, locally and systemically,

as a result of implantation — that is, the host response.

2.5 Implant Life History

The thermal, mechanical, and chemical parameters described in previous

sections are sufficient to predict, in general, the acute or instantaneous bio

logical environment encountered by an implant. These acute values differ

little from patient to patient; differences have only small effects on acute host

and material responses. Phenotypic and genotypic biological differences that TABLE 2.2 Physicochemical and Mechanical Conditions in Humans Value Location pH 1.0 Gastric contents 4.5–6.0 Urine 6.8 Intracellular 7.0 Interstitial 7.15–7.35 Blood pO 2 (mmHg) 2–40 Interstitial 12 Intramedullary 40 Venous 100 Arterial 160 Atmospheric pCO 2 (mmHg) 40 Alveolar 2 Atmospheric Temperature (°C) 37 Normal core 20–42.5 Deviations in disease 28 Normal skin 0–45 Skin at extremities Mechanical Stress (MPa) Tissues 0–0.4 Cancellous bone 0.08–0.1 Across aortic valve (ventricular diastole) 0.12–0.16 Across mitral valve (ventricular systole) 0–4 Cortical bone 4 Muscle (peak stress) 40 Tendon (peak stress) 80 Ligament (peak stress) Stress Cycles (per year) Activity 3 × 10 5 Peristalsis 3 × 10 6 Swallowing 0.5–4 × 10 7 Heart contraction 0.1–1 × 10 6 Finger joint motion 1–2 × 10 6 Walking

affect chronic host response to materials do exist. These may only be dis

cernible by clinical testing of a specific patient; analyses of body fluids and

tissues are probably inadequate for a full understanding of individual dif

ferences. It is unfortunate that technology for determination of the functional

behavior of implants and implant-patient interactions is weak compared

with that available to biological scientists for the study of natural organs in

situ.

Beyond these obvious similarities and possible individual biological dif

ferences, the demands and expectations of individuals vary considerably. A

total hip replacement prosthesis for a 40-year-old head of a family presents TABLE 2.3 Inorganic Composition of the Human Body Total Body Burden Conc. (aver.) Basic elements a Oxygen Carbon Hydrogen Nitrogen 43,000 g 16,000 g 7,000 g 1,800 g 61.4% 22.9% 10.0% 2.6% Total 67,800 g 96.9% Physiological elements a Calcium Phosphorus Potassium Sulfur Sodium Chlorine 1000 g 780 g 140 g 140 g 100 g 95 g 1.43% 1.11% 0.20% 0.20% 0.14% 0.14% Total 2255 g 3.22% Trace elements a Magnesium Iron Zinc Iodine Copper Aluminum Vanadium Selenium Manganese Nickel Molybdenum Titanium Chromium Cobalt 19 g 4.2 g 2.3 g 130 mg 72 mg 61 mg 18 mg <13 mg 12 mg 10 mg <9.5 mg 9 mg <6.6 mg <1.5 mg 271 ppm 61.4 ppm 33 ppm 1.9 ppm 1.0 ppm 0.9 ppm 260 ppb <190 ppb 170 ppb 140 ppb <136 ppb 130 ppb <94 ppb <21 ppb Total <25.84 g <0.37% a Total of body burdens exceeds 70,000 g and 100% due to variety of primary sources and experimental error in individual values. Source: Data from Lentner, C. (Ed.), Geigy Scientific Tables, Ciba-Geigy, Basle, 1981. TABLE 2.4 Components and Composition of Human Blood Blood Packed cell volume 38.5% Serum volume 61.5% Serum composition (mean values) Cations mEq/l Anions mEq/l Sodium 142 Chlorine 101 Potassium 4 Bicarbonate 27 Calcium 5 Phosphate 2 Magnesium 2 Sulfate 1 Total 153 Organic acids 6 Proteins 16 Total 153 Other elements Iron 0.75–1.75 mg/l (ppm) Nickel 1.0–5.0 μg/l (ppb) Titanium 3.3 μg/l Aluminum 2.0 μg/l Copper 0.8–1.4 μg/l Chromium 0.3 μg/l Manganese 0.4–1.0 μg/l Vanadium <0.2 μg/l Cobalt 0.15 μg/l Serum proteins Total 65–80 g/ l Distribution (%): Albumin 61.5 Globulins (total) 34.5 α 8.2 β 10.3 δ 12.6 Fibrinogen 4.0 Cellular Distribution Type Blood Concentration Typical Dimension (μm) Erythrocyte 4–5.6 × 10 6 /μl 8–9 Platelet 1.5–3 × 10 5 /μl 2–4 Leukocyte 2.8–11.2 × 10 3 /μl — Leukocyte Distribution Type (%) Typical Dimension (μm) Neutrophils 59 10–15 Eosinophils 2.4 10–15 Basophils 0.6 10–15 Monocytes 6.5 12–20 Lymphocytes 31 7–18 Sources: Data from Lentner, C. (Ed.), Geigy Scientific Tables, Ciba-Geigy, Basle, 1981, and author’s research.

a quite different engineering problem from such a device for an 80-year-old

nursing home resident. Accounting for these functional differences com

pletes the description of the service environment; the full picture thus formed

is termed, as previously defined, the implant life history.

Implant life histories vary considerably from application to application

and, of necessity, involve a high degree of engineering estimation. Within

given target (patient) groups, the choice and intensity of work and leisure

activities will vary widely (e.g., Schmalzried et al. 2000). As a result, implant

life histories can only be regarded as predictive guides in the development,

evaluation, and study of implantable biomaterials.

Table 2.5 gives an example of an implant life history, in this case for a

permanent anterior cruciate ligament replacement. The supposed patient

presents an example of an individual with moderate demands: presumably

a full-time worker with evening and/or weekend physical recreational inter

ests. If this individual were disabled in some manner or employed in a setting

with unusual physical demands, such as mining or construction, or took

part in other more demanding physical activities, such as wind surfing,

mountain climbing, or parachute jumping, these facts should be noted and TABLE 2.5 Implant Life History Implant: anterior cruciate ligament replacement Type: permanent Patient indications: Post-traumatic replacement, age: 35–48 (est. mean life expectancy: 40 years) pH = 7 ± 0.3 pO 2 = <40 mmHg pCO 2 = <40 mmHg 25°C ≤ T ≤ 37°C Mechanical

conditions a Strain (range of maximum): 5–10% Loads: (moderate activity level, including recreational jogging) Activity Peak Load (N) Cycles/Year Total Cycles Stairs: Ascending 67 4.2 × 10 4 1.7 × 10 6 Descending 133 3.5 × 10 4 1.4 × 10 6 Ramp walking: Ascending 107 3.7 × 10 3 1.5 × 10 5 Descending 485 3.7 × 10 3 1.5 × 10 5 Sitting and rising 173 7.6 × 10 4 3.0 x 10 6 Undifferentiated <210 9.1 × 10 5 3.6 × 10 7 Level walking 210 2.5 × 10 6 1.0 × 10 8 Jogging 630 6.4 × 10 5 2.6 × 10 7 Jolting 700 1.8 × 10 3 7.3 × 10 5 Totals 4.2 × 10 6 2.9 × 10 8 a Adapted from Table III in Chen, E.H. and Black, J., J. Biomed. Mater. Res., 14, 567, 1980.

the physical consequences accounted for, in terms of different estimated peak

loads and numbers of repetitions.

Asymmetry may also be a factor. Whether it is intrinsic or acquired, “hand

edness” is a possible source of laterality in physical properties of tissues,

such as bone (Dane et al. 2001), subject to dynamic remodeling (see Chapter

10). Less controversial and more obvious are the visible effects of repetitive

asymmetric physical activities, such as certain sports (soft- and hard-ball

pitching, golf, archery, etc.) or work tasks (using a sledge hammer, painting,

etc.). In some individual cases, laterality in tissue properties or material

response (Joshi et al. 2001) is observed without any obvious source.

Within a particular application, the selection of particular materials and

designs incorporating them has come to be termed demand matching.

Demand matching cannot account for changes in a patient’s life postimplan

tation, but it can be used to guide selection of technologies preimplantation.

In the best of all possible words, one would try to design the longest lived,

most durable materials that evoked optimum responses. However, present

concerns about the cost of medical care and the way in which biomaterials

and biomedical devices contribute to these costs result in cost containment,

or more properly cost minimization, as a stimulus for “good enough” pro

vided devices (and their constituent biomaterials) — that is, that will meet

the patient’s needs and expectations without excessive cost.

There is no general agreement on what patient features contribute to

demand and how these features should be balanced in deriving a predictive

formula. Demand matching tends to be individualized for the medical prac

titioner and to depend upon subjective as well as objective measures. Of the

objective measures available, age (as measured by life expectancy) and gen

der (as a predictor of body weight and activity level) are the most widely

accepted.

The mean U.S. life expectancy as a function of age is shown graphically

in Figure 2.1 (NCHS 2002). Life expectancy now declines nearly linearly from

early childhood (~6 months of age) to around age 50. Thereafter, however,

the curve has a positive upward bend. Thus, mean life expectancy at age 60

is 21.6 years and, by age 70, it has declined by only 7.2 years to 14.4 years.

Table 2.6 shows the clear effect of gender and national origin on life expect

ancy. It should be remembered that these data are averages.* Therefore,

although mean life expectancy of U.S. residents at 75 is 11.3 years, only 24

of every 1000 that turn 75 will die before their next birthday.

In an example of demand matching (Black 1997), I have discussed selection

of alternate bearing technologies in implants for total hip replacement arthro

plasty; patient age at surgery, as well as other, less well defined demand

components, has been taken into account.

* It is interesting to note that U.S. life expectancy at birth continues to increase, although it rose

by more than 50% (49.2 to 76.9 years) during the 20th century. Thus, although Figure 2.1 and

Table 2.6 reflect data only to age 100, U.S. life insurance underwriters have recently begun to use

tables that extend to 110 years of life.

FIGURE 2.1

Average U.S. life expectancy 2000 mean (average of male and female, all national origins).

(National Center for Health Statistics (NCHS), National Vital Statistics Reports, 51(3), 29, 2002.)

TABLE 2.6

U.S. Life Expectancy (Years) a All Races White Black

Age Total Persons Male Female Male Female Male Female 0
76.9 74.1 79.5 74.8 80.0 68.2 74.9 20 57.8 55.2 60.3 55.7
60.7 49.9 56.3 35 43.6 41.3 45.8 41.7 46.1 36.6 42.1 50
30.0 27.9 31.8 28.2 32.0 24.2 28.9 65 17.9 16.3 19.2 16.3
19.2 14.2 17.4 70 14.4 13.0 15.5 13.0 15.5 11.7 14.1 75
11.3 10.1 12.1 10.3 12.1 9.4 11.2 80 8.6 7.6 9.1 7.6 9.1
7.3 8.6 85 6.3 5.6 6.7 5.5 6.6 5.7 6.5 90 4.7 4.1 4.8 4.0
4.7 4.5 4.8 100 2.6 2.4 2.7 2.2 2.4 2.9 2.7

a Year 2000.

Source: National Center for Health Statistics (NCHS),
National Vital Statistics Reports,

51(3), 29, 2002. 0 10 20 30 40 50 60 70 80 Age (years)
Life Expectancy (years) 0 10 20 30 40 50 60 70 80 90 100

2.6 Preimplantation Handling Effects

One tends to think of the biological environment as that
into which the

implant passes after manufacture and storage. This
assumption overlooks

two intermediate processes common to all implant
applications. In the first

place, the implant may become contaminated, accidentally or
as a side

effect of planned processing and handling during
manufacture, storage,

and insertion. It is usually assumed that the implant
surface is a pure, clean

one with the composition of the bulk material. The truth
may be far dif

ferent. Organic films introduced during manufacture or by
inadvertent

handling may persist. Oxidation or other attack may occur
during preop

erative storage. Materials may be picked up from packaging used for

storage or during sterilization. Contaminants may be transferred from

surgical instruments.

For this reason, experimental studies of biological performance should

include surface characterization of actual implant specimens selected from

the full group fabricated in a particular study in the condition just before

surgical insertion. Furthermore, care should be taken when materials are

incorporated into devices for clinical trials and use, to see that the surface

conditions are the same as those found during earlier developmental studies.

Second, all implants must be cleaned and sterilized before use; the man

ufacturer may supply some in sterile, double-wrapped packages, but others

must be sterilized in the laboratory or hospital before use. The common

forms of sterilization used in implant practice are:

- Cold solution
- Dry heat
- Moist heat (steam)
- Gas
- Gas plasma
- Gamma irradiation

Some typical sterilization parameters for each of these common methods are

listed in Table 2.7. The particular method and parameters used must be

suited to the individual implant type to provide maximum safety with

minimum cost and implant degradation. Newer methods include electron

beam irradiation and radio frequency plasma gas sterilization (Chau et al.

1996; Feldman and Hui 1997), which have the virtue of cleaning implant

surfaces as well as sterilizing them.

The process of sterilization, if overlooked, may affect perception of the

material and the host response. It is possible for some sterilization processes,

such as irradiation, to change material properties, particularly of polymers,

immediately (Nuutinen et al. 2002) and/or during subsequent preimplanta

tion storage (Edidin et al. 2002). This might be interpreted, in error, as a

material response effect if it is detected after implantation, or it might pro

duce changes in host response secondary to the changes in the materials'

properties (Stanford et al. 1994). It is also possible for traces of liquid or

gaseous sterilants to be carried into the implant site, thus modifying the host

response. Finally, sterilization of an unclean implant may render it sterile

but not clean or pyrogen free (Gorbet and Sefton 2005), thus affecting the

host response (see Section 8.2.2). Therefore, in any examination of material

and host responses to implanted materials, it is necessary to pay close atten

tion to actual surface conditions and sterilization effects as a prologue to

exposure to the biological environment.

Black, J., Prospects for alternate bearing surfaces in total replacement arthroplasty of the hip, in Performance of the Wear-Couple BIOLOX Forte in Hip Arthroplasty, Puhl, W. (Ed.), Enke Verlag, Stuttgart, 1997, 2.

Black, J. and Hastings, G.W. (Eds.), Handbook of Biomaterial Properties, Part 1, Chapman & Hall, London, 1998.

Chau, T.T. et al., Microwave plasmas for low-temperature dry sterilization, Biomaterials, 17, 1273, 1996.

Chen, E.H. and Black, J., Materials design analysis of the prosthetic anterior cruciate ligament, J. Biomed. Mater. Res., 14, 567, 1980.

Dane, S. et al., Differences between right- and left-femoral bone mineral densities in right- and left-handed men and women, Int. J. Neurosci., 111(3-4), 187, 2001.

Edidin, A.A. et al., Accelerated aging studies of UHMWPE. I. Effect of resin, processing, and radiation environment on resistance to mechanical degradation, J. Biomed. Mater. Res., 61(2), 312, 2002.

TABLE 2.7

Methods and Typical Parameters of Sterilization Method Temperature Time Notes

Cold solution RT 1–3 h Commercial solutions; usually include formaldehyde or gluteraldehyde

Dry heat 160–175°C (max.) 0.5–2 h Time/temperature vary inversely

Moist heat 120–130°C (max.) 2–15 min Time/temperature vary inversely

Gas RT — 55°C 1–24 h Gas is usually ethylene oxide, 400–1200 mg/l; 48-h degassing required

Plasma discharge 45–55°C 1–2 h RF discharge (var. frequencies) in <0.5 torr gas; hydrogen peroxide or peracetic acid most common

Irradiation RT 2–24 h 60 Co gamma irradiation, 10–40 kGy dose; time/dose rate vary inversely

Feldman, L.A. and Hui, H.K., Compatibility of medical devices and materials with low-temperature hydrogen peroxide gas plasma, Med. Dev. Diagn. Ind., 19(12), 57, 1997.

Gorbet, M.B. and Sefton, M.V., Endotoxin: The uninvited guest, Biomaterials, 26, 6811, 2005.

Joshi, A., Ilchmann, T. and Markovic, L., Socket wear in bilateral simultaneous total hip arthroplasty, J. Arthrop., 16(1), 117, 2001.

Konttinen, Y.T. et al., The microenvironment around total hip replacement prostheses, Clin. Orthop. Rel. Res., 430, 28, 2005.

Lentner, C. (Ed.), Geigy Scientific Tables, Ciba-Geigy, Basle, 1981.

National Center for Health Statistics (NCHS), National Vital Statistics Reports, 51(3), 29, 2002.

Nuutinen, J.P. et al., Effect of gamma, ethylene oxide, electron beam, and plasma sterilization on the behavior of SR-PLLA fibers in vitro, J. Biomater. Sci. Polym. Ed., 13(12), 1325, 2002.

Schmalzried, T.P. et al., Wear is a function of use, not time, Clin. Orthop. Rel. Res., 381, 36, 2000.

Stanford, C.M., Keller, J.C. and Solursh, M., Bone cell expression on titanium surfaces is altered by sterilization treatments, J. Dent. Res., 73(5), 1061, 1994.

Altman, P.L. and Dittmer, D.S. (Eds.), Biological Handbooks: Blood and Other Body Fluids, 1961; Biology Data

Book, 1964. Federation of American Societies for Experimental Biology (FASEB), Bethesda, MD.

Åstrand, P.-O. et al., Textbook of Work Physiology: Physiological Bases of Exercise, 4th ed., Human Kinetics Pub., Champaign, IL, 2003.

Baier, R.E. et al., Radiofrequency gas plasma (glow discharge) disinfection of dental operative instruments, including handpieces, J. Oral Implantol., 18(3), 236, 1992.

Block, S.S. (Ed.), Disinfection, Sterilization and Preservation, 5th ed., Lippincott, Williams & Wilkins, Philadelphia, 2000.

Cooney, D.O., Biomedical Engineering Principles, Marcel Dekker, New York, 1976.

Ganong, W.F., Review of Medical Physiology, 21st ed., McGraw-Hill, New York, 2003.

Gaughran, E.R.L. and Kereluk, K. (Eds.), Sterilization of Medical Products, Johnson & Johnson, New Brunswick, NJ, 1977.

Kurtz, S.M. et al., Advances in the processing, sterilization, and crosslinking of ultrahigh molecular weight polyethylene for total joint arthroplasty, Biomaterials, 20, 1659, 1999.

LeVeau, B. (Ed.), Williams and Lissner: Biomechanics of Human Motion, 2nd ed., W.B. Saunders, Philadelphia, 1977.

Matthews, I.P., Gibson, C. and Samuel A.H., Sterilization of implantable devices, Clin. Mater., 15, 191, 1994.

Nair, P.D., Currently practiced sterilization methods — some inadvertent consequences, J. Biomater. Appl., 10, 121, 1955.

Nordin, M., Frankel, V.H. and Frankel, V.H., Basic Biomechanics of the Skeletal System, 3rd ed. Lippincott Williams & Wilkins, Philadelphia, 2001.

Northrip, J.W., Introduction to Biomechanic Analysis of Sport, 2nd ed., Wm. C. Brown, Dubuque, IA, 1979.

Snyder, W.S. (Ed.), Report of the Task Group on Reference Man, International Commission on Radiological Protection, No. 23, Pergamon, Oxford, 1975.

Staff, Plastics Design Library (Eds.), The Effect of Sterilization Methods on Plastics and Elastomers. W.A. Morris, Inc. (for Plastics Design Library), Norwich, NY, 1994.

Wise, D.L. et al. (Eds.), Encyclopedic Handbook of Biomaterials and Bioengineering, Part B: Applications. (Vols. 1, 2), Marcel Dekker, New York, 1995.

Material Response: Function and Degradation of Materials In Vivo

Carmen, R. and Kahn, P., In vitro testing of silicone rubber heart-valve poppets for lipid absorption, J. Biomed. Mater. Res., 2, 457, 1968.

Chien, Y.W., Rate-control drug delivery systems: controlled release vs. sustained release, Med. Prog. Technol., 15, 21, 1989.

McHenry, M.M. et al., Critical obstruction of prosthetic heart valves due to lipid absorption by Silastic, J. Thorac. Cardiovasc. Surg., 59, 413, 1970.

Mitragotri, S. et al., A mechanistic study of ultrasonically enhanced transdermal drug delivery, J. Pharmaceutical Sci., 84(6), 697, 1995.

Pfleiderer, B. et al., Study of aging of silicone rubber biomaterials with NMR, J. Biomed. Mater. Res., 29, 1129, 1995.

Refojo, M.F., Vapor pressure and swelling pressure of hydrogels, in Hydrogels for Medical and Related Applications, Andrade, J.D. (Ed.), American Chemical Society, Washington, D.C., 1976, 37.

Singh, P. and Maibach, H.I., Transdermal iontophoresis. Pharmacological considerations, Clin. Pharmacol., 26(5), 327, 1994.

Swanson, A.B. et al., Durability of silicone implants — an in vivo study, Orthop. Clin. N. Am., 4(4), 1097, 1973.

Berti, J.J. and Lipsky, J.J., Transcutaneous drug delivery: a practical review, Mayo Clin. Proc., 70, 581, 1995.

Brophy, J.H., Rose, R.M. and Wulff, J., Thermodynamics of Structure, Vol. II of The Structure and Properties of Materials, Wulff, J. (Ed.), John Wiley & Sons, New York, 1964.

Crank, J., The Mathematics of Diffusion, 2nd ed., Oxford University Press, London, 1975.

Daugherty, A.L. and Mrsny, R.J., Emerging technologies that overcome biological barriers for therapeutic protein delivery, Expert Opin. Biol. Ther., 3(7), 1071, 2003.

Edwards, D.A. and Langer, R., A linear theory of transdermal transport phenomena, J. Pharmaceutical Sci. 83(9), 1315, 1994.

Kost, J., Biomaterials in drug delivery systems, in Encyclopedic Handbook of Biomaterials and Bioengineering, Part A: Materials, Vol. 2, Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, Chapter 34.

Purdon, C.H. et al., Penetration enhancement of transdermal delivery — current permutations and limitations, Crit. Rev. Ther. Drug Carr. Sys., 21(2), 97, 2004. 49

4

Corrosion and Dissolution

4.1 Chemistry of Corrosion

Everyone has an intuitive understanding of corrosion. The purpose of this

chapter is to consider the principles of chemistry that underlie this under

standing, to characterize and classify the types of corrosion that may occur,

and to see how these considerations apply to the use of metals as implants.

The layperson tends to equate corrosion with the “rusting” of iron. How

ever, the term has a far broader application. The word corrosion derives from

the Latin rodere, to gnaw. The chemical processes that contribute to the

phenomenon of corrosion can be strictly termed processes of reaction and/

or dissolution in the presence of water. However, it has come to be used to

describe any chemical attack on solid materials, especially metals. In the case

of metals, reaction tends to dominate; for ceramic and

polymeric biomateri

als, dissolution dominates. The bulk of this chapter will address the corrosion

of metals; Section 4.11 and Section 4.12 deal briefly with dissolution of

ceramics and polymers, respectively.

In the case of metals, the following four generic reactions are the most usual

(note: typical valence states and changes are given; other values are possible):

Ionization: the direct formation of cations (positively charged metallic ions) generally under acidic or reducing (oxygen-poor) conditions: M → M + + e − 0 +1 (= valence of metallic atom) (4.1)

Oxidation: the direct reaction of metal with gaseous or dissolved oxygen, without the participation of water. In the extreme examples, oxidation is recognized as burning: M + O 2 → MO 2 0 +4 (4.2)

Hydroxylation: the reaction of metal with water under alkaline (basic) or oxidizing conditions to yield a hydrated oxide or hydroxide. Because most hydroxides are only sparingly soluble in alkaline conditions, this process often leads to the formation of a passivating film, of which more will be said later: 2M + O 2 (diss.) + 2H 2 O → 2M(OH) 2 0 +2 (4.3)

Reaction: the combination of metal or metallic ions with other cations and anions (negatively charged ions); this is often termed complex formation: MO 2 2− + HCl → MOCl − + OH − +2 +2 (4.4)

In biomaterials' applications, the presence of specific and nonspecific organic

binding molecules results in the formation of organometallic complexes as

a general rule.

Each of these processes has the effect of decreasing the amount of pure

metal present and of producing metal-bearing ions and compounds. Con

sideration of the effects of corrosion must take note of the attack on the

parent metallic component as well as the formation of reaction products.

4.2 Classification of Reactions

It is necessary to make some order out of these various chemical processes

that contribute to corrosion so that one can approach the prediction of cor

rosive attack in a systematic manner. All of these and other processes

involved in corrosion can be classified by answering two questions:

- Does the reaction depend upon pH?
- Does the reaction depend upon local electrical potential?

For the purpose of discussion, the answers to these questions will be

designated with “+” or “–.” Thus, a reaction such as dissolution of gas, which

is independent of pH and potential, would be an example of a “– –” reaction.

There may be as many as several dozen possible reactions for the interaction

of an elemental metal with pure water in the presence of oxygen.

A further observation simplifies these efforts of organization. For any

particular combination of pH and potential, there will be a single dominant

reaction for a specific metal in a specific solution; that is, of all of the possible

reactions, one will be the maximum or principal contributor to the degrada

tion of a metallic part and to the concentration of metal in solution.

4.3 The Pourbaix Diagram

4.3.1 Reactions of Chromium in Pure Water

Classification of all possible reactions between a metallic element and water

(and its constituents) by their pH and potential dependence, combined with

the determination from various types of experiments of those combinations

that favor particular reactions provides the information needed for a graphic

representation of the overall reaction system (see Figure 4.1). This is called

a pH-potential or, more usually, a Pourbaix (poor BAY) diagram, after Marcel

Pourbaix (Pourbaix 1966) who popularized its use. This diagram is for pure

chromium in pure water and summarizes the reactions among five primary

species (Cr, O 2 , H 2 , H + , and OH −).

A Pourbaix diagram has three major regions. Each of these represents

combinations of ranges of pH and potential for which a reaction or a related

group of reactions is dominant; each region corresponds to one of the three

fundamental conditions that describe the response of metals to aqueous

solutions:

• Immunity. In this region, the dominant reaction is ionization. However, throughout the region the resulting equilibrium concentration of chromium in solution, in all ionic forms, is less than 10 −6 M. This

FIGURE 4.1

Pourbaix diagram for chromium in pure water. pH passivation corrosion immunity b a EM (volts) - 1.6 1.6 0.8 0 - 0.8 0 4 8 12 concentration is generally taken as the threshold between corrosion and immunity. If reaction processes yield a total equilibrium concentration (of all metal-bearing ions) of less than this value, it is engineering practice to speak of the metal as immune from corrosion, or more simply immune, under that particular set of conditions. Because the level of 10 −6 M (typically 50 ppb) greatly exceeds normal physiological concentrations for most of the less common ions (especially those containing trace metals), it is good practice to assume in implant applications that some metal is released for all combinations of pH and potential.

• Passivation. In this region, the dominant reactions lead to the formation of oxides and hydroxides. Because these products for chromium are largely insoluble at a pH above 4, they cling to the interface between the metal and the solution, reducing and eventually preventing further reaction. This renders the chromium passive. Throughout this region, the solubility of the oxides and hydroxides is low enough that the total concentration of chromium in solution is, as it was in the immune region, less than 10 −6 M.

• Corrosion. In this region, a variety of processes can attack metallic chromium (at low or high values of pH) or its passive coating (if present, at intermediate values of pH). The result throughout the region is a total equilibrium concentration of chromium in solution that equals or exceeds 10 −6 M; thus, in engineering terms, the chromium is said to corrode.

Two additional features are of interest. The diagonal dotted lines in Figure

4.1 define the reactions of gaseous oxygen and hydrogen with water. The

upper line, b, is that for oxygen; the lower line, a, is that for hydrogen. Both

of these reactions are of the “++” type, so the lines slope. The region between

the lines is that in which water is stable. Above the oxygen line, b, oxygen

is released, and below the hydrogen line, a, hydrogen is released. Dominant

reactions of the “+ –” type produce vertical region boundary segments; those

of the “– +” type produce horizontal segments. Reactions of the “– –” type

do not produce regions of dominance on this type of diagram.

In biological systems that are pH controlled by buffering, the local oxygen

or hydrogen partial pressure defines an effective local potential. Thus, tissues

perfused with arterial blood and maintained at pH 7.37 have an equivalent

potential of + 0.782 V. This last fact makes it possible to apply the Pourbaix

approach to the prediction of metallic corrosion in vivo.

4.3.2 Reactions of Chromium in the Presence of Aqueous Chloride Ion

Figure 4.2 is again the Pourbaix diagram for chromium, but with two impor

tant changes:

- The solution is now water with 1.0 N chloride ion (Cl^-) to simulate the situation in vivo more closely. The principal effect of this addition is to shrink the passive region radically. This results from reaction of the chloride anion with free metal ions and the passive layer to form soluble complexes, thus raising the effective solubility of chromium.

- The areas of pH and potential (as defined by pO_2) for various body fluids have been superimposed. Note that the

areas for interstitial and intracellular fluids actually lie closer to pH 7.0; they are plotted as more alkaline for clarity. From this, it can be seen that pure chromium would perform satisfactorily in neutral conditions in the bile duct or urinary tract, but would be unsatisfactory in the stomach, where pH may approach 1. General tissue applications for pure chromium might be considered to be marginal because they lie on the boundary between the passivation and corrosion regions.

It should be clear that a Pourbaix diagram is useful in predicting corrosion

in only a general way. The following limitations should be realized:

• As determined by local ionic conductivity and by limitations in the diffusion of oxygen, hydroxide, and hydrogen ions, the local microconditions dictate the exact equivalent potential that may be expected. Thus, the regions shown on this diagram for different physiological situations may be considered as reflecting average conditions. In particular, pericellular conditions may be radically different.

FIGURE 4.2

Pourbaix diagram for chromium in water (1 N Cl −). 0 4 8 12 passivation corrosion immunity EM (volts) pH gastric fluid bile, urine saliva interstitial fluid intracellular fluid b a - 1.6 1.6 0.8 0 - 0.8

• The areas of dominance and other details of the diagrams are those that prevail after all reactions have come to equilibrium. Reactions may be very slow, as is the case for many involving chromium compounds, leading to prolonged nonequilibrium conditions.

• Reactions and their kinetics depend upon the history of the metal to some degree. Thus, a bare piece of chromium placed under conditions that lie within the passive region of the Pourbaix diagram will undergo reactions leading to formation of hydroxides; however, if its surface is pretreated* to produce an oxidized (passive) layer, the dominant reactions under the same set of conditions will be hydration and partial dissolution of this surface layer. Such reactions may be very slow; in the case of prepassivated chromium-containing alloys, they are so slow that such passive films are termed metastable and the materials may be used for some applications with conditions

within the corrosion region of the diagram.

• Pourbaix diagrams are available for most elemental metals in pure water, but they do not exist for the vast majority of alloys or for other aqueous solutions. However, because the corrosion resistance of chromium-containing stainless steels and cobalt-base “super alloys” depends to a great degree on the presence of chromium hydroxide passivation films, the diagram for chromium in the presence of chloride ion (Figure 4.2) is quite useful in understanding the chemical aspects of their material response in vivo.

• Finally, as will be discussed in Section 4.10, the presence of active cell products in vivo may modify the rate of reactions and the nature of their products.

4.4 The Electrochemical Series

4.4.1 Ideal Series

It is possible to plot a complete Pourbaix diagram for any real metal or alloy

in a defined solution. However, a further simplification may be made if one

is only interested in the relative corrosion resistance of metals. One can begin

by noting that the boundary between the immunity region and the corrosion

region for acid and neutral pH is horizontal. The left-hand intercept (or more

correctly, the potential for pH = 0) is a single potential value. This potential

will be different for each metal alloy.

* Passivation by acid treatment or by anodic polarization (see Section 4.7.2) is common practice

for engineering application within this pH-potential region. Many proprietary surface treat

ments also take advantage of control of structural and compositional features of the passive

layer to gain maximum kinetic protection from dissolution.

On the left side of Table 4.1, a number of metals are ranked by this potential

in an ideal (sometimes termed absolute) electrochemical series. This electro

chemical series is arranged with the most noble or cathodic potentials (with

respect to the H/H + half cell reaction) at the top and increasingly base or

anodic potentials as one proceeds down the list. Note that the apparent sign

of an electrode depends upon whether it is self-polarized (as in corrosion)

or externally polarized (as in electroplating). A self-polarized anode is neg

ative and an externally polarized one is positive and vice versa for the

cathode. The oxidation-reduction nature of the reactions is identical in both

situations: reduction takes place at the cathode and oxidation at the anode.

Despite the use of potentials obtained under acidic, oxygenated conditions,

the ideal series is a reasonable measure of the relative corrosion resistance

of metals under a variety of conditions in pure water. The higher the place

in the list (the more cathodic the potential), the more noble or corrosion

resistant the metal is. Section 4.7.2 will show that the relative position in an

electrochemical series determines which of a coupled pair of dissimilar met

als may undergo corrosion.

4.4.2 Practical Series

In the right-most column of Table 4.1, many of the same metals, and some

alloys, are listed in a practical electrochemical series. The use of a practical

series, in this case for the exposure of these metals to seawater, begins to

take into account the situation peculiar to a specific application. Seawater

exposure, particularly in tropical climates, is the engineering condition that

most closely simulates environments encountered by implants, except for

the general lack of soluble organic species. Comparison of the practical to TABLE 4.1 Ideal and Practical Electrochemical Series Potential Ideal Practical Noble or cathodic Gold Platinum Platinum Gold Silver Stainless steel (passive) Copper Titanium E = 0 - - - - - - - - - - - - - - Hydrogen Silver Lead Nickel Tin Stainless steel (unpassivated) Nickel Copper Cobalt Tin Iron Lead Chromium Cast iron Aluminum Wrought iron Titanium Aluminum Magnesium Magnesium Base or cathodic

the ideal series demonstrates some interesting differences related to the

differences in environment:

• The two noblest metals in both series, platinum and gold, change their relative positions. This reflects the fact that, although neither is strongly attacked by seawater, gold forms chlorides more readily than does platinum.

• Titanium moves well up the list, reflecting the highly insoluble nature of most of its compounds, particularly its TiO 2 passivation layer that forms spontaneously in air.

• Unpassivated stainless steel, a class of alloys of iron, nickel, and chromium (as well as other minor elements), is not particularly high on this list. The choice of stainless steels as implant materials (primarily in temporary applications, such as in internal fixation devices for

fractures) depends primarily upon their mechanical properties and machinability in the presence of an acceptable level of corrosion resistance (when passivated before use) and moderate local host response to its corrosion products.

A practical series begins to take factors of corrosion other than equilibrium

thermodynamics into account. That is, it reflects not only the possibility of

corrosion, but also details of actual attack in specific environments. Pourbaix

diagrams and electrochemical series tell something about the likelihood of

corrosion. They define equilibrium conditions and imply rates of corrosion

as proportional to deviations from equilibrium. It is important to know

something about the rates of corrosion. These rates will help to determine,

for instance, the rate of release of metallic ions from an implant.

4.5 Corrosion Rate

In engineering applications, corrosion rates are expressed as rates of surface

dissolution or recession per year. The common unit is the mpy (mil [0.001

in.] per year). This unit is far too big to be used to examine corrosion rates

in the biological environment for the same reasons that an equilibrium con

centration of 10 −6 M is too high to be considered indicative of immunity.

A more direct measure may be obtained by examining Equation 4.1

through Equation 4.3. These are characteristic of metallic corrosion. Note

that in each case the valence of the metal is reduced, with a required transfer

of charge or electrons to another species. Because the sites of reduction

(cathode) and oxidation (anode) are separated in space, an equivalent current

must flow.

Corrosion (at the anode) of one molecular weight of metal, with an accom

panying valence change of +1 (for instance, from 0 to +1), will result in the

transfer of 1 faraday (F) of charge. Thus, for a corroding anode, one may

determine the corrosion rate by measuring the net current flow and dividing

by the area. The unit of corrosion, defined in this way, is then amp/cm 2 .

4.6 Potential-Current Relationships in Corrosion

Briefly consider an ideal case of corrosion, taking the reaction at the anode

to be Equation 4.1. $M \rightarrow M^{+} + e^{-}$

At the cathode, assume that the reaction is the reduction of dissolved oxygen: $O_2 (d) + 2H_2O + 4e^{-} \rightarrow 4OH^{-}$ (4.5)

An alternative reaction — the reduction of hydrogen ion with the release of

gaseous hydrogen — is also possible: $2H^{+} + 2e^{-} \rightarrow H_2 (g)$ (4.6)

The latter reaction will occur preferentially if the oxygen potential is very

low or the metal is extremely active (base or non-noble).

In this case, consider

Equation 4.5 to be the cathodic reaction.

Now look at Figure 4.3. The initial potentials at the anode and cathode are

E Ao and E Co . Due to the differences in potential, current begins to flow (cor

rosion takes place). This may be represented by moving to the right of the

diagram. Due to the familiar Ohm’s law relationship among current, poten

tial difference, and resistance, the effective potential of the cathode drops

and that of the anode rises. If nothing happens to intervene, the potentials

become equal. This mixed potential, E M , is then maintained, and the current,

i 3 , is defined by (4.7)

The current (i 3) divided by the area of the anode yields the corrosion rate.

If an external resistance, R ex , that is large compared to the previous resis

tance is inserted between anode and cathode, the resulting current is i 2 and

is defined by E i M Total resistance = 3 (4.8)

The current i 2 is less than i 3 ; thus, less corrosion takes place in a given

period of time. This is the situation when a passivation or insulating layer

can be maintained on a metal in a pH-potential region that would normally

promote corrosion. If the supply of oxygen is limited by diffusion, for

instance, the potentials of anode and cathode may remain more widely

separated, and a still smaller current i 1 , resulting in less corrosion, may flow.

In either case (i = i 1 or i 2), the effective potential will be somewhere between

E Co and E Ao , depending upon the relative areas of the cathode and anode.

Thus, it should be clear that the actual rate of corrosion may vary widely

for a given set of equilibrium conditions. Local oxygen supply, conductivity

of the bathing electrolyte, and the extent of the electrode surfaces, as well

as the presence of various inhibitors and enhancers of corrosion, may affect

the result.

Corrosion in real environments is not usually detected by measurement

of potentials and currents or of concentrations of ions in solutions. Rather,

it is recognized by the evidence of attack on the bulk material, the chemical

gnawing away of the fabricated part.

4.7 Forms of Corrosion

I am indebted to Mars Fontana and Norbert Greene (Fontana 1985), who

have collected many diverse descriptions of the physical appearance of

corrosion and grouped them into eight categories or forms, depending upon

mechanism and common features of the result of attack. The eight forms of

FIGURE 4.3

Potential–current (log) relationships in corrosion. E C o E M i 1 i 2 i 3 E A o Potential 0 O 2 + 2 H 2 O + 4 e 4 O H M M + + e Current (log) E E i R i C A ex o o − − = 2 2 Total resistance

corrosion will be briefly examined and some comments made on their mech

anisms.

4.7.1 Uniform Attack

Uniform attack, or general overall corrosion, is a self-explanatory term. This

is the process that is taking place in the corrosion region and, by oxide/

hydroxide dissolution, in the passivation region of the Pourbaix diagram. It

is the most common form of corrosion. In the absence of equilibrium con

centrations of their constituent ions in the bathing solution, it will occur for

all metals. Even in the immunity region, uniform attack will result in a slow

removal of metal from implants. Thus, it is fair to state that, due to uniform

attack, all metals have a finite corrosion rate in vivo. However, uniform attack

may not be noticed until, or unless, significant amounts of metal are lost.

Because all metals currently used in implants are relatively highly resistant

to uniform attack, little evidence of such attack is ever seen in implant

applications.

Uniform attack is usually measured in terms of surface recession. An

approximation to this rate may be obtained from Equation 4.9 if the surface

area of an implant (A, in. 2), the density of the alloy used (D, g/cm 3), the

exposure time (T, hours), and the total weight loss (w, mg) are known: (4.9)

For a typical implant alloy with a density near 8 g/cm 3 , 1 mpy ≈ 0.7 mg/

cm 2 /day. In vivo uniform corrosion rates for well-passivated alloys are

thought to be about 1/100 of this value (Steinemann 1980), reinforcing the

prior statement of the low utility of this measure in biomedical applications.

4.7.2 Galvanic Corrosion

Galvanic (or two-metal) corrosion takes place when two different metals are

in physical (electronic) contact and are immersed in an ionic conducting fluid

medium such as serum or interstitial fluid. This is also referred to as couple

corrosion. An example of a situation that may lead to this is shown in Figure

4.4. The “difference” between the screw and plate, responsible for the gal

vanic process, may be due to different compositions (major and/or minor

constituents) and/or processing.

For a particular combination of pH and potential (defined by pO 2), the

two metals will have different electrochemical potentials.

The one that is less

noble than the other — that is, below it on a suitable practical electrochemical

series — becomes anodic. The surface of the less noble metal that is in contact

with the solution will experience attack, of a uniform nature, with a release mpy w DAT = 534

of metallic ions. The other metal becomes cathodic. Electrons move to it

through the physical connection, driven by the intermetallic potential dif

ference. The electrons may then reduce dissolved oxygen or hydrogen ions,

depending upon local conditions. Although the less noble metal of the pair

may not corrode because it is in a passive region in its respective Pourbaix

diagram, the more noble metal cannot corrode under any conditions. Thus,

because it is cathodic, it is said to have cathodic protection.

The actual details of galvanic corrosion depend upon a large number of

complicating factors, including the relative size of the areas of electronic and

ionic contact, as well as on the actual metal pair involved. However, although

some exceptions occur in actual practice, it is safe to assume that galvanic

corrosion can occur in any metal pair in acid pH. Note that all three condi

tions must be met for galvanic corrosion to take place; thus, the presence of

two or more different compositions of metallic implants within an animal

or patient will not produce galvanic effects unless the implants are in direct

physical contact so that an electron current may flow between them.

4.7.3 Crevice Corrosion

Crevice corrosion is one of a number of forms of corrosion related to struc

tural details. The basic requirement for the occurrence of this process is the

presence of a crevice (a narrow, deep crack): an interface between parts of a

device, such as between plate and screw head, or a defect such as an incom

plete fatigue crack. The details of the initiation of crevice corrosion are not

yet clear. Once begun, however, it is characterized by oxygen depletion in

the crevice, anodic metallic corrosion along the crevice faces, and cathodic

protective conditions on the metal surface around its mouth.

FIGURE 4.4

Conditions for galvanic corrosion. Metallic (electronic) contact Interstitial fluid (ionic) contact Plate Screw Interstitial fluid ACTUAL SCHEMATIC

Static nonflowing conditions in the solution seem to favor crevice corro

sion, perhaps because of the formation of a metallic ion concentration gra

dient away from the open end of the crevice. Because the areas of attack are

concentrated, evidence of crevice corrosion can easily be

seen in the mating

areas in multipart devices, such as between screw and plate in retrieved

fracture fixation devices (Colangelo and Greene 1969). This is a frequently

observed effect; the majority of multipart fracture fixation devices retrieved

from patients show crevice corrosion and/or pitting corrosion (see Section

4.7.4) (Cook et al. 1985). High local concentrations of corrosion products may

also result in precipitation of oxides, hydroxides, or phosphates in adjacent

tissues (Jacobs et al. 1995). In conjunction with stress corrosion, crevice cor

rosion may change the mechanical behavior of metals subjected to cyclic

loading (see Section 6.5.2).

4.7.4 Pitting Corrosion

Pitting corrosion is a special case of crevice corrosion. It is a more isolated,

symmetric form of attack; inclusions, scratches, or handling damage may

initiate it. Pitting corrosion proceeds through processes similar to those for

crevice corrosion, although static conditions and reduced oxygen potential

seem less important and autocatalysis may play an important role (Punckt

et al. 2004). Thus, pits often occur in large numbers, like freckles, and grow

down in the direction of gravity in unstirred solutions.

It would be desirable to avoid pits in highly stressed implants because

they constitute points of stress concentration and may serve as the starting

points for mechanical cracks to develop. Like the effects of crevice corrosion,

pits are easy to see. When they are very small, they change the surface finish,

often producing a “frosted” or matte appearance. Larger, more developed

pits often have accumulations of colored corrosion products in them and

may show up as green, brown, or black spots against the otherwise polished

surface of the implant. For this reason, it is inadvisable to clean implants

vigorously after removal before they have been examined for evidence of

corrosion. In practice, it may be difficult to distinguish between pitting and

crevice corrosion at early stages of attack. Multiple part implants have, in

the past, often shown evidence of crevice, pitting, and fatigue corrosion

(Cohen and Lindenbaum 1968); however, as alloy cleanliness has improved

with time, the prevalence of these effects has declined.

4.7.5 Intergranular Corrosion

Intergranular corrosion is somewhat related to crevice corrosion but has

different origins and produces different effects. It is more common in devices

that are made by casting. Cast metals have multiple

crystals or grains, with

impurities preferentially deposited between the grains during solidification.

As a result, the chemistry of a grain boundary will be different from that of

the grains on either side and will probably have a different, and generally

less noble, electrochemical potential. The consequence in a corrosive envi

ronment is an intergranular attack resembling crevice corrosion. A part may

appear essentially normal and then suddenly crumble into grains under a

mechanical stress. A less radical effect is sometimes seen in brass doorknobs

in old houses. Because of the perspiration left on the knob by generations

of hands, the intergranular corrosion of zinc precipitates “etches” the surface

and makes the individual grains visible.

Intergranular corrosion is obviously more common in alloys than in pure

metals and is favored by high levels of impurities and inclusions. If not

properly heat treated, stainless steel may corrode by this mechanism due to

a relative depletion of chromium from the grain boundaries. Welding of

alloys that results in local melting and resolidification can also lead to a

variant of this called knife-edge attack. The name derives from the appear

ance of the failure: a straight crack through the metal

parallel to and near

the weld. Again, proper heat treatment after welding will restore the right

compositional distribution and reduce or prevent this type of attack.

4.7.6 Leaching

Leaching is similar to intergranular corrosion. However, in this case the

components of a particular alloy are sufficiently weakly bound to each other

and differ enough in chemical reactivity so that there is a large difference in

the rate of loss of the alloy components by uniform attack. Thus, leaching

as a form of corrosion is a special case of leaching (discussed in Chapter 3),

with an accompanying chemical reaction. Attack of this kind will remove

metal with a regular periodic variation of effect at a microscopic level. It is

peculiar to certain alloy systems but can be induced by two conditions:

• The introduction into the solution around the metal of an agent that attacks one component of the alloy in preference to another. For instance, fluoride ion (F^-) will selectively remove aluminum from copper–aluminum alloys.

• The presence of more than one phase in the alloy. Usually, all of the grains in an alloy have the same composition. The alloy is then said to have a single phase. However, it is possible for individual grains to be of two or more different, discrete compositions. Such an alloy is said to possess multiple phases. Because electrochemical potential varies as chemical composition, these phases may have a different susceptibility to various forms of corrosive attack. Note that heat treatment to reduce the size of the grains will not change this situation. For this reason, multiphase alloys are not usually used in corrosive

applications. Thus, considerable academic concern arose when ASTM F-562 — a multiphase alloy of cobalt, nickel, chromium, and molybdenum containing 35% nickel — was introduced for use in implants. However, experience suggests that, despite the differences in the phase compositions, all of the phases are sufficiently passive under the conditions experienced in soft and hard tissue implant sites so that leaching does not occur in this alloy.

Leaching produces surface appearances similar to those produced by pitting

or intergranular attack.

4.7.7 Erosion Corrosion

Erosion corrosion is a rare form of corrosion. This is an acceleration of attack

on a metal because of relative movement between the surrounding fluid and

the metallic surface. It is not a unique process, but it serves to increase the

rate of attack by several other mechanisms. This happens because many

corrosion processes tend to be self-limiting. That is, the accumulation of the

products of corrosion at the interface between metal and solution tends to

reduce the rate of reaction. Flowing solution will sweep away these corrosion

end products as well as provide new amounts of dissolved reactants, such

as chloride ion and oxygen. In extreme cases, the solution may physically

erode the passive layer in regions of passivity. The reformation of this layer

and its removal by continued flow produces progressive attack on the metal

and renders that region of the pH-potential diagram corrosive rather than

passive as predicted.

The physical damage resembles pitting, except that these pits are elongated

in the direction of flow and are generally larger and less symmetric than

those seen in pitting corrosion under static conditions. The peculiarities of

flow, especially if it is a stable pattern, will often result in etching a clear

picture of the course of the flow on the surface of the metal.

4.7.8 Stress and Fatigue Corrosion

Stress corrosion is the last of the eight forms of corrosion. Simply stated,

tensile stress increases the chemical activity of metals. A flexed metal com

ponent will sustain a tensile stress on one side and a compressive stress on

the other side. This produces a difference in electrochemical potential that

renders the convex surface anodic with respect to the concave one. As an

acceleration of uniform attack or, perhaps, secondary to tensile rupture of

the passive film, corrosion may then attack the convex surface. Local corro

sion rates (as measured by corrosion current) may be two- to threefold

elevated over the uniform corrosion rate (Bundy et al. 1991)

Because the formation of even a small crack in a loaded structure, such as

a flexed plate, will concentrate stress, this attack tends to initiate cracks

that grow rapidly, leading to possible structural failure. The cracks

extend between grains; however, this process can be differentiated from

intergranular cracking due to the small number, relative isolation, and

branched structure of stress corrosion cracks.

Many metals display an endurance limit to cyclic loading. In the presence

of crevice corrosion in physical cracks or in crack-like defects in a passive

surface layer produced by single or repeated cyclic loading, this limit may

be abolished. That is, the maximum stress that can be reached without failure

continuously decreases as the number of load cycles increases instead of

reaching a lower limit. This phenomenon, which is a dynamic form of stress

corrosion, is termed fatigue corrosion and may be an important limit on the

life of metallic implants undergoing cyclic mechanical deformation.

4.8 Corrosion in Implant Applications

Which of these eight forms of corrosive attack are important in implant

applications? As a general rule, corrosive attack is more common on multi

part implants than single part devices. Some studies indicate that a majority

of multipart orthopaedic fracture fixation devices show evidence of corrosion

after recovery at the end of treatment (Cook et al. 1985). Uniform attack

occurs on these as on all other implants. The primary physical evidence

suggests that crevice and pitting corrosion are the next most important forms

(Cohen and Lindenbaum 1968). Crevice corrosion occurs in the gap between

the screw and the plate in screw-plate assemblies. The attack is most often

seen on the plate — within the hole, but near the longitudinal surfaces.

Occasionally, crevice attack will be noted on the portions of the screw oppo

site these areas. Due to the reduction in the cross section of the plate at the

hole, these areas have a high stress concentration. Frank mechanical fracture

of the plate through a screw hole can often be associated with microscopic

evidence of crevice corrosion. The introduction of modularity into joint

replacement devices has produced a range of apparent crevice and related

corrosion effects, with occasional but rare component failure, which have

not previously been seen (Gilbert et al. 1993).

Pitting most often occurs on the underside of screw heads. Despite the

characteristic freckle appearance of the pits, they may be hard to distinguish

from mechanical scoring of the screw head and shaft during insertion and/

or removal. Such scoring may result from rubbing against a burr in the hole

in the plate or against a fragment of bone caught between plate and screw

during removal.

Galvanic corrosion may also occur between plates and screws. There is a

slight tendency for this naturally because the plates and screws are fabricated

by different processes; thus, if they are not properly heat treated, they may

have slightly different electrochemical potentials. Mixing screws and plates

from different manufacturers may also produce galvanic effects because each

manufacturer uses a slightly different heat treatment schedule. Screws of a

different composition from the plate, as well as metallic foreign bodies such

as drill bit fragments inadvertently introduced into an implant site, may also

cause galvanic corrosion (Fothi et al. 1992).

Attack of this sort is often discovered through reports of persistent, very

localized operative site pain. It may occur, however, as judged by frequent

observations of tissue discoloration during routine device removal proce

dures, without any apparent sensation. Galvanic corrosion may leave a dis

coloration with a “burned” or sooty appearance on the screw

or the plate in

the area of contact.

Stress corrosion is also possible but extremely rare. Intergranular corrosion,

leaching, and erosion do not occur to any real extent in modern multipart

devices in orthopaedic applications. A solid-state version of erosion corro

sion may occur if an interface is loose or fixation is poor. Relative motion

between plate and screws may result in physical removal of material, or

fretting. This may disrupt the passive film and produce accelerated corrosion

in much the same way that erosion corrosion takes place. This phenomenon

is difficult to distinguish from simple wear and is called fretting corrosion

(Brown and Merritt 1981).

In single part devices such as cranial plates, intramedullary rods,

endoprostheses, pins, and cerclage wire, the effects are rather more limited.

Uniform attack does occur, as previously noted. Stress corrosion or, more

generally, stress enhancement of fatigue failure (fatigue corrosion) is proba

bly the most common destructive form. Although rare in prostheses, its

incidence is very high in the highly stressed cerclage wire used for uniting

bone fragments. Intergranular corrosion does occur occasionally and is prob

ably most often associated with surface inclusions or casting defects in cast

prosthetic sections. It is rarely active enough to lead to mechanical failure

in the absence of cyclic loading.

Corrosion in blood contact areas is much more complex. The abundant

supply of oxygen and the continued flow of electrolytes render most pro

cesses highly active. In addition, the presence of many small organic mole

cules influences rates. Sulfur-bearing molecules such as cystine appear to

accelerate corrosion; neutral molecules such as alanine may inhibit corrosion

(Svare et al. 1970) in much the same way as rust inhibitors in engineering

applications. Furthermore, corrosion may profoundly affect surface proper

ties and thus influence thromobogenic behavior; this will be discussed in

Section 9.3.2.

Corrosion is generally considered to be undesirable. However, in some

biomaterial applications the response to local concentrations of corrosion

products is necessary to the successful function of an implant. For instance,

the copper IUD (intrauterine device) depends for its contraceptive properties

on the release of copper ions by a corrosion process.

It may also be desirable to accept a higher corrosion rate

because of other

more critical properties of an alloy. In a surgical setting, the stainless steel

spring clips used for the repair of large cranial aneurismal defects have been

deliberately fabricated from type 301, 416, and 420 steel alloys (McFadden

1969). These alloys corrode at a more rapid rate than the more usual grade

of stainless steel used in implants, 316L (ASTM F 138). However, these alloys

are superior to 316L for spring fabrication. One feature of local response to

these products is undoubtedly an increased fibroplasia — perhaps producing

a more rapid and mechanically sound scarring process — but otherwise they

appear to be adequately tolerated.

4.9 Engineering Variables Affecting Corrosion Rates

Despite the prevalence of corrosive attack on implanted devices, the rate of

failure of structure or of function is quite small. Why is it that a particular

device can perform well in 99 patients and then cause problems in the 100th?

Conversely, why do materials known to be prone to corrosion occasionally

survive for very long periods in vivo (Blackwood and Periera 2004)? The

answers are not simple. To all of the normal biological variables of human

health and disease, at least four “engineering” variables must be added:

• Composition of the implants — in particular, variations within the implant and extremes of implant-to-implant variation — can affect corrosion rates in many ways, as has been discussed.

• Manufacturing variables, including casting conditions, metal purity, amount of cold work, and the degree and type of heat treatment, have a profound effect on corrosion rates (Sutow et al. 1976). Corrosion rates, at least initially, are markedly affected by the details of the passivation process used (Browne and Gregson 1994; Callen et al. 1995).

• Handling in manufacture, delivery, and insertion can affect results. Occasionally, corrosion initiation can be traced to unintended physical damage (Gray 1974).

• Positioning of the implant will affect the stresses upon it as well as the local environment that it experiences. Anatomical location and small differences in it may have an important effect (Oron and Alter 1984), primarily due to local differences in pH and pO 2 (Morita et al. 1992).

4.10 Corrosion Factors Peculiar to Biological Environments

In addition to the factors just discussed, it is apparent that organic molecules

present in implant sites may affect corrosion rates. These are thought to act

in four ways:

• Formation of organometallic complexes. If conditions at any point in the pH-potential region of interest favor the formation of organometallic complexes, the metallic content of these represents an addition to the corrosion rate.

• Alteration of charge of corrosion products. Many organic molecules are potent oxidizing agents, producing the possibility of different ionic valences than predicted by pH-potential considerations. For example, in the presence of serum proteins, it is probable that significant amounts of chromium may be released from alloys as Cr +6 rather than Cr +3 (Rogers 1984). Despite the high degree of oxidation, Cr +6 may persist for several minutes (Liu and Shi 2001) before even partial reduction occurs.

• Modification of the passive layer. Combination of organic

species with the passive layer, in the passive region or in adjacent regions of metastability (low passive film-dissolution rate), may alter the nature of the passive film. These may act to stabilize or destabilize the film or to change its electrical conductivity, thus altering corrosion rates (Svare et al. 1970).

• Changes in wear conditions. Although the presence of serum proteins generally elevates corrosion rates, in in vitro experiments, it markedly reduces fretting corrosion rates of stainless steel (Brown and Merritt 1981; Merritt and Brown 1988).

Previously, I have emphasized the need to distinguish among physiolog

ical, biophysiological, and pericellular environments (Section 2.3). The addi

tion of cells and bacteria to a biological environment produces the possibility

of true “bio” corrosion phenomena. Degradative cells such as macrophages

(Yang et al. 1992), as well as a wide range of bacteria (Wilson et al. 1997),

can directly corrode metals without phagocytosis (see Section 8.2.3), prima

rily by modification of the pericellular environment. This latter phenomenon

mirrors that encountered in marine environments (Thomas et al. 1988).

4.11 Ceramic Dissolution

As a class of materials, ceramics are most generally defined as inorganic,

nonmetallic solids. This category contains a wide range of compounds and

mixtures, primarily compounds of metals, such as oxides, carbonates, sul

fates, etc. They may be crystalline or amorphous; if they contain chain form

ers, such as elemental carbon or silica (SiO_2), amorphous materials may be

glassy. Multiphase physical mixtures and, in the presence of glassy phases,

compound alloys, are also possible.

Metals under immune conditions, whether deliberately passivated or not,

have surface films composed of oxides or hydroxides. In the most common

biomaterial alloy systems, the surfaces of stainless steels and cobalt-base

super alloys are primarily chromium oxide and hydroxide, while the surfaces

of titanium-base alloys are primarily titania (titanium dioxide, TiO_2). Thus,

the behavior of metals (with or without prior passivation), under chemical

conditions producing immunity for the underlying alloy, is essentially that

of dissolution of a ceramic. In fact, very small metallic wear debris may be

completely ceramic in nature and their reactions with biological environ

ments may be better considered in this light.

Two main classes of ceramics are used as biomaterials: structural (or tech

nical) and resorbable (or soluble); the latter includes so-called “bioceramics.”

Structural ceramics such as alumina (Al_2O_3) and zirconia (ZrO_2) are selected

for, among other properties, their low chemical reactivity and essential insol

ubility in water. Along with some forms of carbon — especially vitreous

carbon — these materials may be regarded as insoluble in biomaterial appli

cations. In general, reports of dissolution products from solid structural

ceramic biomaterials should be regarded as artifactual; however, very large

surface area/volume ratio ceramic materials, such as aggregations of small

(submicron) wear debris, may be able to release measurable amounts of

dissolution products. No evidence indicates that biophysiological, biological,

or pericellular conditions affect this conclusion.

Soluble ceramics are an example of type 2 or interactive biomaterials (see

Section 1.4). The most common types are those that resemble calcium-based

minerals that naturally occur in mammalian bodies, such as calcium

hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), tricalcium phosphate ($Ca_3(PO_4)_2$), octacal

cium phosphate ($Ca_8H(PO_4)_6 \cdot 5H_2O$), etc. However, other resorbable mate

rials, such as hydrated calcium sulfate ($CaSO_4 \cdot 2H_2O$), Bioglass™ (see Section

10.3.4.3), etc., are in use as biomaterials.

The dissolution behavior of these more soluble ceramic materials depends

upon their composition, processing, and final form, as well as on local pH

and pO_2 (but not on local applied potential because, as a

class [with the

exception of carbons and graphites], these materials are electrical insulators).

In addition, phagocytic cells (see Section 8.2.3) are able to attack many of

these materials, thus raising their solubility in pericellular environments.

Although general rules are hard to draw, the following principles may be

useful:

- Crystalline (polycrystalline) forms tend to be less soluble than glassy or amorphous ones of the same composition.

- Polycrystalline forms tend to be more soluble than single crystal forms of the same composition.

- Hydrated forms tend to be more soluble than nonhydrated forms of the same composition.

- Mass loss per unit time depends significantly on specific surface area; thus, porous or fine particulate materials tend to dissolve more rapidly than equal weights of the same material in a solid, nonporous form.

- Cellular attack, when successful, is more rapid on small particles (<25 μm) than on solid bodies of the same composition.

4.12 Polymer Dissolution

Polymers possess such a wide range of compositions, structures, and molec

ular weight that it is difficult to make any generalizations concerning their

dissolution behavior. One worthwhile distinction is whether a polymeric

material is hydrophilic or hydrophobic. Dissolution of hydrophilic polymers,

especially low molecular weight, resembles uniform

corrosion of metals, in

that the result is a surface recession (Figure 4.5, right). By contrast, hydro

phobic polymers, which will nevertheless absorb polar fluids such as water,

may undergo a form of internal attack in which amorphous regions dissolve

preferentially to crystalline ones (Figure 4.5, left). The effect is to produce

increased surface area, increasing the effective dissolution rate and leading,

perhaps, to structural effects similar to those of intergranular corrosion, with

sudden loss of integrity and release of small particles.

FIGURE 4.5

Comparison of dissolution of hydrophobic and hydrophilic polymers. Hydrophobic Hydrophilic

4.13 Final Remarks

The one certain thing that can be said about corrosion is that it results in the

release of cations from all metallic implants. Cations also form a wide variety

of organometallic complexes. Some of these soluble products, such as the

ferric and ferrous ions, are familiar parts of the internal environment. Some

are trace elements with known biological roles, such as trivalent chromium

ions. Others are rare enough in nature that they do not have known metabolic

roles and are released in the body — even in the absence of abnormal

corrosion processes — at concentrations orders of magnitude above their

normal in vivo occurrence. Under certain conditions, small particles also may

be released or formed by precipitation, locally or at remote sites, of soluble

products. Dissolution of nonmetallic materials is still more complex and

difficult to summarize, but it too results in release of soluble and particulate

materials of a wide range of compositions. The consequences of such release

will be considered at length in later chapters.

Blackwood, D.J. and Pereira, B.P., No corrosion of 304 stainless steel implant after 40 years of service, J. Mater. Sci.: Mater. Med., 15, 755, 2004.

Brown, S.A. and Merritt, K., Fretting corrosion in saline and serum, J. Biomed. Mater. Res., 15, 479, 1981.

Browne, M. and Gregson, P.J., Surface modification of titanium alloy implants, Biomaterials, 15, 894, 1994.

Bundy, K.J., Williams, C.J. and Luedemann, R.E., Stress-enhanced ion release — the effect of static loading, Biomaterials, 12, 627, 1991.

Callen, B.W. et al., Nitric acid passivation of Ti6Al4V reduces thickness of surface oxide layer and increases trace element release, J. Biomed. Mater. Res., 29, 279, 1995.

Cohen, J. and Lindenbaum, B., Fretting corrosion in orthopedic implants, Clin. Orthop. Rel. Res., 61, 167, 1968.

Colangelo, V.J. and Greene, N.D., Corrosion and fracture of type 316 SMO orthopedic implants, J. Biomed. Mater. Res., 3, 247, 1969.

Cook, S.D. et al., Clinical and metallurgical analysis of retrieved internal fixation devices, Clin. Orthop. Rel. Res., 194, 236, 1985.

Fontana, M.G., Corrosion Engineering, 3rd ed., McGraw-Hill, New York, 1985, Chapter 4, 137.

Fothi, U., Perren, S.M. and Auer, J.A., Drill bit failure with implant involvement — an intraoperative complication in orthopedic surgery, Injury 23 (Suppl 2), S17, 1992.

Gilbert, J.L., Buckley, C.A. and Jacobs, J.J., In vivo corrosion of modular hip prosthesis components in mixed and similar metal combinations. The effect of crevice, stress, motion, and alloy coupling, J. Biomed. Mater. Res., 27, 1533, 1993.

Gray, R.J., Metallographic examinations of retrieved intramedullary bone pins and bone screws from the human body, J. Biomed. Mater. Res. Symp., 5(1), 27, 1974.

Jacobs, J.J. et al., Local and distant products from modularity, Clin. Orthop. Rel. Res., 319, 94, 1995.

Liu, K.J. and Shi, X., In vivo reduction of chromium (VI) and its related free radical generation, Mol. Cell. Biochem., 222, 41, 2001.

McFadden, J.T., Metallurgical principles in neurosurgery, J. Neurosurg., 31(4), 373, 1969.

Merritt, K. and Brown, S.A., Effect of proteins and pH on fretting corrosion and metal ion release, J. Biomed. Mater. Res., 22, 111, 1988.

Morita, M. et al., Influence of low dissolved oxygen concentration in body fluid on corrosion fatigue behaviors of implant metals, Ann. Biomed. Eng., 20, 505, 1992.

Oron, U. and Alter, A., Corrosion in metal implants embedded in various locations of the body of rats, Clin. Orthop. Rel. Res., 185, 295, 1984.

Pourbaix, M., Atlas of Electrochemical Equilibria, Pergamon Press, Oxford, 1966.

Punckt, C. et al., Sudden onset of pitting corrosion on stainless steel as a critical phenomenon, Science, 305, 1133, 2004.

Rogers, G.T., In vivo production of hexavalent chromium, Biomaterials, 5, 244, 1984.

Steinemann, S.G., Corrosion of surgical implants — in vivo and in vitro tests, in Evaluation of Biomaterials, Winter, G.D., Leray, J.L. and deGroot, K. (Eds.), John Wiley & Sons, Chichester, U.K., 1980, 1.

Sutow, E.J., Pollack, S.R. and Korostoff, E., An in vitro investigation of the anodic polarization and capacitance behavior of 316-L stainless steel, J. Biomed. Mater. Res., 10, 671, 1976.

Svare, C.W., Belton, G. and Korostoff, E., The role of organics in metallic passivation, J. Biomed. Mater. Res., 4, 457, 1970.

Thomas, C.J., Edyvean, R.G.J. and Brook, R., Biologically enhanced corrosion fatigue, Biofouling, 1, 65, 1988.

Wilson, M. et al., Corrosion of intraoral magnets by multi-species biofilms in the presence and absence of sucrose, Biomaterials, 18, 53, 1997.

Yang, J. et al., Human neutrophil response to short-term exposure to F-75 cobalt-base alloy, J. Biomed. Mater. Res., 26, 1217, 1992.

Bundy, K.J., Corrosion and other electrochemical aspects of biomaterials, Crit. Rev. Biomed. Eng., 22, 139, 1994.

Deltombe, E., De Zoubov, N. and Pourbaix, M., Chromium, in Pourbaix, M., Atlas of Electrochemical Equilibria, Pergamon Press, Oxford, 1966, 256.

Fraker, A.C. and Griffin, C.D. (Eds.), Corrosion and Degradation of Implant Materials: Second Symposium, STP 859, American Society for Testing and Materials, Philadelphia, 1985.

Fusayama, T., Katayori, T. and Nomoto, S., Corrosion of gold and amalgam placed in contact with each other, J. Dent. Res., 42, 1183, 1963.

Hofmann, G.O., Biodegradable implants in traumatology: a review on the state-ofthe-art, Arch. Orthop. Trauma Surg., 114, 123, 1995.

Jacobs, J.J., Gilbert, J.L. and Urban, R.M., Current concepts review: corrosion of metal orthopedic implants. J. Bone Joint Surg., 80A, 268, 1998.

Luckey, H.A. and Kubli, F., Jr. (Eds.), Titanium Alloys in

Surgical Implants. STP 796. American Society for Testing and Materials, Philadelphia, 1983.

Marcus, P. and Oudar, J. (Eds.), Corrosion Mechanisms in Theory and Practice, Marcel Dekker, New York, 1995.

Pohler, O.E.M., Degradation of metallic orthopedic implants, in Biomaterials in Reconstructive Surgery, Rubin, L.R. (Ed.), C.V. Mosby, St. Louis, 1983,158.

Pourbaix, M., Electrochemical corrosion of metallic biomaterials, Biomaterials, 5, 122, 1984.

Ravaglioli, A. and Krajewski, A. (Eds.), Bioceramics, Chapman & Hall, London, 1992.

Scully, J.C., The Fundamentals of Corrosion, 3rd ed., Pergamon Press, Oxford, 1990.

Shahgaldi, B.F. et al., In vivo corrosion of cobalt-chromium and titanium wear particles, J. Bone Joint Surg., 77B, 962, 1995.

Schweitzer, P.A. (Ed.), Corrosion Engineering Handbook, Marcel Dekker, New York, 1996.

Syrett, B.C. and Acharya, A. (Eds.), Corrosion and Degradation of Implant Materials, STP 684, American Society for Testing and Materials, Philadelphia, 1979.

Tengvall, P. and Lundström, I., Physicochemical considerations of titanium as a biomaterial, Clin. Mater., 9, 115, 1992.

Vermilyea, D.A., Physics of corrosion, Physics Today, Sept. 1976, 23.

Williams, D.F., Corrosion of implant materials, Ann. Rev. Mater. Sci., 6, 237, 1976.

Zitter, H. and Plenk, H., Jr., The electrochemical behavior of metallic implant materials as an indicator of their biocompatibility, J. Biomed. Mater. Res., 21, 881, 1987. 73

5

Reactions of Biological Molecules with

Biomaterial Surfaces

5.1 Introduction

Strictly speaking, in a biomaterials-tissue system, there are no surfaces; as

Andrade (1973) has pointed out, there are only interfaces. In this chapter, the

solid-liquid interface produced by the contact of a solid biomaterial with body

fluids will be considered briefly. The solid-liquid interface can affect dissolved

species in the surrounding fluid at two levels of characteristic dimension:

- The molecular level (3 to 15 Å): these effects are essentially chemical.

- The macromolecular level (15 to 500 Å): these effects are more of a mechanical nature.

Chemical effects depend upon the detailed chemistry and ionic charge dis

tribution of the surface. The effects that local chemistry can have on some of

the events of coagulation (Section 9.3.2) and on adaptation (Chapter 10),

immune response (Section 12.2.1), and carcinogenesis (Section 13.2) will be

considered. These effects can be undesirable side aspects of the biomaterial

selected for other properties (as in the general blood conduit problem) or

deliberately induced effects required to mediate a cellular response. Examples

of induced effects are common in the results of various surface treatments

used to reduce or eliminate thrombus formation on the surface of blood contact

materials. A less common induced effect is the production of surface activity

(in the chemical sense) to stimulate directly adaptive cellular response.

In addition to the direct chemical (inorganic) effect of surface modification

on cellular activity, local changes in composition, pH, and molarity will

produce a variety of physiochemical changes in proteins, including dissoci

ation and denaturation. The observed cellular response may be secondary

to these physiochemical changes in proteins.

Dissociation is understood in the general chemical sense as the separation

of ions from molecular species. In addition, it refers to the disaggregation of

multimolecular organic complexes, such as enzyme-cofactor complexes.

These associations, like all chemical bonding processes, depend upon free

energy considerations and may be affected by local pH and ionic concentra

tion. On the other hand, denaturation can be viewed as a purely topological

and mechanical process and will be discussed in the next section.

5.2 Denaturation

Denaturation is a problem peculiar to large organic molecules such as pro

teins. Four levels (or orders) of structure are recognized in these molecules:

1° The chemical composition as defined by atomic content

and primary bonds between atoms

2° The spatial arrangement of portions of a molecule as defined by the requirements of bond angulation at each atomic center and by the intramolecular bonds other than main chain bonds

3° The spatial arrangements determined by strong intramolecular bonds and secondary folding to produce stable domains

4° The aggregation of three structures by weak associative bonding (hydrogen or Van der Waals bonds)

The primary and, to some degree, secondary levels of structure are deter

mined during synthesis. The tertiary may be produced by a self-assembly

process or occur secondarily to a usually extracellular, one-time cleavage of

a portion of the synthesized molecule. Thus, if these structures are disturbed

by heat or local chemical activity, the molecule may not be able to revert to

its original or native structure. Such a molecule is said to be denatured and

may arouse a variety of biological responses despite a normal or near normal

chemical composition (primary structure). Finally, because it depends upon

weak bonds, the quaternary of structure is quite sensitive to pH and con

centration changes. The results of these changes may be as simple as slight

alterations in configuration or as profound as the dissociation of multimo

lecular structures, such as those formed by enzymes and cofactors.

5.3 Organometallic Compounds

5.3.1 Definitions

Beyond the effects on structure, surfaces may obviously be chemically reac

tive. As a class, metals are the most reactive implant materials. They may

provoke a host response due to the formation of corrosion products (dis

cussed in Section 8.2.5). However, many of these corrosion products are

organometallic complexes or compounds and, as such, have a special behav

ior of biological importance.

As the name implies, organometallic compounds have two components:

one is an organic moiety and the other is the metallic moiety. The association

between the two can be a weak interaction or, at the other end of the

spectrum, a very strong interaction, as in the case of the Fe-containing por

phyrin heme in the hemoglobin complex. There also can be a degree of

specificity of structure, again as seen in the heme molecule. If another metal

lic ion were to replace the iron, the function of oxygen transport would be

impaired. This is apparently the case when elevated chromium levels are

present in heme synthesis sites (Smith 1982).

Three terms are useful in discussions of organometallic compounds:

• Chelation: a type of interaction between an organic compound (having two or more points at which it may coordinate with a metal) and the metal to form a ring-type structure

• Coordination: the joining of an ion or molecule to a metal ion by a nonionic valence bond to form a complex ion or molecule

• Ligand: any ion or molecule that, by donating one or more pairs of electrons to a central metal ion, is coordinated with it to form a complex ion or molecule, as in the cobalt complex [CoCl(NH 3) 5]Cl 2 , in which Cl and NH 3 in the bracketed portion are ligands coordinated with Co

5.3.2 Stability

In a free metal cation, all of the five d orbitals have the same energy level.

However, in a chelate or complex, some of the filled orbitals are oriented

toward the chelating atoms. Repulsion between nonbonding electrons in a

d orbital and those of the chelating atom causes electrons in these orbitals

to be less stable with respect to the other orbitals. In addition, bonding can

preferentially stabilize one orbital with respect to the others. The theory

dealing with repulsion from the field produced by the chelating atoms is

called crystal field theory; the total effects are dealt with in ligand field theory.

By preferentially filling low-energy orbitals in organic ions, the metallic d

orbitals can stabilize the molecular system. For example, if three orbitals

have a low energy and two have a higher energy, as in an octahedral complex,

the configuration would be much more stable with six electrons occupying

the low-energy levels than with the electrons spread throughout all five

orbitals. The gain in bonding energy achieved in this manner is referred to

as the crystal field stabilization energy (CFSE).

Complexes with more of the electrons in the lower energy levels are more

stable than those with all the d orbitals equally filled. Trivalent chromium

and cobalt, for example, with three and six electrons, respectively, will form

very stable complexes or ions. Consequently, the tendency of these ions to

form complexes is very great. A complex of univalent copper, on the other

hand, has zero CFSE because the five orbitals are completely filled. As a

result, cuprous complexes will be less stable than those of trivalent cobalt

or trivalent chromium.

Crystal field effects are important in predicting the rates and mechanisms

of reactions of coordination compounds. The essential feature here is that ions

that are strongly crystal-field stabilized will be slow to react, and nonstabilized

ions will be more liable (reactive). This explains why Co +3 , which has consid

erable CFSE, is so nonreactive. In order for Co +3 to react, the octahedral con

figuration, which creates the large CSFE, must first be

disrupted.

5.3.3 Production

The production of the organometallic compounds by implants is controlled

by a dynamic equilibrium that occurs after implantation of a metallic spec

imen or device. This equilibrium is established between the alloy and the

intermediate organometallic compound, as well as between the alloy and

the more traditional inorganic ions. The rate of corrosion will then depend

on the removal of the intermediate compound. If more is removed by dep

osition in tissues, then corrosion could proceed at an increased rate. Because

the removal of the intermediate is the rate-limiting step, differences seen

between biological response to powder and bulk implants probably reflect

different surface (interface) reaction conditions.

The equilibrium will also depend upon three other factors:

• The organometallic complex may be formed on the surface or in solution. If it is formed on the surface, the ratio of the implant surface area to the fluid volume available for equilibrium (SA/FLV) will govern the formation rate and the equilibrium concentration. This is apparently the case for complexes formed between chromium or nickel and serum proteins (Woodman et al. 1984). If the complex forms preferentially in solution, then SA/FLV affects only the rate of formation, as is apparently the case for cobalt.

• The chemical composition of the surface may affect the strength of the initial association and the rate of loss (desorption) of complexes that form at the interface. Table 5.1 presents data for absorption and desorption of albumin, the most common serum protein, by a variety of materials. A

single monolayer corresponds to 0.2 to 0.7 μg cm −2 , depending upon packing of molecules. “Desorption” in this context is actually exchange because release in the absence of proteins in solution (a highly unphysiological condition) may be different. In particular, under these conditions, polyethylene releases no measurable albumin into an albumin-free solution (Brash et al. 1974). Fluid flow near the interface also has an effect, with release/exchange rates increasing with increasing flow rate. The situation at the implant–tissue interface is more complex than this, due to competition between proteins (see Section 5.5).

• The surface energy, which expresses not only chemical composition, but also local spatial arrangement of atoms and bonds as well, also may affect the adsorption/desorption rate (Baszkin and Lyman 1980).

5.4 Mechanical Aspects of Interfaces

Far more important than these chemical effects that take place at atomic

dimensions are the mechanical effects that occur on a larger scale. These are

primarily associated with the fact that the solid–liquid interface is a phase

boundary. As such, it has an interfacial energy proportional to its area asso

ciated with it.

Consider the following situation (Figure 5.1). Five molecules of identical

composition are shown; however, kinetic and other local affects may produce

transient changes in shape, despite the fact that a sphere presents the lowest

area, and thus the lowest energy state, of the phase interface. For simplicity,

a molecule, P, will be considered to be spherical as it approaches a solid TABLE 5.1 Albumin Absorption and Desorption from Surfaces Material Absorption (μg.cm −2 /24 h): Desorption (%/24 h): (Conc.: 2 mg/ml) (Conc.: 1 mg/ml)

Metals Silver 2.01 ± 0.22 23 Vanadium 0.13 ± 0.06 73 Titanium 0.05 ± 0.02 86 Oxides TiO 2 0.15 ± 0.02 70 Al 2 O 3 0.06 ± 0.01 83 Polymers (Conc.: 3.7 mg/ml) (Conc.: 0.1 mg/ml) Polyethylene 0.28 (Conc.: 1 mg/ml) 42 (Conc.: 0.2 mg/ml) Cuprophane™ 0.28 ± 0.05 90+ Polyurethane 1.0–2.8 Undetermined Note: Metals and oxides: absorption/desorption in 0.01 M citrate/phosphate buffered saline (pH = 7.4) at 37°C using 125 I-labeled human albumin. Polymers: absorption/desorption in Tyrodes solution (pH = 7.4) at 25°C using 125 I-labeled human albumin. Source: Williams, R.L. and Williams, D.F., Biomaterials, 9, 206, 1988. Brash, J.L. et al., Trans. Am. Soc. Artif. Int. Organs, XX, 69, 1974.

surface, S, in liquid, L. Suppose that it will stick or adhere to the surface; the

work of adhesion is then (for adhesion of phase A to B): W AB = γ A + γ B – γ AB (5.1)

where

γ A , γ B = “free” surface tensions

γ AB = interfacial surface tension

For this situation, one can write: W SP = γ SL + γ PL – γ PS (5.2)

Remember that the surface tensions are negative and that W SP must be

negative for adhesion to take place. For example, suppose: γ SL = 70 dyn/cm γ PL = 40 dyn/cm γ PS = 50 dyn/cm

then, W SP = –70 – 40 + 50 = –60 (a change from –110 → –50) (5.3)

Thus, adhesion would result.

However, now look more closely at the interface between the molecule

and the solid (Figure 5.2). The normal interfacial equilibrium condition (the

Young-Dupree equation) must be satisfied:

FIGURE 5.1

Molecules near a liquid (L)-solid (S) interface. L S P γ SL = γ PS + γ PL cosθ (5.4)

Note that, for any degree of adhesion (W SP ≤ 0), θ will be less than 180°.

Because the molecule was initially considered to be a sphere, this condition

can only be achieved by deformation of the natural (free) shape. A careful

analysis combining the Young-Dupree equation with the restoration forces

resulting from this molecular deformation would permit a more exact cal

culation of θ. However, the simple form can be taken as an estimator of the

deformation. Thus, the larger the value of θ is, the smaller the deforming

force and the likelihood of permanent mechanical damage to the molecule

are.

An interesting point concerns the opposite extreme, i.e., when θ goes to

zero (cos θ = 1). This is called full wetting and requires that: γ PS = γ PL ; γ SL = 2γ PL (5.5)

This value of surface tension is called the critical surface tension (γ c). It can

be determined by measuring θ for a variety of structurally related liquids

and extrapolating the data to determine the limiting value of surface tension

(γ c) as θ approaches zero. A plot of cos θ vs. γ LV is called a Zisman plot. The

critical surface tension, γ c , is determined by the intercept at cos θ = 1. A

schematic result is shown in Figure 5.3 for a material surface with γ c = 28

dyn/cm.*

FIGURE 5.2

Conditions for molecular adhesion at an interface.

* See Section 9.3.3 for a discussion of the supposed role of γ c in cell-surface interactions; de Palma

et al. (1972) present interesting examples of Zisman plots obtained on metallic implants before

and after blood contact. S θ P θ θ “Little” θ “Big” θ L

5.5 Results of Interfacial Adhesion of Molecules

A few of the effects that can result from molecular adhesion to biomaterials

or tissues are:

• Enzyme activity and rate constants depend closely upon details of the 3° and 4° molecular structure of enzymes. Accidental or deliberate enzyme adhesion at interfaces can be expected to modify their functional behavior significantly.

• Organic substrate response to enzymatic action is also structure specific. Many substrate molecules have a degree of orientational freedom, possessing features such as saturated bonds about which free rotation is possible. Association of this type of substrate with a surface could hinder or prevent such rotation. Depending upon the configuration in which the molecule is “frozen,” enzymatic attack might be accelerated or inhibited.

• Many complex organic molecules, as synthesized, have a “tail” portion that serves to inactivate them. In the normal course of events, enzymatic processes act to strip this small segment and release the molecule into an active substrate pool. Contact with surfaces and the forces resulting from adhesion may cause premature activation.

FIGURE 5.3

Model Zisman plot (five fluids). (Note: 1 dyn/cm = 1 erg/cm 2) γ 0 10 20 30 40 50

60 1.0 0.8 0.6 0.4 0.2 0 Cos θ C (28 dyne/cm) γ LV (dyne/cm) Some molecules are apparently designed specifically to become activated in this manner by contact with foreign surfaces. An example is fibrinogen, which is reduced slightly in molecular weight and converted to the active protein, fibrin, by surface contact-induced cleavage.

• Immunological response to proteins also depends strongly upon 2°, 3°, and 4° structure. Contact with surface by native proteins produces unnatural configurations of the following types: • Conversion or activation of molecules (as mentioned above) • Transient deformations during surface contact that are restored upon subsequent desorption • Partial or total denaturation due to surface adhesion forces Considerable evidence indicates that molecular deformations of each of these three types can excite antibody production and trigger a variety of immune responses, directly or on a subsequent challenge.

In an effort to study the possible immunological results of the surface

denaturation of proteins, Stern et al. (1972) exposed a series of polymers,

including epoxies, silicones, and poly(acryl)amide), to fresh rabbit serum.

The serum was then injected into the host animals, and the production of

antibodies was investigated. Unless the in vitro exposure included exposure

to macrophages as well as serum, no antibody titers were developed. How

ever, in the presence of peritoneal macrophages, a number of these materials

produced positive titers. This is evidence of a cell-mediated response to

denatured serum proteins, recognized as foreign bodies (see Section 12.4.1).

The absence of effect (antibody production) when the serum was directly

injected suggests that the denaturation was reversible and present only when

the serum proteins were adsorbed to the test surfaces.

This experiment reminds one of a further complication. The data in Table

5.1 were obtained from pure albumin (one protein) solutions. The actual

exposure in the biological environment involves many proteins, as in Stern’s

use of serum in vitro. In such a situation, proteins encounter the surface

depending upon the product of their concentration and their self-diffusion

velocity, which is approximately inversely related to the square root of their

molecular weight. (Additional factors, such as molecular shape, also affect

self-diffusion rates.)

Thus, protein–surface interactions in vivo (or in vitro from mixed solutions)

should be thought of as a succession of events; early arrivers (low molecular

weight/high concentration) may be potentially displaced by late arrivers

(high molecular weight/low concentration). This process, first recognized

by Leo Vroman in the blood coagulation process (see Section 9.2) and termed

by others the Vroman effect, is shown schematically in Figure 5.4:

Here, even after the total surface concentration of protein (solid line)

reaches a steady state value, the composition of the film

continues to change,

as molecules of B displace those of A and, in turn, are displaced by molecules

of C. Remember also that these are equilibrium surface concentrations; the

data of Table 5.1 suggest that continuing exchange of each species may take

place.

5.6 Effects of Charged Interfaces and Ions

The discussion so far has focused upon interfaces considered to be electri

cally neutral. That is, the deforming force on molecules results simply from

interfacial free energy and the equilibrium requirements for adhesion. If

there is a net surface charge, then a potential gradient will exist in the vicinity

of the surface. This has four major consequences:

- Uncharged molecules will suffer deformation in structure due to the interaction of their internal dipoles (primarily associated with covalent bonds) with the electrical field.

- Charged molecules and zwitterions (molecules with no net charge but with equal amounts of negative and positive charge) will undergo an additional set of constraints due to attraction or repulsion of their charge centers. These additional forces will produce additional structural deformation.

FIGURE 5.4

Vroman effect (schematic).

See Section 9.3.3 for a discussion of the supposed role of γ_c in cell-surface interactions; de Palma

et al. (1972) present interesting examples of Zisman plots obtained on metallic implants before

and after blood contact. C o n c e n t r a t i o n (μ g · c m 2) Time Total (A+B+C) A B C

• Charged molecules and ions will also move along the electrical field gradient, attracted to surfaces of opposite charge. This motion, called electrophoresis, is utilized in analytical processes to separate ions with different ratios of charge to ionic mobility. Electrophoresis can act in vivo to change the concentration of ions as well as pH, thus potentially altering 3° and 4° structure.

• Finally, charged molecules and ions may interact with magnetic fields. Moving charges experience a transverse force from constant magnetic fields; time-varying magnetic fields can produce oscillatory rotation of zwitterions and local current flow through motion of ions and molecules with net charge.

One should also remember that net (nonzero) surface potentials may arise

(1) by electrochemical equilibria; (2) from differences in dielectric constant

across the interface; (3) from external sources such as direct potential impo

sition (as suggested by the experiments of Sawyer et al., 1965, in the reduction

of thrombogenic behavior by changing surface potential; see Section 9.3.2);

or (4) from the other member of a galvanic (corrosion) couple (see Section

4.7.2).

5.7 Final Comments

The reader will note that much of the material cited in this chapter does not

have recent publication dates. This is due to the fundamental nature of the

considerations and to the lack of broad interest in the topic of nonchemical

physiochemical events at interfaces, other than in the issues of blood coag

ulation and hemolysis. However, recent developments in several areas,

including design, evaluation, and, in some cases, clinical application of so

called “bioactive” materials — as well as the rising interest in cellular and

tissue engineering (see Chapter 11) — suggest that this will become a much

more vigorous research area. This is especially true because the combination

of ultrahigh speed chemical analysis and large capacity very fast computers

now permits gathering molecular configuration data and fitting it to models

of molecule-surface interaction (West et al. 1997). These developments are

certain to have a profound effect on knowledge of the fundamental mechan

ics of biological performance of materials; once again, they emphasize the

need for biomaterials investigators to maintain a high level of alertness for

scientific and technical advances in fields seemingly far removed from their

day-to-day concerns.

Andrade, J.D., Interfacial phenomena and biomaterials, Medical Instrumen. 7, 110, 1973.

Baszkin, A. and Lyman, D.J., The interaction of plasma proteins with polymers. I. Relationship between polymer surface energy and protein adsorption/desorption, J. Biomed. Mater. Res., 14, 393, 1980.

Brash, J.L., Uniyal, S. and Samak, Q., Exchange of albumin

adsorbed on polymer surfaces (1974), Trans. Am. Soc. Artif. Int. Organs, XX, 69, 1974.

dePalma, V.A. et al., Investigation of three-surface properties of several metals and their relation to blood compatibility, J. Biomed. Mater. Res. (Symp.), 3, 37, 1972.

Sawyer, P.N. et al., Electrochemical precipitation of blood cells on metal electrodes: an aid in the selection of vascular prostheses, Proc. Natl. Acad. Sci., 53, 294, 1965.

Smith, G.K., Systemic transport and distribution of iron and chromium from 316l stainless steel implants, Ph.D. thesis, University of Pennsylvania, Philadelphia, 1982.

Stern, I.J. et al., Immunogenic effects of foreign materials on plasma proteins, Nature, 238, 151, 1972.

West, J.K., Latour, R., Jr. and Hench, L.L., Molecular modeling study of the adsorption of poly-L-lysine onto silica glass, J. Biomed. Mater Res., 37, 585, 1997.

Williams, R.L. and Williams, D.F., Albumin adsorption on metal surfaces, Biomaterials, 9, 206, 1988.

Woodman, J.L., Black, J. and Jiminez, S.A., Isolation of serum protein organometallic corrosion products from 316LSS and HS-21 in vitro and in vivo, J. Biomed. Mater. Res., 18, 99, 1984.

Adamson, A.W. and Gast, A.P., Physical Chemistry of Surfaces, 6th ed., John Wiley & Sons, New York, 1997.

Andrade, J.D. et al., Proteins at interfaces: principles relevant to protein-based devices, in Proc. 2nd Intern. Symp. Bioelectron. Molecular Electron. Devices, Dec. 12-14, 1988, Fujiyoshida, Japan (unpaginated), 1988.

Bamford, C.H., Cooper, S.L. and Tsurta, T. (Eds.), The Vroman Effect, VSP, Utrecht, 1992.

Bernabeu, P. and Caprani, A., Influence of surface charge on adsorption of fibrinogen and/or albumin on a rotating disc electrode of platinum and carbon, Biomaterials, 11, 258, 1990.

Elwing, H., Protein absorption and ellipsometry in biomaterial research, Biomaterials, 19(4-5), 397, 1998.

Friedberg, F., Effects of metal binding on protein

structure, Q. Rev. Biophys., 7(1), 1, 1974.

Gabler, R., Electrical Interactions in Molecular Biophysics, Academic Press, New York, 1978.

Gray, J.J., The interaction of proteins with solid surfaces, Curr. Opin. Struct. Biol., 14(1), 110, 2004.

Hallab, N.J. et al., Systemic metal-protein binding associated with total joint replacement, J. Biomed. Mater. Res., 49, 353, 2000.

Hench, L.L. and Wilson, J., Surface-active biomaterials, Science, 226, 630, 1984.

Ivarsson, B. and Lundstrom, I., Physical characterization of protein adsorption on metal and metaloxide surfaces, Crit. Rev. Biocompatibil., 2(1), 1, 1986.

Lomer, M.C.E., Thompson, R.P.H. and Powell, J.J., Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease, Proc. Nutr. Soc., 61, 123, 2002.

Manly, R.S. (Ed.), Adhesion in Biological Systems, Academic Press, New York, 1970.

Morra, M. (Ed.), Water in Biomaterials Surface Science, New York, John Wiley & Sons, 2001.

Tanford, C., Physical Chemistry of Macromolecules, John Wiley & Sons, New York, 1961.

Vogler, E.A., Structure and reactivity of water at biomaterial surfaces, Adv. Colloid Interface Sci., 74, 69, 1998.

Zangwill, A., Physics at Surfaces, Cambridge University Press, Cambridge, 1988. 87

6

Mechanics of Materials: Deformation and Failure

6.1 Introduction

Mechanical integrity is a nearly universal requirement for biomaterials. All

materials must cohere or “hold together” if they are to be expected to stay

in one shape and in one location, and to perform their designed function.

The requirement may be only that they withstand the various stresses that

exist in an implant site. A more rigorous requirement exists if part of the

intended function for the implant is a mechanical one, such as a heart valve

replacement or a fracture fixation device. Then, the application may require

the preservation of a minimum value of a property, such as ability to with

stand permanent deformation, or of a design (mean) value of another one,

such as possessing a particular spring constant. These are extrinsic behaviors

but they depend in part on intrinsic properties: in this case, on yield strength

and elastic modulus, respectively.

Unfortunately, environmental exposure of materials alters their mechanical

properties in a variety of ways. As discussed in Section 2.2, the chemical and

physical environment of the human body is different from external engineer

ing environments and is, by comparison to many, quite severe. This chapter

will briefly consider the origin of intrinsic mechanical properties of materials.

It will also consider how materials fail in mechanical applications and how

the biological environment affects these properties and types of failure.

6.2 Mechanics of Materials

The simplest experiment that can be performed to characterize the mechan

ical properties of a solid material is to machine a specimen with well-defined

dimensions (a “standard” specimen) and load it to failure in tension. Figure

6.1 shows the result of such a model experiment, obtained by plotting the

applied load directly against the resulting elongation. The following points

characterize this load-elongation curve:

F_m : maximum load that can be sustained

ΔL: elongation to failure

F_u : load at failure

Unfortunately, these numbers are extrinsic (dependent upon the specific

dimensions of the specimen). It is common practice to transform the load

elongation curve into a stress–strain curve. Stress, σ, is given by the force

divided by the cross-sectional area perpendicular to the direction of force

application: (6.1)

Strain, ε, is given by the ratio of the change in length, ΔL, to the original

length, L_o : (6.2)

These conversions produce intrinsic values that are independent of spec

imen dimensions as long as certain basic rules are obeyed in the design of

the specimen. In particular, it is necessary to assure that the specimen is

uniform in cross section in the region in which L o , ΔL, and A are measured.

Figure 6.2 shows a stress-strain curve that might be obtained by conversion

of the model load-elongation curve of Figure 6.1. This curve is characterized

by several intrinsic parameters (Table 6.1).

FIGURE 6.1

Load-elongation curve. LOAD ELONGATION Δ L F m F u x σ = F A ε = ΔL L o

Of course, other intrinsic parameters characterize materials, and these may

be determined in forms of load application other than pure tension. How

ever, this chapter will concentrate on tensile behavior and, in particular, the

elastic modulus, E, the yield stress, σ y , and the ultimate stress, σ u . These

three parameters tend to dominate mechanical design. The relationship of

these parameters to mechanical design may be summarized as follows:

• Elastic modulus is the intrinsic “spring constant” of the material; thus, it specifies the proportional deformation as a result of stress within the limit of recoverable deformations.

FIGURE 6.2

Stress-strain curves.

TABLE 6.1

Intrinsic Parameters from a Stress–Strain Curve

Symbol Name Units Definition

σ y Yield stress MPa Stress to start permanent (plastic) deformation

ε y Yield strain MPa Strain at the moment of yielding

σ 0.2% 0.2% offset stress MPa Stress to produce 0.002 strain

σ u Ultimate stress MPa Stress to produce fracture

ε u Ultimate strain None Total strain to fracture

M Modulus GPa Ratio of stress divided by strain (slope of line in elastic (proportional) region (= σ y /ε y))

E Young’s modulus GPa Modulus determined in tension

-Work of fracture J/m 3 Area under the stress–strain curve

Notes: MPa: megapascals; GPa: gigapascals; J/m 3 : joules/cubic meter. x x x x Metal Ceramic Polymer STRAIN Model ε u σ u σ y σ 0.2% ε y 0.002 M STRESS

• Yield stress sets the upper stress limit for the design of a body fabricated from a plastically deformable material that under load must not undergo permanent deformation from its original shape.

• Ultimate stress defines the stress that produces fracture and thus sets the maximum stress, termed the strength, that the material can withstand.

Taken together, these three parameters provide a measure of stiffness,

deformability, and strength of a material.

It should be noted that the model stress–strain curve (Figure 6.2) is only

a schematic. The relative values of these three parameters are governed to

a large degree by the nature of the atomic bonds within a material; thus,

classes of materials tend to have different general shapes of stress–strain

curves. These are shown schematically for metallic, ceramic, and polymeric

materials in the lower part of Figure 6.2.

6.3 Elastic Modulus

6.3.1 Fundamental Aspects

The elastic behavior of materials has its origin in the basic chemical bond

structure at the atomic level. That is, for deformations below the yield point,

the major effect is the elastic (recoverable) deformation of interatomic bonds.

Each of the four major materials classes — metals, ceramics, polymers, and

composites — possesses its characteristic bond structures.

The metals are characterized by the looseness of binding of their valence

electrons. Thus, solid metals are thought of as aggregates of positively

charged ions with a neutralizing negative electron cloud. The resulting cohe

sion is high but the individual bonds lack strong directionality. In real metals,

regions of high order with almost exclusively metallic bonding (grains) are

separated by zones of disorder (grain boundaries) that contain impurities

and other forms of bonding.

Ceramic materials, on the other hand, are primarily ionically bonded. They

are made up of geometric arrays of cations and anions with strong ordering

and a resulting high directionality of bonds. Again, real (nonideal) ceramics

contain grains (ordered) and grain boundaries (disordered) in combination,

as do metals. In this case, ionic bonding is possible in the boundary regions,

but is usually weaker than within the grains because of inclusions, mis

matches between adjacent grains, and disorder effects.

Polymers exhibit the third type of bond, the covalent bond. Although it is

not particularly strong, this bond, formed by orbital sharing of electrons

between atoms, is highly directional. Engineering polymers consist of long

chain molecules with covalently bonded “backbones.” The chains may be

ordered in a regular array in regions, forming crystals, or may be uniformly

amorphous; the more usual structure is, again, a combination of order and

disorder. The overall structure is stabilized by occasional interchain covalent

bonds or ionic bonds between charged side groups (cross links) and by

diffuse attraction of hydrogen, oxygen, and nitrogen atoms to –OH groups

(Van der Waals bonds).

In order of strength, these bonds may be classified as follows: Ionic > metallic > covalent > Van der Waals

Thus, it should come as no surprise that elastic moduli can

be ranked as: Ceramic > metallic > polymeric

Composite materials do not appear in this range because they can be

particle- or fiber-reinforced ceramics, metals, or polymers and thus display

a wide range of elastic moduli, depending upon the arrangements and

relative moduli of their components. A further complication is introduced

by the nature of the bonding between the matrix and the reinforcing material.

This bonding depends on the chemistry and microstructure of the interface;

it affects yield and failure but has little effect upon elastic behavior. The

ability to adjust the modulus (and other properties) to meet the requirements

of a specific application is, of course, one of the great attractions of compos

ites.

6.3.2 Environmental Effects

Practically speaking, the elastic moduli of metals and ceramics are unaffected

by exposure to biological environments. This is due to the great strength of

internal bonding in these materials, to the relative simplicity of their struc

ture when compared with polymers and composites and to the typical tem

peratures encountered in vivo. Polymers may experience profound changes

in elastic moduli in response to the internal environment. Table 6.2 summa

rizes the principal mechanisms and their effects. TABLE 6.2 Environmental Effects on Mechanical Properties of Polymers Effects on Phenomenon Modulus (E) Yield stress (σ_y) Absorption Decrease (“plasticizing”) Increase Leaching Increase (“antiplasticizing”) Decrease Chain scission Decrease Decrease Cross linking Increase Increase

Absorption and leaching have been discussed in Section 3.3 and Section

3.6. The principal effect of absorption of low molecular weight species is to

swell the amorphous matrix, moving the crystalline “islands” further apart

and thus weakening the already weak bonds between them. This permits

easier deformation in the same way that lubrication makes it easier for

surfaces to move over each other. However, many polymers already contain

plasticizers in the form of low-molecular-weight fragments of the basic poly

mer, deliberately added low-molecular-weight agents, and water. Thus, the

loss of these by leaching would be expected to reverse the effect of absorption

and increase the elastic modulus. In real applications, there is competition.

However, because biomedical polymers tend to be simple (low additive)

materials due to host response considerations and tend to have high molec

ular weight due to strength and stability considerations, the usual effect of

exposure to physiological fluids is to lower the effective elastic modulus.

Elastic moduli of highly crystalline or highly cross-linked polymers should

be less sensitive than amorphous, low-molecular-weight ones.

An illustration of plasticizing and antiplasticizing effects can be seen in

data on the elastic moduli of polymers in compression in Table 6.3. In this

study (Jacobs 1974), standard compression test cylinders were made of a

commercial poly(methyl)methacrylate (PMMA) surgical cement, a duplicate

formulation compounded in the laboratory, and a commercial medical grade

of ultrahigh molecular weight polyethylene (UHMWPE). These were tested

as fabricated (except for UHMWPE, for which the fabrication date was TABLE 6.3 Variation of Compressive Moduli of Polymers with Environmental Exposure PMMA (raw materials) PMMA (commercial) a UHMWPE (commercial) b Test condition: E 1 % (× 10 5 psi) E 1 % (× 10 5 psi) E 1 % (× 10 5 psi) As fabricated 3.0 ± 0.2 c 3.4 ± 0.2 NA

Postlaboratory storage (24°C/120 days) 3.9 ± 0.2 3.8 ± 0.5 0.83 ± 0.06 Post humid storage (97%RH/37°C/120 days) 2.7 ± 0.3 d 2.6 ± 0.2 d 0.81 ± 0.05 Post saline storage (0.9% NaCl/37°C/120 days) 2.7 ± 0.4 d 2.8 ± 0.2 d 0.80 ± 0.06 Post implantation (rabbit, subcutaneous/120 days) 3.2 ± 0.2 d 3.1 ± 0.4 0.80 ± 0.05 Notes: E 1% = tangent modulus at 1% strain; NA = not available. a Simplex-P™ (North Hills Plastics, Ltd.). b Zimmer-USA. c ±95% confidence interval. d Different from “post laboratory storage” ($p < 0.05$).

Source: Adapted from Jacobs, M.L., M.S. thesis, University of Pennsylvania, Philadel

phia, 1974.

unknown) and after 120 days’ exposure to a variety of environments, includ

ing subcutaneous implantation in the rabbit. The slope of the stress–strain

curve at 1% strain, E 1% , was used for comparison because, in common with

most other polymers, these polymers do not possess a single well-defined

elastic modulus in the elastic region of the stress-strain curve. Exposure of

both PMMA formulations to high humidity or saline solutions that dupli

cated the ionic concentration of serum at 37°C produced a reduction of ~30%

in E 1% when compared with dry, room-temperature storage. This illustrates

the plasticizing effect of absorbed water. Although it produced a similar

reduction, implantation was much less damaging. This could be interpreted

in one of two ways:

• Implantation might have prevented the loss of residual monomer by leaching. An effect similar to leaching — loss of monomer by evaporation — is probably responsible for the increase of E 1% due to dry storage when compared with the as-fabricated value. Residual monomer would serve as a plasticizer; however, because it is hydrophobic, it might exclude the more efficient plasticizer, water.

• A cross-linking agent or an antiplasticizer might be absorbed from serum in the animal, counteracting the plasticizing effects of water absorption.

On the other hand, UHMWPE, with its more crystalline nature and far

higher average molecular weight (≈2 × 10 6 vs. 2 × 10 4), is unaffected by the

environmental exposures used in this experiment.∗

Chain scission is the polymeric equivalent of the processes of corrosion

and dissolution of metals discussed in Section 4.1 and Section 4.2. The prin

cipal mechanisms are intrinsic scission (no external chemical species

involved), oxidation, hydrolysis, or chemical attack. Figure 6.3 summarizes

these mechanisms and provides some generic examples.

Chain scission reduces the elastic moduli of polymers through three routes:

• The scission reaction may release a very small molecular fragment, such as a water molecule, that can act as a plasticizer.

• Although the principal resistance to small deformations in polymers is due to stretching and/or disruption of weak bonds, some contribution is due to “tangling” of long molecules. In much the same way that long strands of spaghetti tend to entrap each other, this tangling forces an elongation of a portion of the strong, covalently bonded molecules, even at modest deformations. Thus, scission of molecules by reducing average molecular weight releases these

* In this study, the implants were sterilized chemically. If they had been irradiated, chain scis

sion, cross-linking, and oxidation of residual free radicals would have affected the results. See

the subsequent part of this section. trapped molecules and permits greater strain before covalent bond stretching can contribute significantly to the elastic modulus.

• The disorder associated with shorter chain length may reduce crystallinity and thus reduce the average strength of bonding, leading to lower moduli.

Cross linking is the reverse of scission. The formation of new bonds

between chains increases the effective molecular weight, further tangles and

traps molecules, and may reduce the effective concentration of plasticizers

by chemical combination. A common mechanism for cross-linking polymers

in the laboratory is exposure to ionizing radiation. This produces active free

radicals, as in chain scission, that link with free radicals in neighboring

chains, forming covalent cross links. Although clinical doses of x-radiation

do not produce measurable changes in the properties of polymeric implants

in patients (Eftekhar and Thurston 1975), high-dose γ-radiation in the

FIGURE 6.3

Mechanisms of chain scission in polymers. (Adapted from Adams, R. and McMillan, P.W., J.

Mater. Sci., 12, 643, 1977.) n + INTERNAL MECHANISMS OXIDATION HYDROLYSIS OTHER CHEMICAL REACTIONS Elimination Depolymerization Random Scission Depolymerization slow unless catalyzed – CH = CH – + HX n (– CH = CH – + HCI) C · H · CH 2 X X X · or CH – CH 2 CH = CH 2 C CH 2 COOCH 3 COOCH 3 COOCH 3 n CH 3 e.g. PVC H X C C H H n e.g. PMMA CH 3 CH 2 C CH 2 C n n n Amine elimination also possible C O OH CH CH 2 H 2 0 Accelerated by O 2 , light Free radical reaction with O 2 and photo-oxidation Chain oxidation H + , OH C C Cl H H H e.g. H H C C + 2 HCl H C H Cl C H H Cl Addition of HCl, SO 2 , SO 3 , NO 3 , etc., to unsaturated bonds

laboratory is a convenient process to enable studying the mechanical conse

quences of cross linking.

Irradiation of simple pure polymers such as polyethylene suggests a linear

increase of modulus with the number of cross links (Grobbelaar et al. 1978),

and a more pronounced effect may occur if a number of low-molecular

weight agents that can be incorporated are present during irradiation. Fur

thermore, unless they are removed by annealing or doping with reducing

agents such as vitamin E, residual free radicals produced by γ or electron

beam irradiation may produce progressive in vitro and in vivo property

changes by continuing reaction with polymer molecules and diffusible small

molecules, such as water or oxygen.

The environmental effects on the elasticity of composites are more difficult

to generalize. In an ideal model, the elastic modulus of a randomly oriented

composite, E C , made of materials A (matrix) and B (reinforcing or filler phase)

can be calculated from E C = E A V fA + E B V fB (6.3)

where V fi = volume fraction of material (phase) i. Then, any effect on the

modulus of either material is seen as a proportional effect on the modulus

of the composite. A special case would be the formation of voids in a material,

by leaching of a second phase or by aggregation of internal defects. Because

the modulus of a void is zero, the modulus of a porous material, for small

pore volumes, can be given by E = E o (1 – V fP) (6.4)

where E o = elastic modulus of fully dense material. Thus, the modulus would

be expected to decrease linearly with increasing volume

fraction of pores.

In real materials, the effect is somewhat greater at small void volume

fractions but becomes less pronounced for more porous materials. Equation

6.5 was derived for rigid ceramics (MacKenzie 1950) and has been shown

experimentally to describe effects in materials with Poisson ratios near 0.3: E = E o (1 – 1.9 V fP + 0.9 V fP 2) (6.5)

There is a further problem in describing the effects of environment on the

elastic moduli of composites. Equation 6.3 is based upon an assumption that

a perfect bond exists between the phases so that each phase experiences an

equal internal strain for a given external uniform deformation of the com

posite material. Real composites rarely display such perfect bonding, and

the bond is often the weak point for environmental attack. The consequences

of this are unpredictable but the usual effect is a reduction in modulus.

6.4 Yield Strength

6.4.1 Fundamental Aspects

The yield strength is defined by the stress necessary to produce unrecover

able deformation in a material. Deformation at lower stresses may be linear

in the case of a simple solid or increasingly nonlinear as strain increases, as

in the case of many polymers. Recovery may be rapid at

lower strains and

become slower as peak strain increases. Finally, at the yield stress, conditions

of deformation are such that a residual unrecoverable strain remains, even

after long times at zero stress.

Within crystals, unrecoverable strain is produced by migration and aggre

gation of defects and by the slippage of material along defect planes. How

ever, in complex materials and composites, slip, leading to unrecoverable

deformation, may occur preferentially along grain and phase boundaries.

6.4.2 Environmental Effects

At room and body temperature, the processes leading to crystalline defor

mation or grain boundary slip in metals and ceramics are little affected by

environmental exposure because of the relatively high bonding energies.

However, the situation for polymers and polymer-based composites is dif

ferent, as noted in the earlier discussion of elastic modulus. The effects are

summarized in Table 6.1.

Absorption and leaching produce what appear to be paradoxical effects

on yield strength. That is, a lower modulus, as results from absorption of a

plasticizer, might be expected to accompany a lower yield strength. In gen

eral, however, the yield strength is raised. Motion along a particular grain

boundary may become easier; however, this may lead to increased load

sharing with adjacent material and, in fact, may produce modest elevations

of yield stress in inhomogeneous materials. A similar but inverse effect is

seen when plasticizers are leached from the material.

On the other hand, chain scission produces an overall reduction in molec

ular weight, making plastic deformation more dependent upon the inter

ruption of weak bonds and thus reducing the yield stress. Cross linking

increases the tangling effect of long molecules, thus substituting strong cova

lent bonds for weaker bonds and raising the yield stress.

The situation in composites is more complex, and no generalizations can

be made. This is the case because the environment may affect the matrix and

the matrix-filler bond as well. The results depend upon the details of the

composite material in question and its exposure.

It is possible for materials to undergo unrecoverable deformation under

constant load at stress below the yield stress. This is the familiar creep

process. Creep rates are generally very slow for temperatures below one-half

the melting temperature of the material. However, for temperatures above

one-half the melting temperature, or in the presence of plasticizers, creep

can be significant. Creep is possible in many biomedical polymers at room

temperature and is generally increased at body temperature.

Creep is characterized by an initial or primary creep phase in which the

creep rate diminishes rapidly. This is followed by a long secondary creep

phase with a strain rate that is essentially constant in logarithmic time. In

this secondary creep phase, the Dorn-Weertman equation can be used to

describe the creep rate: $\dot{\varepsilon} = A\sigma^n e^{-Q/RT}$ (6.6)

where

$\dot{\varepsilon}$ = creep rate

σ = stress

n = experimentally fitted parameter ($\cong 5$)

Q = activation energy

The activation energy (Q) is usually taken to be the activation energy for

self-diffusion, but may be considered more generally as an intrinsic activa

tion energy for creep (Parsons and Black 1977). Thus, environmental effects

on the creep rate can be interpreted in terms of changes in the activation

requirements of the creep process.

The final or tertiary process of creep is characterized by a rapidly increasing

strain rate leading to fracture. Little is known about the mechanism of this

process or about environmental effects on it.

It should also be clear from this discussion that creep in biomedical appli

cations is observed primarily in polymers and polymer-based composites.

In general, secondary creep rates decrease with increasing yield stress at a

given temperature, but the relationship is weak. However, they increase with

increasing temperature and with the presence of plasticizers. This latter effect

may dominate in polymer matrix composites, producing significant

increases in creep rate (Soltész 1986).

6.5 Fracture Strength

6.5.1 Fundamental Aspects

Fracture occurs when the cohesive strength of a material is exceeded. It

represents an accentuation and final stage of the processes that earlier led

to yielding — if that is possible in a particular material. However, it is

generally observed that ultimate strengths, such as the ultimate tensile stress,

are small compared with those expected, based upon cohesive energy cal

culations.

Typical calculations of cohesive energy or theoretical maximum strength

lead to values of σ_u equal to $E/10$. This would predict a

tensile strength of

12.7 GPa for Ti6Al4V, a common alloy useful in implant applications. The

actual value of σ u is typically 0.9 GPa (900 MPa), that is, ≈ E/140. This is a

relatively strong material; weaker materials such as stainless steels have σ u

in the range of E/250 to E/350.

Griffith (Guy 1971) was the first to explain this observation for brittle

materials (those that fail without significant unrecoverable strain) by sug

gesting that defects exist on the surface and within the body of real materials

as seen in Figure 6.4. He calculated that the presence of an elliptical crack

in brittle materials produces a stress concentration at the “point” of crack,

as given by: (6.7)

where

σ = apparent or “macro” stress

σ m = elevated stress at “point” of crack

c = 1/2 major diameter of internal elliptical crack = major width of surface crack

r = radius of curvature at “point” of crack (r << c)

Thus, Griffith suggested that, although the macrostress might be well

below the true ultimate stress, the elevated local stress, σ m , near a defect

might exceed the ultimate strength, and a crack would propagate. By con

sidering the energy required to form the crack (the difference between elastic

strain energy released in the material near the newly formed crack and the

increase of interfacial surface energy due to formation of the new

FIGURE 6.4

The ideal Griffith crack. c 2c r A F (s = F/A) σ σ m c r ≅ ⎡ ⎣ ⎤ ⎦ 2 1 2/

material-environment interfacial area along the crack), he also calculated the

minimum stress required to propagate the crack: (6.8)

where

γ = surface tension (material-environment)

E = elastic modulus

Fortunately, most materials undergo plastic deformation before fracture.

Thus, as stresses about a defect are increased, as predicted by Equation 6.7,

plastic deformation will take place before fracture, even if the macrostress

is below the yield stress. Orowan (Guy 1971) dealt with this problem by

replacing the term γ in Equation 6.8 with the quantity (γ + p), where p = the

work of plastic deformation at the “point” of the propagating fracture.

Because p is typically 1000 times γ in magnitude, Equation 6.6 then becomes

approximately, (6.9)

Such materials will be proportionally stronger because they will require far

higher stresses to propagate existing defects into fracture surfaces.

A special case of Equation 6.7 occurs for spherical pores, the situation

discussed previously with respect to the reduction of elastic modulus by

pores. This has been studied empirically, and the usual relationship (parallel

to Equation 6.5) derived by Ryskewitsch (Kingery 1976) is (6.10)

where σ′ u is the actual fracture strength for a material with pore volume

fraction V fP , and n is an empirically fitted constant with a value between 4

and 7.

The difference between the stresses predicted by Equation 6.8 and Equa

tion 6.9 results in the classification of materials as those that fail in a brittle

mode and those that fail in a ductile mode. Characteristic of ceramics and

of polymers at low temperatures, brittle failure occurs without significant

residual deformation and is governed by relations of the form of Equation

6.8. Materials with yield stresses well below ultimate stresses tend to be

ductile and fail in a manner governed by Equation 6.9. Because yielding

occurs during failure, they also exhibit significant unrecoverable strain. σ γ π = ⎡ ⎣ | ⎤ ⎦ | 2 1 2 E c / σ ≅ ⎡ ⎣ | ⎤ ⎦ | Ep c 1 2/ ′ = − ( ) σ σ u e nV e fP

The existence of Griffith defects has been shown

repeatedly. An elegant

example is the work of Takahashi (1973) in poly(methyl)methacrylate, as

shown in Figure 6.5. The A-type cracks are those seen after modest stresses,

and B- and C-types after higher stresses, presumably exceeding the limit

imposed by Equation 6.9.

Given that Griffith defects exist two conclusions can be drawn from this

analysis:

• Equation 6.7 predicts that the magnitude of the stress concentration near a defect will vary inversely with the minimum radius of curvature, r, of the defect. Thus, a sharp crack is a more extreme stress riser than a semicircular notch. This effect is the basis of the commercial practice of drilling a hole at the advancing tip of a slowly propagating crack, as in a cracked bridge strut, to prevent further defect propagation by reducing σ_m. In implant design, this suggests that it is desirable to avoid “sharp” features, such as edges, grooves, and surface structure, to minimize stress concentration effects.

• As the defect major diameter (= 2c) increases, stress concentration increases (Equation 6.7), and the stress necessary to propagate brittle fracture (Equation 6.8) or ductile fracture (Equation 6.9) decreases. Thus, there is a critical minimum size for a Griffith defect to contribute to fracture, given that r remains constant. In practice, larger defects decrease strength to a limit beyond which the process is reversed because r begins to increase.

Calculations of minimum crack lengths in composites are much more com

plex. Marom (1975) has shown that the minimum or critical defect size in

FIGURE 6.5

Plausible crack discs in section. Note: vertical dimension exaggerated. (Adapted from Taka

hashi, K., J. Macromol. Sci. Phys., B8(3-4), 673, 1973.)
(III) (IV) (II) (I) (I') A-type C-type B-type

polymer-based composites is much greater than that in the unfilled resin

and depends upon orientation of stresses with respect to the reinforcing fiber.

Attempts to improve mechanical properties of polymers by processing

may lead to paradoxical results, due to the differences between brittle and

ductile fracture strength. Fatigue processes require accumulation of microf

ractures to produce reduction in area leading to a final single cycle failure.

Thus, cross linking a polymer, such as ultrahigh molecular weight polyeth

ylene, can increase its ultimate and yield strengths; however, because this

also reduces ductility, it may produce dramatic decreases in fatigue strength

at high cycle numbers (N > 10 6) due to brittle rather than ductile crack

propagation (Sauer et al. 1996).

6.5.2 Environmental Effects

The biological environment can have significant effects upon the details of

crack propagation and, thus, upon the strength of materials. These effects

will now be briefly discussed.

Any form of chemical attack, whether corrosion, oxidation, dissolution, or

leaching, that can increase the size of pre-existing

defects or produce new

defects by preferential attack clearly weakens a material. Such an attack may

take place preferentially near defects in stressed materials and is termed

“stress-enhanced attack” or “stress corrosion” in the case of metals. Such

effects are well recognized in metals and have been demonstrated in silicone

rubber (Rose et al. 1973). Crazing due to swelling can also produce Griffith

defects where none previously existed or can expand preexisting ones.

In brittle materials, the fact that γ SL < γ SA for all but hydrophobic materials

reduces the required propagation stress predicted by Equation 6.8. Thus, any

of the degradative phenomena discussed in Chapter 3 and Chapter 4 can be

expected to reduce the ultimate strength of biomaterials, and all classes of

materials are susceptible.

Table 6.4 summarizes behavior for a range of typical polymeric implant

materials, nonabsorbable sutures, during a 24-month experiment in rabbits

(Postlethwait 1970). The data given in the table are the ultimate tensile loads

normalized by dividing by the strength of materials retrieved after 1 week

of implantation (in the abdominal wall) to remove the effect of differing

diameters of specimens.

Absorbable materials, such as gut (natural) or polygalactic acid (synthetic)

sutures, will show more pronounced and rapid loss of strength. However,

the rate for an individual material and surgical situation is hard to predict.

The loss of strength is affected by the material composition, fabrication, and

postfabrication handling (production of surface defects), and because of

possible pH dependence of degradation by hydrolysis (Chu 1982) and/or

enzymatic attack (Salthouse et al. 1969; Lotan et al. 1995).

In addition to failure by fracture at stresses that exceed ultimate strength,

materials may fail by fatigue. Fatigue fracture — fracture at stresses below

ultimate after a number of cyclic deformations — is recognized as one of the

major sources of mechanical failure of implants. Fatigue failure is character

ized by the construction of an S-N (stress vs. number of cycles) curve as

shown in Figure 6.6. The ultimate (fracture stress) decreases with cyclic

loading in air until an apparent limit, termed the “endurance limit,” is

reached. In this example, the endurance limit is reached between 10 6 and 10 7

cycles. However, in an aqueous or corrosive environment where stress cor

rosion is possible during the high-stress part of each cycle, this endurance

limit is apparently abolished, and the fracture strength continues to decrease

with cyclic loading. The presence of defects, such as surface markings, may

lead to stress concentration and apparent reduction in fatigue strength; alter

ation of such defects by corrosion processes may accentuate the effect of

their presence (Naidu et al. 1996).

TABLE 6.4

Degradation of Tensile Strength of Sutures in Vivo Suture Type Multifilament Monofilament

Period of

Implantation Silk Cotton Polyamide (Nylon™) Polypropylene Polyester (Dacron™)

2 Weeks 0.87 0.98 0.98 1.05 0.92

4 Weeks 0.58 1.07 0.97 1.14 1.03

3 Months 0.20 0.67 0.88 1.03 0.91

6 Months 0.36 0.52 0.79 0.93 0.70

12 Months 0.58 0.50 0.89 0.97 0.96

24 Months Dis. 0.58 0.72 0.99 0.96

Comments Slow dissolution Separated Swollen No visible change No visible change

Note: Data normalized by 1-week value of ultimate tensile stress.

Source: Adapted from Postlethwait, R.W., Ann. Surg., 171, 892, 1970.

FIGURE 6.6

S-N curves for a Cr-V steel. (From Dumbleton, J.H. and Black, J., An Introduction to Orthopedic

Materials, Charles C Thomas, Springfield, IL, 1975.) Number of cycles to failure S t r e s s (p s i / 1 0 0 0) Fatigue test in seawater (estimated) Fatigue test in air Pre-corroded (one week) Fatigue test in air Fatigue test in freshwater 80 60 40 20 100 10 5 10 6 10 7

In polymers and polymer-based composites, similar effects are also seen,

probably secondary to plasticizing and/or “decoupling” (secondary to bond

failure) of the reinforcing phase from the matrix. This phenomenon may be

explored by using drops of polymer matrix formed on long specimens of a

fiber-reinforcing phase (Latour and Black 1993). Figure 6.7 shows the S–N

curves for such specimens, fabricated from polysulfone resin and carbon

fiber, after equilibration in various environments (37°C, 24 h). The two solu

tions used were physiological saline and inflammatory exudate collected

previously by implanting porous capsules of the thermoplastic matrix resin

in soft tissue in rabbits. No endurance limit was observed under dry or wet

conditions up to 2.5 × 10 5 cycles. The effect on shear strength of both solutions

is the same, suggesting that water is the active agent.

In polymer-based composites, a progressive reduction in modulus is also

observed as internal damage accumulates with an increasing number of load

cycles; the decrease is pronounced if the aqueous

environment is such that

the fiber–matrix interface is wetted preferentially (is hydrophilic).

Ceramics display an additional fatigue problem called static fatigue, which

is a sudden failure by brittle fracture at stresses well below ultimate when

subjected to steady (noncyclic) loads. In Al 2 O 3 (Krainess and Knapp 1978)

and in glasses (Adams and McMillan 1977), this effect is believed to be due

to the formation of weak bonds by absorbed water displacing stronger ionic

bonds.

FIGURE 6.7

S–N curves for a polysulfone-carbon fiber interface (group mean values; n = 6 per point). --->#

= number of unbroken specimens at this stress level (N = 2.5 × 10 5). (From Latour, R.A., Jr. and

Black, J., J. Biomed. Mater. Res., 27, 1281, 1993.) 20 40 60 80 100 3 1 10 1 10 2 10 3 10 4 10 5 10 6 Cycles to failure M a x i m u m I n t e r f a c i a l S h e a r S t r e s s (M P a) Key: Dry Saline Exudate

Thus, it should be clearly understood that biological environments, as

encountered by implants, can be expected to produce a wide range of sig

nificant changes in the mechanical properties of materials.

6.6 Final Comment

Notwithstanding the general principles discussed here, two points should

be emphasized:

• Actual or real materials have more complex structures than can be dealt with here in this brief discussion. Therefore, it should be no surprise when apparently paradoxical property changes are encountered as a consequence of exposure to biological environments.

• Because it is extremely difficult to predict quantitative mechanical property changes, care should always be taken to determine the properties of materials before environmental exposure, whether simulated or by implantation. This should be performed on actual specimens, from the same batches of materials to be tested, treated identically to the specimens to be exposed (including sterilization and other postfabrication treatments), concurrently with initiation of testing, because it cannot be assumed that properties will remain unchanged over periods of months and years during laboratory storage.

Adams, R. and McMillan, P.W., Review: static fatigue in glass, J. Mater. Sci., 12, 643, 1977.

Allara, D.L., Aging of polymers, Environ. Health Perspec., 11, 29, 1975.

Chu, C.C., The effect of pH on the in vitro degradation of poly(glycolide lactide) copolymer absorbable sutures, J. Biomed. Mater. Res., 16, 117, 1982.

Dumbleton, J.H. and Black, J., An Introduction to Orthopedic Materials, Charles C Thomas, Springfield, IL, 1975.

Eftekhar, N.S. and Thurston, C.W., Effect of irradiation on acrylic cement with special reference to fixation of pathological fractures, J. Biomech., 8, 53, 1975.

Grobbelaar, C.J., duPlessis, T.A. and Marais, F., The radiation improvement of polyethylene prostheses, J. Bone Joint Surg., 60B, 370, 1978.

Guy, A.G., Introduction to Materials Science. McGraw-Hill, New York, 1971.

Jacobs, M.L. Evaluation of three polymer resins for use in polymer-based composites for hard tissue prostheses. M.S. thesis, University of Pennsylvania, Philadelphia, 1974.

Kingery, W.D., Introduction to Ceramics. 2nd ed. John Wiley & Sons, New York, 1976.

Krainess, F.E. and Knapp, W.J., Strength of a dense alumina ceramic after aging in vitro, J. Biomed. Mater. Res., 12, 241, 1978.

Latour, R.A., Jr. and Black, J., Development of FRP composite structural biomaterials. Fatigue strength of the fiber/matrix interfacial bond in simulated in vivo environments, J. Biomed. Mater. Res., 27, 1281, 1993.

Lotan, N., Azhari, R. and Sideman, S., Enzymic degradation of polymeric biomaterials: a review, in Encyclopedic Handbook of Biomaterials and Bioengineering, Part A, Vol. 1, Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, 757.

MacKenzie, J.K., The elastic constants of a solid containing spherical holes, Proc. Phys. Soc. (London), B63, 2, 1950.

Marom, G., Calculation of effective crack length in composite materials, Int. J. Frac., 11, 534, 1975.

Naidu, S.H., Warner, C.P. and Laird, C., Mechanical stamping: a cause of fatigue fracture, Clin. Orthop. Rel. Res., 328, 261, 1996.

Parsons, J.R and Black, J., On the thermodynamics of the viscous deformational mechanism of articular cartilage, Trans. SFB, 1, 78, 1977.

Postlethwait, R.W., Long-term comparative study of nonabsorbable sutures, Ann. Surg., 171, 892, 1970.

Rose, R.M., et al., The role of stress-enhanced reactivity in failure of orthopaedic implants, J. Biomed. Mater. Res. Symp., 4, 401, 1973.

Salthouse, T.N., Williams, J.A. and Willigan, D.A., Relationship of cellular enzyme activity to catgut and collagen suture absorption, Surg., Gyn. Obstet., 129, 691, 1969.

Sauer, W.L., Weaver, K.D. and Beals, N.B., Fatigue performance of ultra-high-molecular-weight polyethylene: effect of gamma radiation sterilization, Biomaterials, 17, 1929, 1996.

Soltész, U., Fracture, fatigue, and aging behavior of carbon fiber reinforced plastics, in Materials Sciences and Implant Orthopaedic Surgery. Kossowsky, R. and Kossovsky,

N. (Eds.), Martinus Nijhoff, Dordrecht, 1986, 355.

Takahashi, K., Cracking of poly(methyl methacrylate) caused by plane stress waves, J. Macromol. Sci. Phys., B8(3-4), 673, 1973.

Anseth, K.S., Bowman, C.N. and Brannon-Peppas, L., Mechanical properties of hydrogels and their experimental determination, Biomaterials, 17, 1647, 1996.

Chu, C.C., Survey of clinically important wound closure biomaterials, in Biocompatible Polymers, Metals, and Composites, M. Szycher, M. (Ed.), Technomic, Lancaster, PA, 1983, 477.

Coury, A.J., Chemical and biochemical degradation of polymers, in Biomaterials Science, 1st ed., Ratner, B.D., Hoffman, A.S, Schoen, F.J. and Lemons, J.E. (Eds.), Academic Press, San Diego, 1996, 243.

Ducheyne, P. and Lemons, J.E. (Eds.), Bioceramics: material characteristics versus in vivo behavior, Ann. N.Y. Acad. Sci., 523, 1988.

Edidin, A.A. et al., Degradation of mechanical behavior in UHMWPE after natural and accelerated aging, Biomaterials, 21, 1451, 2000.

Ferry, J.D., Viscoelastic Properties of Polymers, 3rd ed., John Wiley & Sons, New York, 1980.

Gibson, L.J. and Ashby, M.F., Cellular Solids: Structure and Properties, 2nd ed., Cambridge University Press, Cambridge, 1997.

Hayden, W., Moffatt, W.G. and Wulff, J., Mechanical Behavior, Vol. III of The Structure and Properties of Materials, Wulff, J. (Ed.), John Wiley & Sons, New York, 1965.

Hertzberg, R.W. and Manson, J.A., Fatigue of Engineering Plastics, Plenum Press, New York, 1980.

Hull, D. and Clyne, T.W., An Introduction to Composite Materials, 2nd ed., Cambridge University Press, Cambridge, 1996.

Jamison, R.D. and Gilbertson, L.N. (Eds.), Composite Materials for Implant Applications in the Human Body: Characterization and Testing STP 1178, American Society for

Testing and Materials, Philadelphia, 1993.

Jones, R.M., Mechanics of Composite Materials, 2nd ed., Taylor & Francis, New York, 1998.

Kronenthal, R.L., Biodegradable polymers in medicine and surgery, in Polymers in Medicine and Surgery, Kronenthal, R.L., Oser, Z. and Martin, E. (Eds.), Plenum Press, New York, 1975, 119.

Kurtz, S.M. et al., Degradation of mechanical properties of UHMWPE acetabular liners following long-term implantation, J. Arthroplasty, 18(7), Suppl 1, 68, 2003.

Ward, I.M. and Sweeney, J., An Introduction to Mechanical Properties of Solid Polymers, 2nd ed., John Wiley & Sons, New York, 2004. 107

7

Friction and Wear

7.1 Introduction

The previous chapter considered the mechanical behavior of materials under

stress. The areas dealt with were those concerning the properties of singular

parts or components. When devices contain more than one component or

are able by design or chance to move against natural tissue, another class of

mechanical effects must be considered.

The general resistance to the motion of one material body over another is

termed friction. When static friction is overcome and relative motion takes

place, it is accompanied by a modification of the interface by a variety of

processes that are collectively known as wear. Introduction of surface treat

ments or interposed materials to make relative motion easier is called, col

lectively, lubrication. The study of these three phenomena (friction, wear,

and lubrication) is the science of tribology. This chapter will consider these

phenomena and their presence in and alterations by biological environments.

7.2 Friction

If an attempt is made to move one body over the surface of another, a

restraining force oriented to resist motion is encountered. This restraining

or frictional force, F_f, is given by $F_f = \mu F_\perp$ (7.1)

where

$F_\perp$ = force perpendicular to interface

μ = coefficient of friction

The force perpendicular to the surface, $F_\perp$, may be generated by compres

sive or gravity forces. The coefficient of friction, μ, is a ratio or unitless

number, with values usually between 0 and 1, which describes the relation

ship of the frictional restraining force to this perpendicular force. It is char

acteristic of the interface, depending upon the composition and finish of the

pair of materials involved, and is affected by lubrication. Furthermore, the

coefficient is greater just before surfaces begin to move (initial conditions $\rightarrow$

μ_i) than when the surfaces are in continuing or steady

motion (sliding con

ditions → μ s). Table 7.1 gives some typical values of μ i and μ s .

Frictional behavior arises from the physical situation of the surfaces having

a relatively small area of contact due to microscopic surface roughness. The

small size of this actual contact area, perhaps as little as 1% of the geometric

interface area, leads to local yielding and bonding due to high stresses at

the points of actual contact. Thus, relative motion results only when these

bonded areas can be disrupted in shear and moved relative to one another.

This disruption produces the frictional restraining force and also clearly

leads to the wear process.

Frictional restraining forces are complex, but a number of generalizations

can be made:

• The coefficients of friction, μ i and μ s , are essentially independent of F ⊥ (they may be affected, however, by tangential (lateral) forces).

• For a given value of F ⊥ , coefficients of friction are generally independent of stress — that is, of the apparent or geometric interfacial surface area. TABLE 7.1 Initial and Sliding Coefficients of Friction Materials Combinations Lubricant μ i μ s Rubber tire/concrete None (dry) 1.0 0.7 Rubber tire/concrete Water 0.7 0.5 Leather/wood None (dry) 0.5 0.4 Steel/steel None (dry) — 0.5 Steel/polyethylene None (dry) — 0.1 Steel/ice Water 0.03 0.01 Cartilage/cartilage (hip) Synovial fluid — 0.002 Ringer’s — 0.01–0.005 CoCr/CoCr (hip prosthesis) a None (dry) — 0.55 Veronate buffer — 0.22 Serum — 0.13 Synovial fluid Albumin (sol.) — 0.12 0.11 CoCr/PE(UHMW) a Serum — 0.08 Al 2 O 3 /Al 2 O 3 b Ringer’s — 0.1–0.05 a Weightman, B. et al., J.

Lubric. Tech., 94, 131, 1972. b Dörre, E. et al., Arch. Orthop. Unfall.-Chir., 83, 269, 1975.

• Coefficients of friction depend upon surface texture, the material pair, and the lubricant involved. However, in general, coefficients are lower for a pair of unlike materials of the same roughness than for identical materials and are lower for a given material pair in the presence of lubricating agents than in their absence.

• Static and dynamic coefficients of friction are not closely related to wear rates (Galante et al. 1973). In particular, low frictional coefficients do not lead necessarily to low wear rates.

7.3 Lubrication

The principle of lubrication is to provide a film or layer to separate two

surfaces during relative motion in order to reduce frictional restraining forces

and wear. Lubrication modes or processes are classified by the nature and

the magnitude of the average surface separation characteristic for each type.

It is clear from Table 7.1 that artificial material pairs do not possess coeffi

cients of friction that closely approach those possible in natural joints,

particularly at the low velocities at which joints operate. Little can be done

about this situation as long as body fluids are depended upon for lubrication.

However, it is important from a design point of view to know the actual

coefficients of friction that may be expected.

Table 7.1 suggests the importance of using an appropriate lubricant in

laboratory determinations of friction and wear. For

materials in contact with

blood, such as heart valve components, the appropriate lubricant is fresh

serum. For device components in soft tissue locations, a 50:50 mixture of

serum and normal saline approximates the intracellular exudates. For joint

replacement components, the appropriate lubricant is synovial fluid. Wood

man and colleagues (1977) showed that the synovial tissue remaining in the

vicinity of a joint produces essentially normal synovial fluid that is available

for lubrication of the artificial joint replacement.

Differences in composition between synovial fluid and serum (Table 7.2)

suggest that dilute serum:saline solutions are generally superior to saline to

simulate synovial fluid. However, serum, whether human or animal, is a

highly variable material. In vitro simulator results, especially for wear rates,

most closely resemble those encountered in implanted joints when total

protein concentration is in the range of 20 to 30 g/L and the albumin to

globulin ratio is adjusted (by albumin addition) to a range of 1 to 1.5 (Wang

et al. 2004). However, such studies, performed on metal/polymer wear pairs,

may not be fully generalizable to other wear pairs because synovial fluid

contains one or more so-called “surfactant” species, such

as phosphatidyl

choline, which avidly bind to surfaces and reduce dynamic coefficients of

friction under boundary lubrication regimes (see Section 7.3.4) (Hills and

Butler 1984). In addition, laboratory testing may not faithfully reproduce in

vivo conditions in which synovial fluid is constantly replaced, even when

the lubricating bath is regularly renewed.

7.3.1 Hydrodynamic

Hydrodynamic lubrication is perhaps the most usual process encountered

in human prosthetic joints in vivo; it occurs when the motion of one body

relative to the other draws a continuous film of lubricant into the contact

area. The characteristic surface separation for typical lubricants and engi

neering finishes is between 10 -3 and 10 -4 cm. In this mode, all of the work

of friction is dissipated by viscous shear of the lubricant.

7.3.2 Elastohydrodynamic

Elastohydrodynamic lubrication occurs at smaller surface separations,

between 10 -4 and 10 -5 cm. In this case, the motion of one body of the pair is

able to transmit force through the lubricant to generate sufficient stress for

transient elastic deformation of the other body. Although this may be satis

factory in the short term, in the long term it may lead to

localized fatigue

failure of one or the other surface, with an accompanying increase in

wear rate. TABLE 7.2 Composition of Synovial Fluid in Comparison to Serum Component Synovial Fluid (g/l) Serum (g/L) Synovial/Serum Protein (total) 18 70 0.26 Albumin 11.3 34.3 0.33 α 1 -Globulin 1.26 4.2 0.30 α 2 -Globulin 1.26 8.4 0.15 β-Globulin 1.62 11.9 0.14 γ-Globulin 3.06 11.2 0.27 Lipid (total) 2.4 7.0 0.34 Phospholipids 0.8 2.0 0.40 Urate 0.016 0.018 0.88 Glucose Hyaluronate: Albumin/globulin ratio 0.66 2-4 1.57 0.91 4.2 × 10 −5 0.96 0.73 ~7 × 10 4 Sources: Proteins: Lentner, C. (Ed.), Geigy Scientific Tables, Vol. 1, Ciba-Geigy, Basle, 1981; other: Levick, J.R., in Joint Loading, Helminen, H.J., Kiviranta, I.A., Säämänen, A.-M., Tammi, M., Paukkonen, K. and Jurvelin, J. (Eds.), Wright, Bristol, 1987, 149.

7.3.3 Squeeze Film

Squeeze film lubrication occurs in hydrodynamic or elastohydrodynamic

conditions if the lubricant is sufficiently viscous to respond elastically (rather

than by increased flow) to temporarily increased normal loads. Thus, a

squeeze film lubricant, although highly viscous, may reduce wear in situa

tions in which transient overloads occur. Hydrodynamic, elastrohydrody

namic, and squeeze film conditions are collectively termed fluid film

lubrication.

7.3.4 Boundary

Boundary lubrication occurs when the lubricant coats the opposing surfaces

rather than acting as a low-shear interface. This coating acts to modify the

frictional character of the surfaces to reduce frictional

restraining forces and

wear. Characteristic mean surface separations depend sensitively on the

nature of the lubricant but are usually less than 10 −5 cm.

7.3.5 Mixed

Mixed lubrication occurs when a fluid lubricant operating in hydrodynamic

or elastohydrodynamic mode is able to coat the surfaces by an adhesive

process, thus providing additional protection at high loads through bonding

lubrication. Natural synovial joints in the skeletal system probably demon

strate a combination of these lubrication modes (Wright 1969):

- Boundary lubrication during motion initiation
- Elastohydrodynamic lubrication during motion
- Squeeze film lubrication during high load events

This combination of behavior results from the structure of the joint and from

peculiarities in the nature of the lubricant, synovial fluid. As previously

noted (Table 7.2), normal synovial fluid resembles serum in inorganic species

but contains 30 to 50% of the amount of protein and lipids, a higher albumin

to globulin ratio, and significantly more hyaluronate.

7.3.6 Types of Lubricant Behavior in Response to Shear

In general, lubricants display three types of relationships between apparent

viscosity and shear rate (Dintenfass 1963) as shown in

Figure 7.1. Conven

tional lubricants have a viscosity that is independent of shear rate. Thus,

surface separation, h c , as a function of relative velocity may be determined

fairly easily, taking the lubricant properties as a constant (Hamrock and

Dowson 1981). Under these conditions the lubrication process may remain

constant over a wide range of velocities. For simple parallel geometries, as

in concentric or parallel sliding interfaces A and B, one may then derive a

dimensionless parameter, λ: λ = h c /(R 2 rmsA + R 2 rmsB) 1/2 (7.2)

where R rmsA , R rmsB = root means square roughnesses of the opposing surfaces.

Thus, for λ < 1, one would expect predominantly boundary lubrication;

for 1< λ< 3, one would expect mixed lubrication and for λ > 3 some form

of fluid film lubrication would be expected.

If the lubricant and the relative surface velocity remain constant, the sur

face separation (h c) remains nearly constant and the mode of lubrication is

affected primarily by surface roughness. Here one can see graphically that,

as the roughness of one of the counterfaces decreases, lubrication can tran

sition from boundary to mixed to fluid film mode.

However, some lubricants are thixotropic; that is, they become reversibly

less viscous as shear rates increase. An everyday example of such a fluid

(although not a lubricant) is nondrip ceiling paint. This appears nearly solid

in the can but becomes quite thin as it is brushed on the wall. The inverse

of thixotropic is also possible; such a material would be called dilatant and

would become reversibly more viscous with increasing shear rate. This

material would not contribute to easy relative motion but might act to reduce

wear at high relative velocities.

Thixotropic or dilatant lubricants can produce a change in lubrication

mode as a function of relative velocity of the surfaces because h c and thus λ

now depend on actual viscosity, pressure, and relative velocity. For instance,

a material pair with a thixotropic lubricant can display hydrodynamic lubri

cation at intermediate pressures and velocities and boundary lubrication at

high pressures and velocities (Figure 7.2).

FIGURE 7.1

Effects of counterface roughness on γ. h c λ↑ λ↓ ROUGHER SMOOTHER

Synovial fluid, which is an ultrafiltrate of serum with the addition of a

long chain polysaccharide complex, hyaluronic acid, is a highly thixotropic

lubricant (Figure 7.3). Trauma resulting in joint effusion

may reduce the

osmolarity of synovial fluid, producing a generally less viscous but still

thixotropic lubricant. However, in the presence of a persistent joint disease

such as rheumatoid arthritis, the fluid thins and tends to lose its thixotropic

property. This permits closer approach of the joint surfaces and may produce

increased wear as a contributing factor to joint degeneration.

FIGURE 7.2

Types of lubricant behavior.

FIGURE 7.3

Viscosity–shear rate relationships for synovial fluid. (Adapted from Dintenfass, L., J. Bone Joint

Surg., 45A, 1241, 1963.) Shear rate (log. D) sec -1 V i s c o s i t y (l o g . η) p o i s e Newtonian Thixotropic Dilatant D (sec -1) P O S T T R A U M A T I C D E G E N E R A T E D N O R M A L η (poise) 1000 100 10 1.0 0.1 0.01 1.0 100 100.1

7.4 Wear

7.4.1 Introduction

Wear is a more pronounced problem than frictional restraint for two reasons:

- Wear produces biologically “active” particles that can excite an inflammatory response (see Chapter 8).
- Wear produces shape changes that can affect function.

There are several mechanisms of wear. Probably the most important mech

anism in biomedical applications is adhesive wear. This arises from the

junction-making and -breaking process previously described. The rate of

production of wear debris, expressed as a volume, is given most generally by: (7.3)

where

V = volume of wear debris

k = Archard’s coefficient

F ⊥ = perpendicular force

p = surface hardness

x = total sliding distance

Figure 7.4 shows the range of k values of typical engineering situations.

For the situation of a polymer on a metal in vivo, values for k should lie

between 10 −5 and 10 −7 with conditions described by the lower right-hand

corner of the diagram. Note that the ordinates are labeled differently. The

left ordinate refers to transfer film formation (see Section 7.4.2) and the right

refers to the production of loose particles.

It is interesting to note that, although values of μ i and μ s lie within a small

range (between 0 and 1), k and thus wear rates vary over many orders of

magnitude. This further reinforces the previous observation that friction

forces and wear rates have little direct relationship.

7.4.2 The Transfer Film

Figure 7.4 suggests that two major wear processes are possible for any

combination of materials: particle production as described previously, or the

formation of a transfer film. This film is produced when a hard material,

such as a metal, moves on a softer material (for instance, a polymer) and

shears off and picks up a coating of polymer, as shown in Figure 7.5. This V kF x p = ⊥ 3

film bridges across the asperities on the surface of the metal, replacing

metal–polymer contact with polymer–polymer contact; by increasing the

actual contact area (as a function of the apparent contact area), it reduces

local stresses.

FIGURE 7.4

Variation of Archard's constant, k, with wear and lubrication conditions. (Adapted from

Rabinowicz, E., Mater. Sci. Eng., 25, 23, 1976.)

FIGURE 7.5

Transfer film vs. particle production. W E A R C O E F F I C I E N T F O R T R A N S F E R W E A R C O E F F I C I E N T F O R P A R T I C L E S CLEAN NO LUBRICANT LUBRICANT POOR FAIR GOOD 10 -2 10 -4 10 -6 10 -2 10 -4 10 -6 S i m i l a r m e t a l s D i s s i m i l a r m e t a l s N o n m e t a l a g a i n s t n o n m e t a l N o n m e t a l a g a i n s t m e t a l Water Gasoline Nonwetting liquid metal in air High Vacuum Pure mineral oil Molten glass Wetting liquid metal Mineral oil with lubricity additive Fatty oil Good synthetic lubricant LOOSE PARTICLE PRODUCTION TRANSFER FILM particle transfer film “small” k “big” k stable film unstable film smaller k bigger k POLYMER METAL

The formation of a transfer film may lead to one of two circumstances:

• If the film is stable, wear rates may be reduced after an initial highwear interval during film formation.

• If the film is unstable, it may peel and result in increased wear by abrasive or “three-body” wear.

McKellop et al. (1978) reported some interesting results involving transfer

films (Table 7.3). The material pair is F138 type steel (316L [vacuum melted])

and ultrahigh molecular weight polyethylene (UHMWPE), with serum, dis

tilled water, or saline as lubricants. Wear rates are reported as a calculated

linear recession of the UHMWPE surface, based upon measurement of the

volume of wear debris. Thus, the wear rate does not include a creep com

ponent. Distilled water apparently permitted the formation of a transfer film

and produced the lowest wear rate. Wear in saline was some 65 times greater

(than in distilled water) and was apparently accompanied by crevice corro

sion of the stainless steel in the interface between substrate and transfer film

as indicated by orange discoloration. This leads to occasional release of the

film and very high wear rates — apparently case 2 cited earlier.

TABLE 7.3

Wear of UHMWPE a in Different Lubricants in Vitro

Lubricant No. Specimens Average Wear Rate (μm/10 6 cycles) (range) Observations (μ s = dynamic coefficient of friction)

Serum (bovine) 4 0.65 (±17%) μ s = 0.07–0.12 normally; μ s = 0.35 during temporary high friction. Polymer transfer onto metal counterfaces occurred only during high-friction phase.

Distilled water 3 0.08 (±60%) μ s = 0.07–0.13 at start. A heavy polymer transfer layer formed by 3 × 10 5 cycles; μ s then ranged from 0.14 to 0.18. The transfer layer remained intact for the duration of the test. b

0.9% saline

(Ringer’s

solution) 3 5.2 (±17%) μ s = 0.07–0.10 at start. Heavy, orange-colored transfer layers formed as μ s increased to 0.27. These layers occasionally broke up and μ s dropped to the initial level.

a Against 316L (VM) stainless steel counterface at 3.45 MPa (500 psi) nominal contact stress,

10 6 sliding cycles @ 60 cpm (travel; 5 × 10 4 m [est.]).

b McKellop et al. (1978) also report transfer layer to be unstable at 6.90 Mpa.

Source: Adapted from McKellop, H. et al., J. Biomed. Mater. Res., 12, 895, 1978.

Serum produced an intermediate wear rate with only occasional transfer.

This suggests that, although serum does not completely reproduce synovial

fluid, active molecules present in vivo, other than surfactants, can coat metal

surfaces in metal/polymer wear combinations and, although preventing the

formation of stable transfer films, the molecules reduce wear through surface

lubrication.

Surface roughness, which plays a role in lubrication, also affects wear.

Early polishing of rough surfaces may produce elevated wear rates that

decline significantly after an initial “wearing in” period. However, a persis

tently rough hard surface bearing against a softer counterface can be

expected to produce wear rates above those predicted by Equation 7.3 (Kurtz

et al. 2000). Finally, surface roughness may change adversely in vivo through

mechanical damage by third bodies or secondarily to intrinsic materials

property changes, such as phase transformations in ceramic surfaces (Hara

guchi et al. 2001).

7.4.3 Other Wear Mechanisms

Three other mechanisms of wear are of concern in this chapter. The first is

abrasive wear — wear of a soft surface produced by a “plowing” of the

surface by large asperities in the harder countersurface. Although this is a

general mechanism in deliberately articulating interfaces, it may also play a

role in supposedly fixed interfaces in modular devices. In this case, such

wear is referred to as fretting and, in the case of metals, may have a corrosive

component. Abrasive wear clearly occurs in vivo, as will be seen in the later

discussion of the size of wear debris.

Corrosive wear of metals occurs secondarily to the physical removal of a

passive or protective surface layer. The exposed surface may be more sus

ceptible to wear, perhaps being softer and/or more chemically reactive, or

wear may be accelerated by the repetition of cycles of passive film formation

and mechanical removal. Figure 7.6 suggests this possibility graphically. In

this experiment, a rod of passivated F-75 cobalt-base alloy was pressed

against a dimple in a block of UHMWPE (Jablonski et al. 1986). After the

equilibrium potential has been established (in an aerated 0.9% saline solu

tion, reference: standard calomel electrode [S.C.E.]), a half sinusoidal stress,

with a peak value of 3.4 MPa, was applied during 40% of a 60° back-and

forth rocking cycle, at 36 cpm (cycles per minute). These conditions replicate

those thought to exist in the human hip joint prosthesis during slow walking.

The potential (vs. S.C.E.) became more negative, indicative of the flow of an

increased corrosion current. When motion ceased, the potential became less

negative, paralleling the (presumed) re-establishment of the passive layer.

The time to 50% of the maximum potential change (t 1/2 max) decreased as

the peak stress and the rate of rocking were increased. Similar results have

been reported in all metal total joint replacement

prostheses (Thull 1977).

The third and final type of wear to be considered is a surface fracture or

fatigue wear. Three routes lead to this process:

• Stresses produced by asperities may not exceed yield stress but may exceed the endurance limit for the softer of the material pair (generally a polymer in biomedical applications). This will lead to local fatigue failure of the softer surface and local fracture, “mud-caking,” or spalling. This process may be accelerated by diffusion and internal reaction of chemical species, such as oxygen, with polymers such as UHMWPE.

• Design of devices may produce a rigid support to the soft component. If this component is too thin in comparison to the magnitude of the contact stress and its apparent contact area, local stress elevation occurs (Bartel et al. 1985), contributing to fatigue failure, as observed previously. Although suggesting alternative mechanisms, Dowling et al. (1978) were some of the first workers to observe such polymer surface failure in UHMWPE/metal hip prostheses after 8 years or more of implantation.

• Free particles, perhaps adventitial (e.g., bone or PMMA fragments), or fragments of incomplete or shed transfer films may roll between the moving surfaces. If these particles are relatively undeformable, they can easily generate stresses above the ultimate tensile strength of the surface, leading directly to surface cracking. As cracks join up, wear debris is released. This process is usually called “threebody” wear.

7.4.4 Evidence of Wear In Vivo

Wear is a considerable problem in vivo. Of the five heart valve poppets

studied and reported in Table 3.2, four showed signs of wear as evidenced

by strut grooves. These would be expected to have a profound effect on local

FIGURE 7.6

Effect of articulation on corrosive wear. (From Stone [Jablonski, J.E. et al., Trans. SFB, 9, 196,

1986], unpublished data.) Time (minutes) 0 2 4 6 8 10 12 14 -200 -300 -400 -500 -600 -700 rest potential equilibrium potential P o t e n t i a l (v s . S . C . E .) (m v) t 1/2 max on off simulator

hemodynamics and on valve closure. All 21 hip cups recovered after periods

of 14 to 159 months and studied by Dowling et al. (1978) showed signs of

adhesive (early) or fatigue (late) wear. Of these, nine showed evidence of

the formation of a secondary socket or bearing area, with resultant theoretical

effects on joint function (Dumbleton et al. 1984). As implant designs and

materials have improved, wear rates in vivo have generally declined, but the

majority of articulating components retrieved after service in vivo show signs

of wear.

However, of more importance may be the formation of wear debris. Par

ticulate materials usually elicit different host responses than bulk materials

do. The observed cellular response is frequently different in nature (see

Section 8.2.2) and far more vigorous than to comparable bulk materials.

7.4.5 Size of Wear Debris

Rabinowicz (1976) discussed a criterion for predicting the diameter of wear

particles produced by adhesive wear processes: (7.4)

where

d = diameter of wear particle

W 12 = surface energy of adhesion between materials 1 and 2

p = hardness of wearing surface

Similar relationships for abrasive wear and for stress concentration phenom

ena would suggest that hardness is the key parameter in determining typical

wear debris particle size. Because the elastic modulus, E, is a good estimator

of the hardness, p, one would expect particle diameter, d, to vary inversely

with E.

Although Rabinowicz suggests that Equation 7.4 correlates well with

observation (presumably in predominantly adhesive wear situations in vitro),

broad ranges of wear debris particle sizes from submicron to hundreds of

microns in principle dimension are seen in biomedical applications. Savio

et al. (1994) conducted an extensive literature survey of debris associated

with total joint replacements, comparing reports of findings at revision, at

autopsy, during in vitro simulator testing, and, finally, during attempts to

reproduce wear debris by other means for host response testing. Polymeric

particles exhibit the largest absolute size as well as the largest size range;

ceramic particles show much smaller sizes and quite small size ranges.

Metals display an intermediate size range, with great differences in shape

among different alloys and situations. d W p = ×6 10 4 12

At the time of this literature study, it was not appreciated that very small

particles below the resolving power of optical microscopy (≈0.25 μm) are

present under many circumstances. Even in vitro wear and joint simulator

studies failed to detect the presence of such ultrafine particles due to the

extensive use of nuclear pore filters with a minimum pore size of 0.22 μm.

More recently, it has come to be appreciated that such small particles may

constitute a significant portion of the volume and the vast majority of the

number of any species of wear debris.

Figure 7.7 compares polymeric wear debris, generated by cobalt-base

alloy/UHMWPE wear pairs in a size range less than 2.0 μm in maximum

dimension, extracted from capsular tissue recovered during total hip and

total knee replacement revision surgery (Shanbhag et al. 1994). Note that,

although essentially all THR-associated debris observed in this study are

less than 2 μm in major dimension, only ~80% of TKR-associated debris is

this small. Similarly, the median major dimension of THR debris is < that of

TKR debris (0.45 vs. 1.10 μm). The differences in

distribution may well reflect

the differences in dominate wear mechanisms in the two types of devices,

as well as differences in regional transport away from the two joints. Finally,

comparison with the size distribution observed in a common resin precursor

of polyethylene suggests that many of the very small particles (<0.25 μm)

may be released by a fatigue mechanism rather than formed by adhesion or

abrasion processes. Note that pre-1990 studies of wear debris tend to under

estimate the prevalence of submicron size particles due to the widespread

use of 0.22-μm pore size filters.

FIGURE 7.7

Cumulative percentile distributions of polymeric wear debris. (From Shanbhag, A.S. et al., J.

Bone Joint Surg., 76B, 60, 1994, and personal communication, A.S. Shanbhag.) Major Dimension (μm) C u m u l a t i v e % 0 0.5 1.0 1.5 2.0 0 20 40 60 80 100 D = 1.10D = 0.45 THR TKR 50

The finding of wear debris particles, in implant sites or in regional lymph

nodes where they were deposited by phagocytosis and transport, during

revision surgery or at autopsy, is quite variable. This suggests that several

different wear processes are taking place simultaneously and that the

mechanical and environmental details of each application influence the types

of particles produced.

Finally, it should be pointed out that no animal or clinical study to date

has shown a good correlation between wear loss of an articulating implant

component and a volumetric estimate of wear debris in the tissues of the

experimental subject. This is due to a number of factors:

• Systemic distribution of particles (previously referred to)

• Dissolution of metallic debris

• Deformational changes in polymeric components (creep, fluid absorption, etc.)

Thus, estimates of wear from examination of implants probably provide only

upper bounds, and examination of tissues provides unrealistic lower bounds

on wear rates. Carefully conducted in vitro wear testing with appropriate

mechanical conditions and lubricants is required to measure actual wear

rates with any degree of certainty.

7.4.6 Anomalous Wear

One final comment is in order. One normally thinks of wear in terms of a

harder material wearing away a softer material. However, ample evidence

suggests that the reverse can occur. In natural tissues, it is observed that soft

tissues, such as tendons, moving over bone will rapidly form grooves while

appearing unchanged. This may reflect dynamic remodeling

but may also

involve a direct wear process of the harder bone by the softer tendon. Gent

and Pulford (1979) have shown a similar situation in the wear, in vitro, of

steel and bronze alloys by a variety of elastomers. Obviously, no dynamic

remodeling is possible here. The mechanism proposed is the formation of

active radicals on the elastomer surface by mechanical cleavage, followed

by chemical attack of the metal surface by these active sites. The enhance

ment of the effect by the exclusion of oxygen seems to support such a

mechanism. The evidence discussed in Section 4.10 for the participation of

amino acids in corrosion processes certainly suggests that one should con

sider the possibility of such anomalous wear processes when implant mate

rials move in contact with biological materials.

7.5 Conclusions

Frictional restraint to relative motion of device components and the associ

ated wear, releasing particulate debris, are inherent in the nature of materials.

Careful material selection and component design can minimize but not elim

inate these phenomena in biomedical devices fabricated from present biom

aterials. Increased knowledge of the mechanistic details of friction and wear

phenomena in these applications can be expected to produce improved

performance. However, it may be the case that accumulation of wear debris

and the host response to such accumulation will prove to be the ultimate

limitation on the useful lifetime of articulating biomedical devices, such as

total joint replacements. With this in mind, the next section of this book

considers host response to biomaterials and their degradation products.

Bartel, D.L. et al., The effect of conformity and plastic thickness on contact stresses in metal-backed plastic implants, J. Biomech. Eng., 107, 193, 1985.

Dintenfass, L., Lubrication in synovial joints: a theoretical analysis, J. Bone Joint Surg., 45A, 1241, 1963.

Dörre, E., Beutler, H. and Geduldig, D., The properties required of bioceramics for artificial joints (author's transl.), Arch. Orthop. Unfall.-Chir., 83, 269, 1975.

Dowling, J.M. et al., The characteristics of acetabular cups worn in the human body, J. Bone Joint Surg., 60B, 375, 1978.

Dumbleton, J.H. and Black, J., Some long-term complications, in Complications of Total Hip Replacement, Ling, R.S.M. (Ed.), Churchill Livingstone, Edinburgh, 1984, 212.

Galante, J.O. and Rostoker, W., Wear in total hip prostheses. An experimental evaluation of candidate materials, Acta Orthop. Scand. (Suppl. 145), 1973.

Gent, A.N. and Pulford, C.T.R., Wear of metal by rubber, J. Mater. Sci., 14, 1301, 1979.

Hamrock, B.J. and Dowson, D., Ball Bearing Lubrication. The Elastohydrodynamics of Elliptical Contacts, John Wiley & Sons, Inc., New York, 1981.

Haraguchi, K. et al., Phase transformation of a zirconia ceramic head after total hip arthroplasty, J. Bone Joint Surg., [Br.] 83B, 996, 2001.

Hills, B.A. and Butler, B.D., Surfactants identified in synovial fluid and their ability to act as boundary lubricants, Ann. Rheu. Dis., 43, 641, 1984.

Jablonski, J.E., Stone, J. and Black, J., The effect of articulation on the corrosion potential of cobalt-chromium alloy in vitro, Trans. SFB, 9, 196, 1986.

Kurtz, S.M., Muhlstein, C.L. and Edidin, A.A., Surface morphology and wear mechanisms of four clinically relevant biomaterials after hip simulator testing, J. Biomed. Mater. Res., 52, 447, 2000.

Lentner, C. (Ed.), Geigy Scientific Tables, Vol. 1, Ciba-Geigy, Basle, 1981.

Levick, J.R., Synovial fluid and trans-synovial flow in stationary and moving normal joints, in Joint Loading, Helminen, H.J., Kiviranta, I.A., Säämänen, -M., Tammi, M., Paukkonen, K. and Jurvelin, J. (Eds.), Wright, Bristol, 1987, 149.

McKellop, H. et al., Wear characteristics of UHMW polyethylene: a method for accurately measuring extremely low wear rates, J. Biomed. Mater. Res., 12, 895, 1978.

Rabinowicz, E., Wear, Mater. Sci. Eng., 25, 23, 1976.

Savio, J.A., III, Overcamp, L.M. and Black, J., Size and shape of wear debris, Clin. Mater., 15, 101, 1994.

Shanbhag, A.S. et al., Composition and morphology of wear debris in failed uncemented total hip replacement arthroplasty, J. Bone Joint Surg., 76B, 60, 1994.

Thull, R., The long-term stability of metallic materials for use in joint endoprostheses, Med. Prog. Tech., 5, 103, 1977.

Wang, A., Essner, A. and Schmidig, G., The effects of lubricant composition on in vitro wear testing of polymeric acetabular components, J. Biomed. Mater. Res. Part B: Appl. Biomater., 68B, 45, 2004.

Weightman, B. et al., Lubrication mechanism of hip joint replacement prostheses, J. Lubric. Tech., 94, 131, 1972.

Woodman, J.L. et al., Isolation of lubricating fraction from human synovial fluid after total-hip implantation, Trans. ORS, 2, 13, 1977.

Wright, V. (Ed.), Lubrication and Wear in Joints, J.B. Lippincott Company, Philadelphia, 1969.

Affatato, S. et al., Wear behavior of cross-linked polyethylene assessed in vitro under severe conditions, Biomaterials, 20, 3259, 2005.

Bartel, D.L., Bicknell, V.L. and Wright, T.M., The effect of conformity, thickness, and material on stresses in ultrahigh molecular weight components for total joint replacement, J. Bone Joint Surg., 68A, 1041, 1986.

Bayer, R.G., Engineering Design for Wear, Marcel Dekker, New York, 2004.

Bayer, R.G. and Ruff, A.W. (Eds.), Tribology. Wear Test Design and Application, STP 1247, American Society for Testing and Materials, Philadelphia, 1993.

Bowden, F.P. and Tabor, D., The Friction and Lubrication of Solids, Oxford University Press, Oxford, 2001.

Bradgon, C.R. et al., Third-body wear of highly cross-linked polyethylene in a hip simulator, J. Arthrop., 18(5), 553, 2003.

Davies, D.V., Synovial fluid as a lubricant, Fed. Proc., 25, 1069, 1966.

Divakar, R. and Blau, P.J., (Eds.), Wear Testing of Advanced Materials, STP 1167, American Society for Testing and Materials, Philadelphia, 1992.

Dumbleton, J.H., Tribology of Natural and Artificial Joints, Elsevier, Amsterdam, 1981.

Freeman, M.A.R., Swanson, S.A.V. and Heath, J.C., Study of the wear particles produced from cobalt-chromium-molybdenum-manganese total joint replacement prostheses, Ann. Rheum. Dis. (Suppl.), 28, 29, 1969.

Good, V.D., Clarke, I.C. and Anissian, A., Water and bovine serum lubrication compared in simulator PTFE/CoCr wear model, J. Biomed. Mater. Res., 33, 275, 1996.

Hall, R.M. and Unsworth, A., Friction in hip prostheses, Biomaterials, 18, 1017, 1997.

Heisel, C., Silva, M., and Schmalzried, T.P., Bearing surface options for total hip replacement in young patients, AAOS Instruct. Course Lecs., 53, 49, 2004.

Hutchins, I.M., Tribology. Friction and Wear of Engineering Materials, CRC Press, Boca Raton, FL, 1992.

Howell, J.R. et al., In vivo surface wear mechanisms of femoral components of cemented total hip arthroplasties, J. Arthroplast., 19, 88, 2004.

Jacobs, J.J. and Craig, T.L. (Eds.), Alternate Bearing Surfaces in Total Joint Replacement, ASTM STP 1346, ASTM, West Conshohocken, PA, 1998.

Lazennec, J.-Y. and Dietrich, M., (Eds.), Bioceramics in Joint Arthroplasty, 9th BIOLOX ® Symp. Proc., Steinkopf, Darmstadt, 2004.

Lee, L.-H. (Ed.), Polymer Wear and Its Control. ACS Symposium Series 287, American Chemical Society, Washington, D.C., 1985.

Ludema, K.C., Friction, Wear, and Lubrication, CRC Press, Boca Raton, FL, 1996.

Mears, D.C. et al., Ferrographic analysis of wear particles in arthroplastic joints, J. Biomed. Mater. Res., 12, 867, 1978.

McCutcheon, C.W., Lubrication of joints, in The Joints and Synovial Fluid, Vol. I., Sokoloff, L. (Ed.), Academic Press, New York, 1978, 437.

McKellop. H.A., Bearing surfaces in total hip replacements: state of the art and future developments, AAOS Instruc. Course Lec., 50, 165, 2001.

Rieker, C., Oberholzer, S. and Wyss, U. (Eds.), World Tribology Forum in Arthroplasty, Hans Huber, Bern, SW, 2001.

Schmalzried, T.P., Dorey, F.J. and McKellop, H. The multifactorial nature of polyethylene wear in vivo, J. Bone Joint Surg., 80A, 1234, 1998.

Semlitsch, M. and Willert, H.-G., Implant materials for hip endoprostheses: old proofs and new trends, Arch. Orthop. Trauma Surg., 114, 61, 1995.

Streichler, R.M. et al., Metal-on-metal articulation for artificial hip joints: laboratory study and clinical results, Proc. Instn. Mech. Engs., 210, 223, 1996.

Torrance, A.A., A method for calculating boundary friction and wear, Wear, 258, 924, 2005.

Walker, P.S. and Bullough, P.G., The effects of friction and wear in artificial joints, Ortho. Clin. N. Am., 4(2), 275, 1973.

Weightman, B., Frication, lubrication, and wear, in The Scientific Basis of Joint Replacement, Swanson, S.A.V. and Freeman, M.A.R. (Eds.), John Wiley & Sons, New York, 1977, 46.

Wright, T.M. and Goodman, S.B. (Eds.), Implant Wear: The Future of Total Joint Replacement, American Academy of Orthopedic Surgeons, Oakbrook, 1996.

Yust, C.S. and Bayer, R.G. (Eds.), Selection and Use of Wear Tests for Ceramics, STP 1010, American Society for Testing and Materials, Philadelphia, 1988. 125

Interpart 1

Implant Materials: Properties

I1.1 Introduction

The preceding discussions concerning material response have necessarily

been generic; that is, they have largely treated biomaterials by classes related

to their predominant chemical bond type (and resulting physical properties)

rather than dealing with the response of a particular, specific composition

of material to the biological environment. This is how it should be because

the details of such response depend upon the composition

(including impu

rities) of the specific material, the methods by which it is fabricated and

finished, the device application in which it is used, the animal and/or clinical

model in which it is evaluated, etc. The professional literature on material

response is broad, so much of the information needed to make a preliminary

selection based upon material response is usually available.

However, before such a selection may be made, a more fundamental ques

tion must be answered: does the material meet the physical requirements of

the design? Again, this is a complex problem, requiring a well-structured

design process for successful solution. This and related issues of design are

dealt with in Chapter 21. In this interpart, tables of basic materials' properties

are provided as an introduction to the broader issue of materials selection.

The reader must be warned that most properties tabulated here are nom

inal or typical properties. Materials specifications, whatever their source,

usually permit a range of compositions and processing conditions; in addi

tion, the choice of starting materials (feed stocks, master blends, etc.) may

also affect final properties, particularly of polymers, fibers, and composites.

Therefore, reference should be made to original sources (as

provided in the

position, fabrication, and test conditions producing the values or ranges

cited.

The properties tabulated are density and typical hardness, when reported,

and those mechanical parameters that may be obtained from a conventional

stress–strain curve. Standards, such as those produced by the ASTM Inter

national (American Society for Testing and Materials), BSI (British Standards

Institute), ANSI (American National Standards Institute), and ISO (Interna

tional Standards Organization) are cited when relevant.* However, whether

they are consensus or regulatory in nature, standards most often describe

minimum requirements; properties of actual manufactured materials fre

quently exceed these values in general and in the case of specific production

lots. Other properties, such as fatigue endurance limit, coefficients of friction

(for material pairs), workability parameters, etc., may be of equal or greater

importance in material selection and should be sought out during the design

process.

It should be remembered that high performance requirement materials

applications, such as medical and surgical devices and implants, require a

high degree of confidence in design and performance parameters. Thus,

some form of intrinsic property verification up to and, in some cases, includ

ing 100% nondestructive preuse “proof” testing is often required to assure

safe and effective material response in medical and surgical applications.

Finally, researchers and designers should remember that when a bioma

terial is used in a new design and/or for a new medical indication, it should

regain its status as a candidate material. That is, although successful perfor

mance under one set of conditions in one design provides useful knowledge,

it does not produce any guarantee of success in another situation. Therefore,

nothing in this interpart should be construed as qualifying or otherwise

recommending any material as safe and/or effective for use in any specific

medical or surgical instrument, implant, or device.

I1.2 Metals

Metallic biomaterials in common use are drawn from the stainless steels

(Table I.1), the cobalt-base “superalloys” (Table I.2), and the titanium/

titanium-base alloy system (Table I.3). Several refractory and precious met

als that have seen limited use in biomedical applications are covered in

Table I.4.

* Where feasible and relevant, the most recent revision of the standard has been cited in foot

notes to the tables. However, some values may have appeared in earlier versions and then been

deleted in revision.

TABLE I.1

Stainless Steels

Material:

Condition:

Source: F138 type 2 AN [1,2] F138 type 2 HF [1,2] F138 type 2 CW [1,2] F745 [3] F1314 An [1,4] F1314 CW [4] F1586 High N 2 AN [5] F1586 High N 2 CW [1,5]

Density(g/cm 3): 7.9 7.98 7.9 – 7.98 – – –

E (tensile) (GPa): 200 200 200 – 200 – – 200

Hardness (Hv): – – 350 – 205 – – ~365

σ 0.2% (MPa): 190 240 690 207 380 862 430 1000

σ UTS (MPa): 490 550 860 483 690 1035 740 1100

Elong. (min.%): 40 55 12 30 35 12 35 10

Notes: AN: annealed; CW: cold worked; HF: hot forged.

Sources: [1]: BSI 3531 (Part 2, Sec.2) (Amend. 2, 1983); [2]: ASTM F138-03; [3]: ASTM F745-00;

[4]: ASTM F1314-01; [5]: ASTM F 1586-02.

TABLE I.2

Cobalt-Base Alloys

Material:

Condition:

Source: Cast CoCrMo AN [1,2] Wrought CoCrMo AN [1,3]

Wrought CoNiCr Mo AN [4] Wrought CoNiCr MoWFe AN [5] Wrought CoCrMo CW [1,3] Wrought CoNiCr Mo CWA [4] Wrought CoNiCr MoWFe CW [5]

Density(g/cm 3): 7.8 9.15 — — 9.15 — —

E (tensile) (GPa): 200 230 — — 230 — —

Hardness (Hv): 300 240 — — 450 — —

σ 0.2% (MPa): 455 310 241–449 275 1000 1585 1310

σ UTS (MPa): 665 860 793–1000 600 1500 1795 1172

Elong. (min.%): 8 30 50 50 9 8 12

Material:

Condition:

Source: Wrought CoCrNiMoFe MoFe grade 2 CW [6] Wrought CoCrNi MoFe grade 2 CWA [6] Wrought CoCrMo AN [7] Wrought CoCrMo HW [7]

Density(g/cm 3): — — — —

E (tensile) (GPa): — — — —

Hardness (Hc): — — 25 28

σ 0.2% (MPa): — 1240–1450 517 700

σ UTS (MPa): 1515–1795 1860–2275 897 1000

Elong. (min.%): — 1–17 20 12

Notes: AN: annealed; CW: cold worked; CWA: cold worked, aged; HW: hot worked; Hv: Vickers hardness; Hc: Rockwell C hardness.

Sources: [1]: BSI 3531 (Part 2, Sec.4–5) (Amend. 2, 1983); [2]: ASTM F75-01; [3]: ASTM F90-86

01; [4]: ASTM F562-02; [5]: ASTM F563-00; [6]: ASTM F1058-02; [7]: ASTM F1537-00.

TABLE I.3

Titanium α–β and β Titanium-Base Alloys

Material:

Type:

Condition:

Source: Ti grade 1 – An [1,2] Ti grade 4 – AN [1,2] Ti3Al2.5V α–β AN [3,4] Ti6Al4V α–β AN [1,5] Ti6Al7Nb α–β HF [6,7] Ti6Al4V α–β HF [8] Ti5Al2.5 Fe α–β AN [9]

Density(g/cm 3): 4.5 4.5 4.51 4.4 4.52 4.4 4.45

E (tensile) (GPa): 127 127 105–120 127 105 127 –

Hardness (Hv): – 240–280 – 310–350 400 – –

σ 0.2% (MPa): 170 483 517–560 760–795 800 825–869 815

σ UTS (MPa): 240 550 621–650 825–860 900 895–930 965

Elong. (min.%): 24 15 15 8 10 6–10 16

Material:

Type:

Condition:

Source: Ti5Al2.5 Fe α–β HF [9] Ti12Mo 6Zr2Fe β AN [10,11] Ti13Nb 13Zr β AN [12,13] Ti13Nb 13Zr β QA [12–14] Ti15Mo β AN [15] Ti15Mo 3Nb0.3O 2 β AN [16] Ti35Nb 5Ta7Zr β AN [17]

Density(g/cm 3): 4.45 5.0 – – – 4.94 –

E (tensile) (GPa): – 74–85 79 77 – 82 55

Hardness (Hv): – 34–35∗ 26∗ 28∗ – – –

σ 0.2% (MPa): 900 897–1000 900 725 483–552 1020 547

σ UTS (MPa): 985 931–1060 1030 860 690–724 1020 597

Elong. (min.%): 13 12–22 15 8 12–20 – 19

Notes: ∗: Rockwell C; AN: annealed; HF: hot forged; QA: Water quenched, aged.

Sources: [1]: BSI 3531 (Part 2, Sec.6) (Amend. 2,1983); [2]: ASTM F67-00; [3]: ASTM F2146-01;

[4]: TIMET, Inc.; [5]: ASTM F136-96; [6]: IMI Titanium Ltd, 1989; [7]: ASTM F1295-01; [8]:

ASTM F1472-93; [9]: Borowy, K.-H. and Kramer, K.-H., in Titanium Science and Technology,

Vol. 2, Luterjering, G., Zwicker, U. and Bunk, W. (Eds.), Deutsche Gesell. f. Metallkunde e.

V., Obureresel, 1985, 1381; [10]: Wang, K. et al., in Beta Titanium Alloys in the 1990s, Eylon,

D., Boyer, R.R. and Koss, D.A. (Eds.), Min. Met. and Materials Society, New York, 1993, 49;

[11]: ASTM F1813-01; [12]: U.S. Patent 5,169,597; [13]: Davidson, J.A. et al., Bio-Med. Mater.

Eng., 4(3), 231, 1994; [14]: ASTM 1713-03; [15]: ASTM F2060-01; [16]: Long, M. and Rack,

H.J., Biomaterials, 19, 1621, 1998; [17]: Ahmed, T. et al., Proc. Inst. Metal. 8th World Titanium

Conf., 1996, 742.

I1.3 Polymers

The cautionary note previously sounded concerning the reliability of tabu

lated materials' properties applies especially to polymers. In the case of this

material class, four additional problems interfere with interpretation of data:

• All polymers are viscoelastic; therefore, mechanical property measurements depend upon the strain rate used in evaluation. Because viscoelastic materials generally become stiffer and less ductile as strain rates increase, testing rates should equal or exceed those expected to be encountered in service.

• Properties of engineering polymers are closely related to average molecular weight and molecular weight distribution as well as to curing conditions and time (thermosets) and fabrication temperatures and postfabrication heat treatment (thermoplastics).

• Postsynthesis processing and/or sterilization, especially by 60 Co γ or electron beam irradiation, may alter final properties of some materials. This is particularly true for ultra high molecular weight polyethylene, for which more than a dozen commercial grades with varying amounts of irradiation and postirradiation heat treatment are now available (Kurtz 2004).

TABLE I.4

Other Metals and Alloys

Material:

Condition:

Source: TaP An [1,2] TaP CW [1,2] Ti54.5 NiMA AN [3,4] Ti55.8 NiMA AN [3,4] PtP AN [1] Pt10 RhTC AN [1] Pt10 RhTC 75% CW [1] WP SN [1] Zr-2.5 Nb α-β CW/AN [5]

Density(g/cm 3): 16.6 16.6 6.5 6.5 21.5 20 20 19.3 6.64

E (tensile) (GPa): 186 186 28–41 41–75 147 — — 345 99

Hardness (Hv): — — — — 38–40 90∗ 165∗ 225 —

σ y (MPa): 140 345 — — — — — — 379

σ UTS (MPa): 205 515 1100 1070 135–165 310 620 125–140 552

Elong. (min.%): 20–30 2 10 10 35–40 35 2 ~0 16

Notes: AN: annealed; CW: cold worked; MA: memory alloy; P: pure (elemental); SN: sintered bar; TC: thermocouple alloy; ∗: Brinell hardness.

Sources: [1]: Metals Handbook, 8th ed., Vol. 1 (ASM, Metals Park, 1961); [2]: ASTM F 560-04; [3]:

ASTM F 2063-00; [4]: National Devices & Components, Inc.; [5] Wah Chang (Zircadyne 705

[contains Hf]); see ASTM B 351, F- standard pending.

• Many polymers are subject to possible oxidation during room temperature storage; therefore, the chronology of production of the material and of the device may affect final properties in clinical use.

The data are presented in two tables: Table I.5 for

thermosets and Table

I.6 for thermoplastics. Both types of polymers have important roles as bio

materials, although thermoplastics tend to be preferred due to the relatively

greater ease in fabricating them without low molecular weight leachable

components.

Finally, fatigue behavior of biomedical polymers, especially of PMMA

type “bone-cements,” is a sufficiently controversial subject that no data are

provided here. The reader is referred to the professional literature. TABLE I.5 Thermoset Resins Material: Condition: Source: EP CR [1] PMMA 10BaSO 4 24 h CR [2,3] PMMA; 24 h CR [3] PEU CR [4] PSU CR [5] SR HV [5,6] SR (HP) HV [6] Density(g/cm 3): 1.11–1.40 1.183 1.088 1.1 1.2 1.12–1.23 1.15 E (tensile) (GPa): 2.4 1.31 2.4–3.1 5.9∗ 3.7∗ <1.4∗ 2.4∗ Hardness (Sh. A): – – – 75 88 25–75 52 σ y(C) (MPa): – – 15.8 – – – – σ UCS (MPa): 100–170 70 69–125 – – – – σ UTS (MPa): 28–90 28–46 9.7–32 45 40 5.9–8.3 8.3–10.3 Elong. (min.%): 3–6 4.6 2.4–5.4 750 540 350–600 700 Notes: CR: room temperature cured; EP: epoxy; HV: heat vulcanized; PMMA: polymethyl methacrylate; SR: silicone rubber; HP: high performance; ∗: MPa. Sources: [1]: Modern Plastics Encylopedia, McGraw–Hill, New York, 1990; note: typical values; not specific medical grades; [2]: ASTM F 451-99a; [3]: Lautenschlager, E.P. et al., in Functional Behavior of Orthopedic Biomaterials, Vol. II, Ducheyne, P. and Hastings, G.W. (Eds.), CRC Press, Boca Raton, FL, 1984, 87; [4]: Boretos, J.W. and Pierce, W.S., J. Biomed. Mater. Res., 2, 121, 1968; [5]: Braley, S., J. Macromol. Sci.-Chem., A4(3), 529, 1970; see also ASTM F604-94 (withdrawn); [6]: Frisch, E.E., in Polymeric Materials and Artificial Organs, ACS Symp. 256, C.G. Gebelein (Ed.), American Chemical Society, Washington, D.C., 1984, 63.

I1.4 Ceramics

At room and body temperature, ceramic materials suitable for biomedical

applications possess negligible ductility; thus, no tensile

or elongation data

are included in Table I.7. Note that strength of ceramics depends very

strongly on density (as percent of ultimate) and grain size, so data on actual

commercial formulations must be sought for engineering use. Data are

provided only for some of the most common structural ceramics; no infor

mation is provided on resorbable or so-called bioactive ceramics due to

their variety and complexity. (See deGroot, 1983; Hench and Wilson, 1984;

and Manley, 1993.)

TABLE I.6

Thermoplastic Resins

Material:

Condition:

Source: PE (UHMW) MM [1] PE (UHMW) EX [1,2] PE (UHMW) CM [1–3] PE (UHMW) HC [3] PLA (STCP) CM [4] PMMA CM [5] PSF IM [6,7] PEEK IM [8]

Density(g/cm 3): 0.927–0.944 0.927–0.944 0.93–0.944 — — 1.186 1.23-1.25 1.28–1.32

E (tensile) (GPa): — 1.24 1.36 2.17 4–5 2.6-3.2 2.3–2.48 3–8.3*

Hardness (Sh. D): 60 60 62 66 — — — —

σ y (MPa): 19–21 19–28 19–29 28 — — 65–96 70

σ UCS (MPa): — — — — — 80–125 — —

σ UTS (MPa): 27–35 37–47 27–40 — 50–60 50–75 106* 90–152

Elong. (min.%): 300 250–300 350 230 2–3 2–10 20–75 4.9**

Notes: IM: injection molded; MM: molded, machined; EX: extruded; CM: compression molded; HC: high crystallinity; PE (UHMW): ultra high molecular weight polyethylene; PLA (STCP): polylactic acid stereo copolymer; PMMA: polymethyl methacrylate; PSF: polysulfone; ∗: flexural; ∗∗: at yield.

Sources: [1]: ASTM 648-00; [2]: Roe, R.-J. et al., J. Biomed. Mater. Res., 15, 209, 1981; [3]: Depuy

(1989); [4]: Christel, P. et al., in Proceedings of the 1st International Conference on Composites in

Biomedical Engineering, November 19–20, London. Imprint of Luton, Luton, 1985, p. 11/1; note:

resorbable; properties depend upon L/D ratio; [5]: Lautenschlager, E.P. et al., in Functional

Behavior of Orthopedic Biomaterials, Vol. II, Ducheyne, P. and Hastings, G.W. (Eds.), CRC Press,

Boca Raton, FL, 1984, 87; [6]: Dunkle, S.R., in Engineered Materials Handbook, Vol. 2: Engineering

Plastics, Dostal, C.A. (Ed.), American Society for Metals Int., Metals Park, 1988, 200; [7]: ASTM

F 702-98a; [8]: Lewis (1990); see also ASTM F 2026-02.

I1.5 Composites

Composites, or more properly composite materials, is a term that has come

to describe a wide range of engineered or designed materials. Mechanical

properties of composite materials depend upon the properties of the phases

(matrix and strengthening, or reinforcing, phase or phases) as well as on the

nature of the phase interfaces, their volume fractions, net porosity, and the

local and global arrangement of the reinforcing phases. This complexity

dictates an economy of action here because an entire volume

could be (and

has frequently been) devoted to the subject. Thus, as a brief guide, Table I.8

presents properties of some more common reinforcing phases useful in com

posite biomaterials design, and Table I.9 presents properties of a few repre

sentative composites that have been evaluated to some degree as

biomaterials.

TABLE I.7

Ceramic Materials

Material:

Condition:

Source: Al 2 O 3 HP [1,2] C LTI [3] C VT [3] C ULTI [3] ZrO 2 SHP [4,5]

Density (g/cm 3): 3.98 1.7–2.2 1.4–1.6 1.5–2.2 6.1

Grain size(μm): 1.8–4 30–40∗ 10–40∗ 8–15∗ <0.5

E (tensile) (GPa): 400–580 18–28 24–31 14–21 200

Hardness (Hv): 2300 150–250 150–200 150–250 1300

σ UFS (MPa): 550 280–560 70–210 350–700 1200

σ UCS (MPa): 4500 – – – –

Notes: HP: high purity; LTI: low-temperature isotropic; SHP: sintered, hot isostatic pressed (5% Y 2 O 3 stabilized); ULTI: ultra low temperature isotropic; VT: vitreous (glassy); ∗: angstroms.

Sources: [1]: CeramTec; [2]: ASTM F603-00; ISO 6474; [3]: various; compilation by Inter

medics Orthopedics (1983); [4]: Christel, P. et al., J. Biomed. Mater. Res., 23, 45, 1989; [5]:

Norton Demarquest; 6ASTM F 2393-04.

TABLE I.8

Reinforcing Phases

Material:

Condition:

Source: E-glass AN, CF [1,2] S-glass AN, CF [1,2] C-glass AN, CF [1,2] C∗ (low E) HT, CF [1] C∗ (High E) HT, CF [1] PA (K29) + CF [1] PA (K49) + CF [1] PA (K149) + CF [1]

Density (g/cm 3): 2.62 2.50 2.56 1.76 1.9 1.44 1.44 1.47

Diameter(μm): 3–20 3–20 3–20 7–8 7 12 12 12

E (tensile) (GPa): 72–81 85–89 69 230 390 83 131 286

σ UTS (MPa): 3450 4580 3000–5300 3300 2400 2800–3600 3600–4100 3400

Elong. (min.%): 4.9 5.7 4.8 1.4 0.6 4.0 2.8 2.0

Material:

Condition:

Source: Al 2 O 3 CF [1] Al 2 O 3- 48SiO 2 DF [1] SiO 2 CF [1] βSiC CF [1] αSiC WH [1] βSiC WH [1] BN CF [3] B 4 C WH [3]

Density (g/cm 3): 3.95 2.73 2.2 2.55 3.2 3.19 1.91 2.52

Diameter(μm): 20 2–3 9 10–15 0.6 0.1–0.5 7 —

E (tensile) (GPa): 379 100 69 180–200 690 400–700 90 483

σ UTS (MPa): 1380 1900 3450 2500–3200 6900 3000–14000 1380 13800

Notes: AN: annealed; CF: continuous fiber; DF: discontinuous fiber; WH: whisker; HT: heat treated; ∗: polyacrylonitrile (PAN) precursor; + : Kevlar™ (DuPont).

Sources: [1]: Composites, Engineered Materials Handbook, Vol. 1, ASM International, Metals Park,

1987; [2]: Lubin, G. (Ed.), Handbook of Composites, Van

Nostrand, New York, 1982; [3]: Schwartz,

M.M., Composite Materials Handbook, McGraw-Hill, New York, 1984.

TABLE I.9

Composite Materials

Material:

Condition:

Source: PMMA2C RT [1] C60SiC [2] C60SiC (5% por.) [3] CFRC [2] CFRC (7% por.) [3] EP12.5C ET [4] CFPSU [5] PE (UHMW)10C [6]

Density (g/cm 3): — 2.6 2.4 1.7 1.78 — — 0.98

E (tensile) (GPa): 5.52 100 80-90 140 40-58 14 110 1.94**

σ UCS (MPa): — 1000 250-370 800 230-320 — — 14.2

σ UTS (MPa): 38 220* 220-360* 800* 350-600 200* 1600* 22

Elong. (min.%): 0.7 <1 — >4 — — 1.3 150

Notes: PMMA: polymethyl methacrylate; RT: room temperature cured; ET: 70°C cured; CFRC: carbon fiber-reinforced carbon; CFPSU: continuous fiber carbon reinforced polysulfone; EP: epoxy; por.: open porosity; *: flexural strength; **: estimated.

Sources: [1]: Pilliar, R.M. et al., J. Biomed. Mater. Res., 10, 893, 1976; [2]: Brückmann, H. and

Hüttinger, K.J., Biomaterials, 1, 67, 1980; [3]: Christel, P. et al., J. Biomed. Mater. Res, Appl.

Biomater., 21(A2), 191, 1987; [4]: Hastings, G.W., Composites, 7, 193, 1978; [5]: Claes, L. et al.,

in Biological and Biomechanical Performance of Biomaterials, Christel, P., Meunier, A. and Lee,

A.J.C. (Eds.), Elsevier, Amsterdam, 1986, 81; [6]: Zimmer, 1978.

Ahmed, T. et al., A new low-modulus, biocompatibile titanium alloy, Proc. Inst. Metal. 8th World Titanium

Conf., 1996, 742.

Boretos, J.W. and Pierce, W.S., Segmented polyurethane: a polyether polymer, J. Biomed. Mater. Res., 2, 121, 1968.

Borowy, K.-H. and Kramer, K.-H., On the properties of a new titanium alloy (TiAl5Fe2.5) as implant material, in Titanium Science and Technology, Vol. 2, Luterjering, G., Zwicker, U. and Bunk, W. (Eds.), Deutsche Gesell. f. Metallkunde e. V., Obureresel, 1985, 1381.

Braley, S., The chemistry and properties of the medical-grade silicones, J. Macromol. Sci.-Chem., A4(3), 529, 1970.

Brückmann, H. and Hüttinger, K.J., Carbon, a promising material in endoprosthetics. Part 1: the carbon materials and their mechanical properties, Biomaterials, 1, 67, 1980.

Christel, P. et al., Mechanical properties and short-term in-vivo evaluation of yttrium-oxide partially stabilized zirconia, J. Biomed. Mater. Res., 23, 45, 1989.

Christel, P. et al., Development of a carbon-carbon hip prosthesis, J. Biomed. Mater. Res, Appl. Biomater., 21(A2), 191, 1987.

Christel, P. et al., PGA (polyglycolic acid)-fiber-reinforced-PLA (polylactic acid) as an implant material for bone surgery, in Proceedings of the 1st International Conference on Composites in Biomedical Engineering, November 19–20, London. Imprint of Luton, Luton, 1985, p. 11/1.

Claes, L., Hüttner, W. and Weiss, R., Mechanical properties of carbon-fiber reinforced polysulfone plates for internal fracture hardware, in Biological and Biomechanical Performance of Biomaterials, Christel, P., Meunier, A. and Lee, A.J.C. (Eds.), Elsevier, Amsterdam, 1986, 81.

Composites, Engineered Materials Handbook, Vol. 1, ASM International, Metals Park, OH, 1987.

deGroot, K. (Ed.), Bioceramics of Calcium Phosphate, CRC Press, Boca Raton, FL, 1983.

Davidson, J.A. et al., New surface-hardened, low modulus, corrosion-resistant Ti13Nb-13Zr alloy for total hip arthroplasty, Bio-Med. Mater. Eng., 4(3), 231, 1994.

Depuy, Warsaw, IN, 1989.

Dunkle, S.R., Polysulfones (PSU), in Engineered Materials Handbook, Vol. 2: Engineering Plastics, Dostal, C.A. (Ed.), American Society for Metals Int., Metals Park, 1988, 200.

Frisch, E.E., Silicones in artificial organs, in Polymeric Materials and Artificial Organs, ACS Symp. 256, Gebelein, C.G. (Ed.), American Chemical Society, Washington, D.C., 1984, 63.

Metals Handbook, 8th ed., Vol. 1, ASM, Metals Park, OH, 1961.

Hastings, G.W., Carbon fiber composites for orthopedic implants, Composites, 7, 193, 1978.

Hench, L.L. and Wilson, J., Surface-active biomaterials, Science, 226, 630, 1984.

Kurtz, S.M., The UHMWPE Handbook: Ultra-High Molecular Weight Polyethylene in Total Joint Replacement, Academic Press (Elsevier), New York, 2004.

Lautenschlager, E.P., Stupp, S.I. and Keller, J.C., Structure and properties of acrylic bone cement, in Functional Behavior of Orthopedic Biomaterials, Vol. II, Ducheyne, P. and Hastings, G.W. (Eds.), CRC Press, Boca Raton, FL, 1984, 87.

Lewis, G., Selection of Engineering Materials, Prentice Hall, Englewood Cliffs, NJ, 1989.

Long, M. and Rack, H.J., Titanium alloys in total joint replacement — a materials science perspective, Biomaterials, 19, 1621, 1998.

Lubin, G. (Ed.), Handbook of Composites, Van Nostrand, New York, 1982.

Manley, M.T., Introduction, in Hydroxyapatite Coatings in Orthopedic Surgery, Geesink, R.G.T. and Manley, M.T. (Eds.), Raven Press, New York, 1993, 1.

Modern Plastics Encylopedia, McGraw-Hill, New York, 1995.

Pilliar, R.M. et al., Carbon fiber-reinforced bone cement in orthopedic surgery, J. Biomed. Mater. Res., 10, 893, 1976.

Roe, R.-J. et al., Effect of radiation sterilization and aging on ultrahigh molecular weight polyethylene, J. Biomed. Mater. Res., 15, 209, 1981.

Schwartz, M.M., Composite Materials Handbook, McGraw-Hill, New York, 1984.

Wang, K., Gustavson, L. and Dumbleton, J., The characterization of Ti-12Mo-6Zr-2Fe — a new biocompatible titanium alloy developed for surgical implants, in Beta Titanium Alloys in the 1990s, Eylon, D., Boyer, R.R. and Koss, D.A. (Eds.), Min. Met. and Materials Society, New York, 1993, 49.

Zimmer, Nonauthored technical material, Warsaw, IN, 1978.

2004 Annual Book of ASTM Standards, Vol. 13.01, Medical Devices, ASTM International, West Conshohocken, PA, 2004.

Ashby, M., Materials Selection in Mechanical Design, 2nd ed., Butterworth-Heinemann, London, 1999.

Ashby, M. and Johnson, K., Materials and Design: The Art and Science of Material Selection in Product Design, Butterworth-Heinemann, London, 2002.

Black, J. and Hastings, G. (Eds.), Handbook of Biomaterial Properties, Chapman & Hall, London, 1998.

Boretos, J.W., Concise Guide to Biomedical Polymers, Charles C Thomas, Springfield, IL, 1973.

Boutin, P. et al., The use of dense alumina-alumina ceramic combination in total hip replacement, J. Biomed. Mater. Res., 22, 1203, 1988.

Brown, S.A. and Lemons, J.A. (Eds.), Medical Applications of Titanium and its Alloys, STP 1272. ASTM, West Conshohocken, PA, 1992

Catledge, S.A. et al., Nanostructured ceramics for biomedical implants, J. Nanosci. Nanotechnol., 2(3-4), 293, 2002.

Cowin, S.C., Bone Mechanics Handbook, 2nd ed., CRC Press, Boca Raton, 2002.

Disegi, J.A., Kennedy, R.L. and Pilliar, R. (Eds.), Cobalt-Base Alloys for Biomedical Applications, STP 1365, ASTM, West Conshohocken, PA, 1999.

Donachie, M.J., Jr. (Ed.), Superalloys Source Book, ASM Int., Metals Park, 1984.

Donachie, M.J., Jr. (Ed.), Titanium: A Technical Guide, ASM Int., Metals Park, 1984.

Epinette, J.-L. and Manley, M.T. (Eds.), Fifteen Years of Clinical Experience with Hydroxyapatite Coatings in Joint Arthroplasty, Springer-Verlag, Paris, 2004.

Fisher, L.W., Selection of Engineering Materials and Adhesives, Taylor & Francis, Boca Raton, FL, 2005.

Ito, A. et al., In vitro biocompatibility, mechanical properties, and corrosion resistance of Ti-Zr-NB-TA-PD and Ti-Sn-Nb-Ta-Pd alloys, J. Biomed. Mater. Res., 29, 893, 1995.

Kingery, W.D., Introduction to Ceramics, 2nd ed., John Wiley & Sons, New York, 1976.

Kokubo T. et al., Bioactive metals: preparation and properties, J. Mater. Sci. Mater. Med., 15(2), 99, 2004.

Lambda, N.M.K., Woodhouse, K.A. and Cooper, S.L. (Eds.), Polyurethanes in Biomedical Applications. CRC Press, Boca Raton, FL, 1997.

Mishra, A.K. et al., Ti13Nb13Zr: A new low modulus, high strength, corrosion resistant, near beta alloy for orthopaedic implants. In: Eylon, D., Boyer, R.R. and Koss, D.A., (Eds.), Beta Titanium Alloys in the 1990's. Warrendale, PA: The Minerals, Metals and Materials Society, 1993, 61.

Pelton, A.R., Stoeckel, D. and Duerig, T.W., Medical uses of nitinol, Mater. Sci. For., 327-328, 63, 2000.

Portnoy, R.C. (Ed.), Medical Plastics: Degradation, Resistance, and Failure Analysis, Plastics Design Library, Norwich, CT, 1998.

Ratner, B.D. and Bryant, S.J., Biomaterials: where we have been and where we are going, Annu. Rev. Biomed. Eng., 6, 41, 2004.

Ravglioli, A. and Karjewski, A. Bioceramics and the Human Body, Kluwer Academic, London, 1992.

Santavirta S. et al., Alternative materials to improve total hip replacement tribology, Acta Orthop. Scand., 74(4), 380, 2003.

Semlitsch, M., Staub, F. and Weber, H., Titanium–aluminium–niobium alloy development for high-strength surgical implants, Biomed. Technik, 30, 334, 1985.

Shackelford, J.F., Alexander, W. and Park, J.S. (Eds.), CRC Practical Handbook of Materials Selection, CRC Press, Boca Raton, FL, 1995.

Szycher, M. (Ed.), Biocompatible Polymers, Metals, and Composites, Technomic, Lancaster, PA, 1983.

Toni, A. et al., Ceramics in total hip arthroplasty, in Encyclopedic Handbook of Biomaterials and Bioengineering, Part A, Vol. 1, Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, 1501.

Willert, H.-G., Buchorn, G.H. and Eyerer, P. (Eds.), Ultra-High Molecular Weight Polyethylene as a Biomaterial in Orthopedic Surgery, Hogrefe & Huber, Toronto, 1990.

Host Response: Biological Effects of Implants

Albrektsson, T. et al., The interface zone of inorganic implants in vivo: titanium implants in bone, Ann. Biomed. Eng., 11, 1, 1983.

Anderson, J.M. and Miller, K.M., Biomaterial biocompatibility and the macrophage, Biomaterials, 5, 5, 1984.

Antti-Poika, I. et al., Hip arthroplasty infection, Acta Orthop. Scand., 61, 163, 1990.

Aronson, A.S., Hansson, L.I. and Selvik, G., Roentgen stereophotogrammetry for determination of bone growth. Comparison with the tetracycline method, Acta Radiol. Diagn. (Stockh.), 18, 87, 1977.

Blaha, J.D. et al., The use of Septopal (polymethylmethacrylate beads with gentamicin) in the treatment of chronic osteomyelitis, Instruct. Course Lect., 39, 509, 1990.

Blomgren, G., Hematogenous infection of total joint replacement, Acta Orthop. Scand., 52(Suppl. 187), 1, 1981.

Brooks, R.A., Wimhurst, J.A. and Rushton, N., Endotoxin contamination of particles produces misleading inflammatory cytokine responses from macrophages in vitro, J. Bone Joint Surg., 84B, 295, 2002.

Chambers, T.J., Fusion of macrophages following simultaneous attempted phagocytosis of glutaraldehyde-fixed red blood cells, J. Pathol., 122, 71, 1977.

Chesmel, K.D. et al., Cellular response to chemical and morphological aspects of biomaterial surfaces: II. The biosynthetic and migratory response of bone cell populations, J. Biomed. Mater. Res., 29, 1101, 1995.

Cordero, J., Munuera, L. and Folgueira, M.D., Influence of metal implants on infection, J. Bone Joint Surg., 76B, 717, 1994.

Elson, R.A. et al., Bacterial infection and acrylic cement in the rat, J. Bone Joint Surg., 59B, 452, 1977.

Frank, M.M., The complement system in host defense and inflammation, Rev. Infect. Dis., 1, 483, 1979.

Goodman, S.B. et al., Pharmacologic modulation of periprosthetic osteolysis, Clin. Orthop. Rel. Res., 430, 39, 2005.

Graham, J.A. et al., Effect of trace metals on phagocytosis by alveolar macrophages, Infect. Immunol., 11, 1278, 1975.

Gristina, A.G., Adhesive colonization of biomaterials and antibiotic resistance, Science, 237, 1588, 1987.

Gristina, A.G. and Costerton, J.W., Bacterial adherence and the glycocalyx and their role in musculoskeletal infection, Ortho. Clin. N. Am., 15, 517, 1984.

Howie, D.W. et al., The response to particulate debris, Orthop. Clin. N. Am., 24(4), 571, 1993.

Kiechel, S.F. et al., The role of implant porosity on the development of infection, Surg. Gynecol. Obstet., 144, 58, 1977.

Krouskop, T.A. et al., Bacterial challenge study of a porous carbon percutaneous implant, Biomaterials, 9, 398, 1988.

Mariano, M. and Spector, W.G., The formation and properties of macrophage polykaryons (inflammatory giant cells), J. Pathol., 113, 1, 1974.

Masui, T., Expression of inflammatory cytokines, RANKL and OPG induced by titanium, cobalt-chromium and polyethylene particles, Biomaterials, 26, 1695, 2005.

McNamara, A. and Williams, D.F., Scanning electron microscopy of the metal-tissue interface. I. Fixation methods and interpretation of results, Biomaterials, 3, 160, 1982.

Merritt, K., Shafer, J.W. and Brown, S.A., Implant site infection rates with porous and dense materials, J. Biomed. Mater. Res., 13, 101, 1979.

Petty, W. et al., The influence of skeletal implants on incidence of infection, J. Bone Joint Surg., 67A, 1236, 1985.

Petty, W., Spanier, S. and Shuster, J.J., Prevention of infection after total joint replacement, J. Bone Joint Surg., 70A, 536, 1988.

Rae, T., A study on the effects of particulate metals of orthopedic interest on murine macrophages in vitro, J. Bone Joint Surg., 57B, 444, 1975.

Remes, A. and Williams, D.F., Chemotaxis and the inhibition of chemotaxis of human neutrophils in response to metal ions, J. Mater. Sci.: Mater. Med., 1, 26, 1990.

Styles, J.A. and Wilson, J., Comparison between in vitro toxicity of two novel fibrous mineral dusts and their tissue reactions in vivo, Ann. Occup. Hyg., 19, 63, 1976.

Teitelbaum, S.L., Bone resorption by osteoclasts, Science, 289, 1504, 2000.

Trampuz, A. et al., Molecular and antibiofilm approaches to prosthetic joint infection, Clin. Orthop. Rel. Res., 414, 69, 2003.

Urban, R.M. et al., Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement, J. Bone Joint Surg., 82(4), 457, 2000.

Ward, P.A., Goldschmidt, P. and Greene, N.D., Suppressive effects of metal salts on leukocyte and fibroblastic function, J. Reticuloendothel. Soc., 18, 313, 1975.

Weinberg, E.D., Iron and susceptibility to infectious disease, Science, 184, 952, 1974.

Willert, H.-G. and Semlitsch, M., Reactions of the articular capsule to wear products of artificial joint prostheses, J. Biomed. Mater. Res., 11, 157, 1977.

Wood, N.K., Kaminski, E.J. and Oglesby, R.J., The significance of implant shape in experimental testing of biological materials: disc vs. rod, J. Biomed. Mater. Res., 4, 1, 1970.

Younger, A.S. et al., The outcome of two-stage arthroplasty using a custom-made interval spacer to treat the infected hip, J. Arthoplasty, 12(6), 615, 1997.

Ziats, N.P., Miller, K.M. and Anderson, J.M., In vitro and in vivo interactions of cells with biomaterials, Biomaterials, 9, 5, 1988.

Aderem, A., How to eat something bigger than your head,

Cell, 110, 5, 2002.

Bauer, T.W., Particles and peri-implant bone resorption, Clin. Orthop. Rel. Res., 405, 138, 2002.

Berry C.L. (Ed.), The Pathology of Devices, Springer-Verlag, Berlin, 1994.

Bisno, A.L. and Waldvogel, F.A., Infections Associated with Indwelling Medical Devices, American Society of Microbiologists, Washington, D.C., 1989.

Brandwood, A. et al., Phagocytosis of carbon particles by macrophages in vitro, Biomatials, 13, 646, 1992.

Cameron, H.U. (Ed.), Bone Implant Interface, Mosby-Year Book, St. Louis, 1994.

Chang, C.C. and Merritt, K., Infection at the site of implanted materials with and without preadhered bacteria, J. Orthop. Res., 12, 526, 1994.

Coleman, D.L., King, R.N. and Andrade, J.D., The foreign body reaction: a chronic inflammatory response, J. Biomed. Mater. Res., 8, 199, 1974.

Costerton, J.W. et al., Microbial biofilms, Annu. Rev. Microbiol., 49, 711, 1995.

Craig, M.R. et al., A novel total knee arthroplasty infection model in rabbits, J. Orthop. Res., 23(5), 1100, 2005.

Duffield, J.S., The inflammatory macrophage: a story of Jekyll and Hyde, Clin. Sci., 104, 27, 2003.

Delle Valle, C.J., Zuckerman, J.D. and Di Cesare, P.E., Periprosthetic sepsis, Clin. Orthop. Rel. Res., 420, 26, 2004.

Ellingsen, J.F. and Lyngstadaas, S.P., Bio-implant Interface: Improving Biomaterials and Tissue Reactions, CRC Press, Boca Raton, 2003.

Esterhai, J.L., Jr., Gristina, A.G. and Poss, R. (Eds.), Musculoskeletal Infections, American Academy of Orthopedic Surgeons, Park Ridge, IL, 1992, 153-300.

Gatti, A.M., Biocompatibility of micro- and nanoparticles in the colon, Biomaterials, 25, 385, 2004.

Greco, R.S. (Ed.), Implantation Biology. The Host Response and Biomedical Devices, CRC Press, Boca Raton, FL, 1994.

Heggeness, M.H. et al., Late infection of spinal instrumentation by hematogenous seeding, Spine, 18, 492, 1993.

Hunt, J.A., Remes, A. and Williams, D.F., Stimulation of neutrophil movement by metal ions, J. Biomed. Mater. Res., 26, 819, 1992.

Ingham, E. and Fisher, J., Biological reactions to wear debris in total joint replacement, Proc. Inst. Mech. Eng., Part H, 214, 21, 2000.

Inghram, J.H. et al., The influence of molecular weight, crosslinking, and counterface roughness on TNF-alpha production by macrophages in response to ultra high molecular weight polyethylene particles, Biomaterials, 25, 3511, 2004.

Ito, A. et al., In-vitro analysis of metallic particles, colloidal nanoparticles, and ions in wear-corosion products of SUS317L stainless steel, Mater. Sci. Eng., C17, 161, 2001.

Kawaguchi, H. et al., Phagocytosis of latex particles by leucocytes. I. Dependence of phagocytosis on the size and surface potential of particles, Biomaterials, 7, 61, 1986.

Leibovich, S.J. and Ross, R., The role of the macrophage in wound repair, Am. J. Pathol., 78, 71, 1975.

Maloney, W.J. et al., Isolation and characterization of wear particles generated in patients who have had failure of a hip arthroplasty without cement, J. Bone Joint Surg., 77A, 1301, 1995.

Merritt, K., Role of medical materials, both in implant and surface applications, in immune response and in resistance to infection, Biomaterials, 5, 47, 1984.

Nagase, M., Host reactions to particulate biomaterials, in Encyclopedic Handbook of Biomaterials and Bioengineering, Part A: Materials, Vol. 1, Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, 269.

Peters, K. et al., Effects of nanoscaled particles on endothelial cell function in vitro: studies on viability,

proliferation, and inflammation, J. Mater. Sci.: Mater. Med., 15, 321, 2004.

Rae, T., Cell biochemistry in relation to the inflammatory response to foreign materials, in Fundamental Aspects of Biocompatibility, Vol. 1, Williams, D.F. (Ed.), CRC Press, Boca Raton, FL, 1981, 159.

Rae, T., Localized tissue infection and the influence of foreign bodies, in Fundamental Aspects of Biocompatibility, Vol. 2, Williams, D.F. (Ed.), CRC Press, Boca Raton, FL, 1981, 139.

Revell, P.A., Pathology of Bone, Springer-Verlag, Berlin, 1986, 217-223.

Rimondini, L., Fini, M. and Giardino, R., The microbial infection of biomaterials: A challenge for clinicians and researchers, J. Appl. Biomater. Biomech., 3(1), 1, 2005.

Sanzén, L. and Linder, L., Infection adjacent to titanium and bone cement implants: an experimental study in rabbits, Biomaterials, 16, 1273, 1995.

Schoen, F.J., Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles, W.B. Saunders, Philadelphia, 1989.

Sethi, R.K. et al., Macrophage response to cross-linked and conventional UHMWPE, Biomaterials, 24, 2561, 2003.

Spector, W.G. and Wynne, K.M., Proliferation of macrophages in inflammation, Agents Actions, 6, 123, 1976.

Sugarman, B. and Young, E.J. (Eds.), Infections Associated with Prosthetic Devices, CRC Press, Boca Raton, FL, 1984.

Trowbridge, H.O. and Emling, R.C., Inflammation: A Review of the Process, 5th ed., Quintessence Pub., Carol Stream, IL, 1997.

Vogler, E.A., Water and the acute biological response to surfaces, J. Biomater. Sci. Polymer Edn., 10(10), 1015, 1999.

Williams, D.F., Tissue-biomaterial interactions, J. Mater. Sci., 22, 3421, 1987.

Yamamoto, A. et al., Cytoxicity evaluation of ceramic particles of different sizes and shapes, J. Biomed. Mater.

Res., 68A, 244, 2004. 165

9

Coagulation and Hemolysis

9.1 Introduction

In the previous chapter, inflammation was presented as a nonspecific

response to tissue damage. This chapter will consider responses to two more

specific events involving the circulatory system and its tributaries:

- Damage to blood carrying vessels and/or contact with foreign materials leading to coagulation

- Damage to the tissue of blood, leading most generally to cellular destruction or hemolysis

9.2 The Coagulation Cascade

9.2.1 Intrinsic Pathway

The coagulation cascade may be thought of as a biological amplifier that

permits an initiating event to be magnified into a process sufficiently wide

spread to produce local homeostasis, prevents further loss of blood (if the

vascular process has been breached), and permits repair of the damaged

tissue. The overall process is referred to as coagulation or thrombosis and

the resulting hemostatic plug is termed a thrombus. If damage to the wall

of a blood vessel (endothelium) is the initiation factor, then coagulation

proceeds by an intrinsic pathway.

In this case, the first two events closely parallel those of inflammation. In

fact, they are essentially those of the inflammatory process. Initially, the

smooth muscle in the vessel wall dilates and then constricts, probably stim

ulated by activated factor XII (also called Hageman factor) (see Figure 9.1).

Although this is formally the first step in the intrinsic pathway, it is preceded

by surface contact (and denaturation) of other molecules, including kinino

gen and prekallikrein. Endothelial permeation also increases but is masked

by the release of serum and blood-borne cells if the vessel wall is ruptured.

In addition, the endothelial lining becomes sticky.

The combination of the presence of activated factor XII and the sticky

quality of the endothelial lining triggers the first step unique to coagulation,

the adhesion and aggregation of platelets. Adhered platelets rapidly lyse

(undergo membrane rupture) through mechanical and biochemical paths,

releasing adenosine diphosphate (ADP), serotonin, and epinephrine. ADP

encourages further platelet adhesion, and the latter two agents cause vaso

constriction. The combination of these agents rapidly produces a platelet

“plug” that serves to staunch further blood loss from the area.

Activation of factor XII and platelet adhesion trigger a complex chain of

events leading to transformation of inactive fibrinogen into an active mole

cule, fibrin. This transformation, accompanied by a shrinking or retraction

of the platelet plug, produces a mature clot, a mesh of polymerized fibrin

strands trapping leukocytes, erythrocytes, and platelet fragments. Within

minutes to hours this clot is invaded by the same series of cells seen in pure

inflammation and then later is perfused by numerous new capillaries. Even

tually, the clot is removed and replaced by fibrous scar and remodeled tissue.

9.2.2 Extrinsic Pathway

The intrinsic pathway to coagulation, as previously described, depends upon

interaction of normal blood components (macromolecules, cells, platelets,

FIGURE 9.1

The coagulation cascade. (Adapted from Salzman, E.W., in The Chemistry of Biosurfaces, Vol. II.

Hair, M.L., Ed., Marcel Dekker, New York, 1972, 489.) Extrinsic Pathway Intrinsic Pathway Ca ++ Ca ++ Ca ++ Ca ++ Ca ++ active IX Tissue Thromboplastin Prothrombin Thrombin Surface contact active XIII Fibrinogen Soluble fibrin Fibrin Platelets XIII XI active XI VIII Surface contact active XII VII XII IX active X V Surface contact X Platelets

etc.) after alteration by an initiation event, usually surface contact. An alter

nate initial coagulation pathway, the extrinsic pathway, involves release of

materials from cells external to the vascular processes. The released material

is termed tissue thromboplastin. This is a protein–phospholipid complex

derived from normal cell contents (otherwise termed factor III) that, with

factor VII and Ca ++ , activates factor X (Figure 9.1). The intrinsic and extrinsic

coagulation pathways merge in this common event leading to the terminal

event of fibrin production and clot formation.

9.2.3 Implant-Induced Coagulation*

The events of the intrinsic pathway are triggered, as previously stated, by

contact between blood elements and a surface. The normal endothelial lining

of blood vessels is not able, fortunately, to induce this response. Damage to

the endothelium may expose collagen, its major structural molecule. Nor

mally, collagen is rendered nonthrombotic (not able to induce coagulation)

by a covering of a family of macromolecules, glycopolysaccharides. This

coating is electropositive, which attracts a layer of neutralizing negative ions

and thus repels the negatively charged erythrocytes and platelets. Exposed

collagen is electronegative, and thus highly thrombotic. This property is

utilized in surgery when powdered crystalline collagen may be used as a

topical hemostatic agent on highly vascular tissues in which electrocauter

ization and/or ligation are not possible — for example, the liver.

The intrinsic pathway may also be triggered by contact with a foreign

body** (such as an implant) and the resulting events are quite similar. In this

case, however, the implant persists after the initial insult. This difference

from the case of isolated vessel wall damage has several possible conse

quences (Figure 9.2):

• Blood-borne proteins retaining native structure may coat the surface and prevent activation of factor XII or adhesion of platelets. Such a surface would have a high degree of hemocompatibility.

• Even if platelet adhesion occurs, it may not be accompanied by sufficiently rapid lysis to promote further progression of the cascade. Such a surface would not actively form a thrombus. However, it would deplete the circulating blood of platelets and thus might reduce the coagulatibility of the host. Such an effect is common in chronic (repeated) hemodialysis, or intraoperatively when an ex vivo blood oxygenator is used. Brash (Skarja et al. 1997) has developed

* See Banerjee et al. (1997) for a review of the interaction between blood and biomaterials.

** We speak here of contact with the surface of a "foreign body"; however, the surface of an

implant so rapidly becomes coated with serum proteins and coagulation factors that it is better

to think of the foreign body contact effect as mediated by surface adhered and denatured organic

molecules. See Vroman (1971) and Chapter 5, particularly Section 5.5. an in vitro test for quantification of platelet adhesion under flow conditions (see Section

17.4.3).

• A thrombus may form but be rapidly removed by blood dynamic forces. Such an implant will “shed” emboli and cause damage by infarction at a remote site. This effect is utilized in the Kusserow test for whole blood compatibility of materials (see Section 18.2.3).

• Remodeling will not remove the obstruction but will tend to encapsulate it, as in the case of the fibrous encapsulation found around implants in soft tissue. If the implant surface is structured (such as a felt or velour) to encourage cellular trapping, the surface exposed to the blood may come to function as the endothelial wall of a normal vessel and is termed “pseudointima” (see Section 10.3.2). It differs, of course, from the normal intima because it has no smooth muscle component and thus no ability to dilate or constrict.

These effects have been summarized by Baier (1972) as seen in Figure 9.3.

In this figure, Baier also indicates possible points and methods of interven

tion that may reduce the thrombogenic potential of implant surfaces.

In the ordinary (implant-free) progression of the intrinsic pathway, the

fibrin clot gradually isolates flowing blood from the site of possible surface

contact insult. However, on a foreign (implant) surface, it is possible for

fibrin to initiate coagulation by itself due to its altered configuration after

surface binding (Lindon et al. 1986). Implants may also initiate coagulation

by binding (and possible activation) of molecules such as complement C3*

that are not normally involved in the intrinsic pathway (Hayashi 1990; Her

zlinger et al. 1981).

FIGURE 9.2

Interaction of implants with blood elements.

* The proteins involved in the complement system are usually associated with blood plasma,

where they are present in abundance. However, due to the close association between comple

ment and immune response, this topic is discussed in Section 12.2.2. BLOOD ELEMENTS + N o n t h r o m b o g e n i c o r p s e u d o i n t i m a T h r o m b o g e n i c a n d n o n a d h e r e n t Thrombogenic and adherent No Thrombus Adherent Thrombus Shed Thrombus

 F I G U R E 9 . 3 C o a g u l a t i o n e v e n t s , t i m i n g , a n d i n t e r v e n t i o n s t r a t e g i e s . (F r o m B a i e r , R . E . , B u l l . N . Y . A c a d . M e d . , 4 8 , 2 5 7 , 1 9 7 2 . W i t h p e r m i s s i o n .)

9.3 Approaches to Thromboresistant Materials Development

9.3.1 General Considerations

In the same article from which Figure 9.3 is drawn (Baier 1972), the various

historical approaches taken to design new surfaces or to render surfaces of

older materials less thrombogenic were summarized (Figure 9.4). The

approaches shown by the solid-line arrows pointing to the left are those that

mimic properties that the natural intact endothelium is known to have. Those

shown by the dotted lines pointing to the right are other proposals not based

so directly upon known natural properties, but rather on theoretical

approaches. All have met with mixed success and failure because, with the

limited exceptions of knitted polyester grafts; felted polyurethane; poly (tet

rafluoro) ethylene and related materials that can sustain “pseudointimal”

linings; certain bulk polymers; and graphites, most materials evoke unac

ceptable host responses for chronic exposure to blood. Even satisfactory

materials tend to thrombose in prosthetic devices with blood conduit internal

diameter less than 6 mm.

Although Figure 9.4 is now more than 30 years old, it is interesting that

no really new approaches to solution of the so-called “blood contact” prob

lem have been developed. The only addition that could be made to this

schematic, other than subtopics under each of the eight main headings,

would be the addition of viable biomaterials as a fifth mimicking approach

FIGURE 9.4

Approaches to producing thromboresistant surfaces. (From Baier, R.E., Bull. N.Y. Acad. Med.,

48, 257, 1972. With permission.)

(right side). This is an extension of the “natural” materials approach, which

is specifically the modification of permanent implantable materials with

natural molecules or a surface-dwelling cell population. In the newer

approach, a composite of resorbable materials and living

cells (smooth mus

cle cells, endothelial cells, etc.) is made and implanted with the hope that it

will eventually remodel into native (host) tissue (Weinberg and Bell 1986).

The lack of new approaches to producing noncoagulating biomaterial

surfaces reflects the complexity of the natural system and the difficulty of

performing reproducible blood contact experiments with generality of

results, whether in vitro or in animal models. This natural complexity has

aroused considerable interest in finding simplifying or dominant factors in

surface properties that affect thrombogenesis. Several of the directions of

biomaterials efforts indicated in Figure 9.4 reflect such a search and are of

historical and practical interest. Three of these will be considered: negative

surface charge, critical surface tension, and “natural” surfaces. Each has

yielded important results and contributed to a better understanding of

thrombogenesis, but has failed to produce the final answer in suppressing

host response to materials in contact with blood.

9.3.2 Negative Surface Charge

The recognition that erythrocytes and platelets have net negative surface

charges has suggested to many investigators that electrostatic repulsion

could be utilized to keep them away from implant surfaces, thus suppressing

thrombogenesis. Sawyer and Srinivasan (1972) were the most active initiators

and proponents of this idea. A series of early experiments suggested that a

relative positive potential on a biomaterial surface exposed to blood pro

motes thrombogenesis and negative potentials tend to suppress thrombo

genesis proportionally to the potential depression below local neutral. These

conclusions arise from a complex series of experiments. Perhaps the most

convincing data are given in Figure 9.5 (Sawyer and Srinivasan 1972), sum

marizing the results of implantation of Gott rings in the canine vena cava

(see Section 18.2.3) and of a related design (Edwards) made from various

materials in the canine aorta.

Under biophysiological conditions, metals with a negative electromotive

potential form a positive interfacial potential with blood (due to the attrac

tion of counter ions, as previously noted) and vice versa. Here, one can see

the rapid and complete occlusion (coagulation sufficient to prevent blood

flow) for silver and platinum, which have positive interface potentials in

vivo, and the increasing patency (proportion of devices permitting flow) at

increasing times for metals, such as iron (in stainless steel), aluminum, and

magnesium, that have negative interface potentials.

The approach is, however, quite limited. The use of rigid metallic surfaces

for vascular prostheses might prove nonthrombogenic by surface interaction

but might produce a pseudoextrinsic thrombogenesis through mechanical

damage to blood-borne cells.* Furthermore, control of interfacial potential

might require an active power source, thus making the implant far more

complex and less reliable than the knitted prostheses discussed in Section

10.3.2.**

FIGURE 9.5

Relationship between interface potential of vascular implants and patency. (From Sawyer, P.N.

and Kaplitt, M.J., Eds., Vascular Grafts, Appleton-Crofts, New York, 1978.)

* However, such considerations might well play a role in selection of materials for uncoated

metallic vascular stents.

** A personal note: as an experimental physicist, I have always been fascinated by Sawyer's

results in this area of research. While I was a predoctoral student in the late 1960s, I conceived

an experiment, based on Milliken's classic oil drop experiment for determination of the charge

of a single electron, to study the approach of platelets to charged surfaces in serum-free saline

solution. I had the pleasure of discussing this idea with Phil Sawyer at the First World Bio

materials Congress (Baden, Austria, 1980). Although he thought it was an interesting idea, nei

ther he nor anyone else to his knowledge had ever done this study (to my knowledge it has not

subsequently been done).

9.3.3 Critical Surface Tension

The critical surface tension approach was proposed some time ago and has

been strongly advanced by Baier (1972) as a significant but not necessarily

dominant solution to the problem of surface thrombogenesis. The basic idea

is to utilize the Young-Dupree equation (Section 5.4; Equation 5.4): γ SL = γ PS + γ PL cosθ (9.1)

If surface tensions combine so that $\theta = 180^{\circ}$, no adhesion of the particle,

p, may occur. Then, of necessity, cosine θ must equal -1. This condition can

be achieved if: γ SL = γ C = γ PS - γ PL (9.2)

(γ C = critical surface tension).

Because γ C is determined by the biological system, the trick is to find a

surface with a suitable surface tension so that Equation 9.2 is satisfied; then

no adhesion would occur for a particular molecular or cellular species and

one or more of the surface contact steps in Figure 9.1 could be prevented.

This can be done at two points in the coagulation cascade:

• The surface may have the appropriate critical surface tension to prevent adhesion of factor XII.

• The surface may have the appropriate critical surface tension to prevent adhesion of platelets in the intrinsic or the final (common) pathway.

This turns out to be far more difficult in practice than in principle. For instance,

a surface might be selected that does not permit adherence of factor XII.

However, other molecular species will probably adhere, γ SL may change, and

adhesion of factor XII may then become possible. Measurements of surface

tension of nonbiological surfaces, such as silicon, exposed in vitro or ex vivo to

sera or whole blood suggest complex time-dependent changes in γ SL .

Notwithstanding these practical problems, a theoretical range of the

material–blood interfacial critical surface tension, γ C , should suppress throm

bogenesis (Figure 9.6). Because most blood contact materials are polymeric, a

fruitful embodiment of this approach has been chemical surface modification

of implants. Studies of a wide variety of as-synthesized and surface-modified

materials show relative improved thromboresistance in this range (20 to 30

dyn/cm*) of surface tension. It is interesting to note that 30 dyn/cm is the so

called “Berg limit” (Vogler 1998); the essential balance point between hydro

phobic and hydrophobic interfacial forces at which the

solid/liquid phase

boundary should exert a minimum deforming effect on proteins.

* Older units; preserved for historical purposes in Figure 9.6. 1 dyn/cm = 10 −3 N . m −1 .

9.3.4 “Natural” Surfaces

The thromboresistance of the undamaged internal surfaces of blood vessels

has attracted the surgeon and the bioengineer for a long time. Direct trans

plants (allografts) and implants of animal material (xenografts) are limited

in utility by host rejection of the implant through an immune response (see

Section 12.1) and by biological degradation of the foreign material. Various

methods of processing have been tried to reduce the immune response and

to improve resistance to degradation. A number of processes in use involve

cleaning the tissue, removing cellular debris, and crosslinking the collagen

component (“tanning”) by a variety of agents such as glutaraldehyde, form

aldehyde, etc. Although human material has been used, the pig is a favorite

donor. Kiraly and Nosé (1974) have summarized some of the early applica

tions of such materials.

These materials seem to have considerable degrees of thromboresistance.

However, they are not incorporated into the body in the same way that

knitted grafts are (Nosé et al. 1977). Thus, a pseudointima does not form

and the surfaces exposed to blood are slow to mature. Although cells are

found on their surfaces, the same low surface tensions that suppress throm

bogenesis seem to retard cellular adhesion. Additionally, these processed

materials are relatively impervious to diffusion of fluids and tend to develop

late calcification, similar to that which occurs naturally in arteriosclerosis.

FIGURE 9.6

Proposed relationship of critical surface tension (γ c) to biological response. (From Baier, R.E.,

Bull. N.Y. Acad. Med., 48, 257, 1972. With permission.)

However, the approach remains interesting, particularly as how calcification

can be inhibited becomes known (Levy et al. 1995), and bears considerable

promise for the future, perhaps utilizing cultured (grown in vitro) tissue. The

“natural” approach is an obvious precursor to the more recent ideas involv

ing viable biomaterials for blood-contacting surfaces (see earlier discussion).

9.3.5 An Overview of Thromboresistant Materials Development

It is difficult to consider in further detail the efforts at bulk and surface

modification that have been made to render implant surfaces friendlier to

blood. In general, the experiments with bulk materials are

straightforward,

but their interpretation depends strongly on the validity of the blood expo

sure test used to evaluate them. Chapter 17 and Chapter 18 will return to

this point.

I think that the experiments in surface modification and coating remain

open to broad, general criticism. In the first place, there is rarely very good

characterization of the bulk materials used. One may ask what the actual

(rather than calculated) structural and energetic properties of the surfaces

of these materials are and how these properties affect the resulting surface

exposed to cells. Furthermore, there is rarely good evidence that the surface

treatments or coatings are homogeneous or even cover the surface com

pletely. The “catalytic” nature and inherent amplification of coagulation

processes suggest that the presence of occasional high-energy defects may

be highly effective as foci for initiation of thrombogenesis and may be far

more important than the anti- or nonthrombogenic properties of the balance

of the surface.

As pointed out previously, it can be generally assumed that implant sur

faces become rapidly protein coated after insertion and that the proteins are

denatured in some degree. I have suggested (Section 5.4) that if a normally

free protein adheres to a biomaterial surface, by definition it must be dena

tured. Whether this is mild and reversible (3 or 4°), moderate (2°), or severe

and essentially irreversible (1°) depends upon the nature of the protein-sur

face interaction forces.* Thus, the central issues concerning adhesion of pro

teins to surfaces are whether they are uniformly distributed or associated

with surface defects and whether the type of denaturation that occurs will

evoke a specific cellular response — in this case, the initiation of coagulation.

Finally, most studies neglect to measure the important physiochemical

properties of the actual material/surface/protein complex during and/or

after blood contact and instead rely on secondary determinations, frequently

in simplified systems with only one or two proteins present at low concen

tration or on theoretical considerations. It seems most likely that, in the

absence of surface-bound molecules for which target cells (platelets, eryth

rocytes, etc.) have specific surface receptors, cells involved in coagulation

are affected by the following properties of biomaterials:

* See Chapter 5 for a more complete discussion.

• Potential gradients and associated ion fluxes near surfaces

• Features of surface geometry with dimensions between 0.1 and 5 μm

• Actual surface/solution interfacial free energy

• Stresses at impact (governed by the preceding three points as well as surface hardness and conditions of the experiment or clinical exposure)

• Presence of specific proteins sufficiently denatured to evoke a biological response

9.4 Hemolysis

9.4.1 General Description

Foreign materials may trigger thrombosis by contact with blood in the

absence of motion at the blood–surface interface. However, motion may

trigger thrombus formation or may cause damage to blood cells in the

absence of thrombosis. Such initially nonthrombotic damage resulting in cell

death and release of cell contents is termed hemolysis. Although hemolysis

can be detected by a reduction in red cell (erythrocyte) count or by the

presence of cell “ghosts” (fragments of empty cell membranes), it is most

usually followed by measuring the level of serum hemoglobin.

Presence of hemoglobin in blood serum is a direct result of erythrocyte

lysis. The normal concentration of serum hemoglobin (in humans) of <1.1

g/l represents in toto no more than 0.4% of hemoglobin in the blood. Serum

hemoglobin is normally bound to a carrier molecule, haptoglobin; however,

the maximum capacity of this fraction in normal serum is 1.4 g/l. Hemolysis

rates above the release due to cell death in normal turnover may overpower

the ability of haptoglobin to bind and thus “detoxify” otherwise free hemo

globin. Modest increases lead to increases in excretion of hemoglobin and

may cause anemia if sustained for long periods. Greater elevations (25 g/l

and higher) will cause systemic clinical symptoms including cyanosis and

hematuria; still higher levels may lead to kidney failure and toxemia.

Hemolysis may occur in freely flowing blood in the absence of foreign

surfaces. Turbulent flow and shear stresses above 150 to 300 Pa will cause

direct lysis. If stagnation points exist, as in some device designs, this lysis

may lead directly to thrombus formation in the apparent absence of surface

contact. Of course, in this case, the initiating surface is damaged cell mem

brane exposed by cell lysis.

9.4.2 Experimental Relation to Flow Velocity

However, flow effects can be seen in the contact between blood and foreign

surfaces at much lower ranges of shear stress. A large number of studies

have demonstrated this effect. One of the best is still that of Lampert and

Williams (1972). These investigators studied hemolysis rates of various mate

rials compared to a standard material, aluminum, at a variety of flow rates.

Their apparatus consisted of a fixed disc with an opposed rotating disc at a

fixed separation distance, both on a common axis (see Figure 9.7 for a

schematic representation). The interdisc separation (H) and the speed of

relative rotation (Ω) could be varied.

The Reynolds numbers (R e) for this apparatus were calculated as shown

below. With respect to separation (H) at the edge of the disc (max r): (9.3)

where

ρ = density of blood

Ω = angular velocity

η = viscosity of blood

R e (H) ≤ 1.5; laminar flow to R e (H) = 10 2 .

With respect to radius (r) at maximum separation (max H): (9.4)

R e (r) ≤ 4.4 × 10 4 , laminar flow to R e (r) = 10 5 .

These conditions yield shear rates, G ≤ 11,200 sec −1 , (r ≤ 5 cm), and shear

stresses that do not exceed 44.8 Pa. In this low shear regime, Lampert and

FIGURE 9.7

Schematic of apparatus for study of shear-induced

hemolysis. (Adapted from Lampert, R.H.

and Williams, M.C., J. Biomed. Mater. Res., 6, 499, 1972.)
H Ω r Blood Test Material (both sides) Reservoir 10 cm.
diameter R e H H ( ) = ρ η Ω 2 R e H r ( ) = ρ η Ω 2

Williams (1972) defined a relative plasma hemoglobin
concentration

increase, ΔC, with respect to aluminum: (9.5)

For a number of materials tested, the following
relationship was found: ΔC = At β (9.6)

For instance, for heat-cured poly (methyl) methacrylate
(Plexiglass™): ΔC = 0.047t 0.84 (9.7)

In general, A was found to be apparatus dependent for this
experiment

and is given by the following relationship: A = 0.020β −5.6
(9.8)

On the other hand, β was found to be a constant
characteristic of the test

material and to have a single unique value for each
material composition

tested. For a group of five polymers (both test surfaces
made from the same

material), β correlated to the critical interfacial
tension, γ C , by a linear nega

tive relationship of the form: β = D − E γ C (9.9)

where D and E are experimentally derived constants.

This can be understood by the following argument. A high
value of γ C

(with respect to a low value) favors rapid early protein
absorption from the

plasma. This increases the adhesion of platelets (increases
the negative work

of adhesion), leading to rapid maturation of a fibrin
layer. This mature fibrin

layer discourages further platelet and cell adhesion, thus lowering hemolysis

rates with respect to those of the surface with lower γ C . Thus, although high

γ C leads to rapid thrombus formation, it may reduce free cell hemolysis.

These experiments suggest that the ideal blood-compatible surface may not

be the least reactive one.

These results were obtained with a constant shear stress. Performing exper

iments at varying values of Ω, Lampert and Williams (1972) formed the ratio,

R, to examine shear stress effects: Δ Δ Δ C C m t C A hb hb = ⎡ ⎣ ⎤ ⎦ ( ) ( ) ⎡ ⎣ ⎤ ⎦ ( ) , , secs 1 30 (9.10)

The results of this analysis are equivocal due to uncertainties in the true

fluid dynamics of the system. They are consistent with a linear rise of R at

low stress (below 40 Pa) and a nonlinear increase at higher apparent stresses.

These results are interpreted as reflecting a constant boundary layer effect

(material effect) and a superimposed bulk shear effect (turbulence effect) at

higher rotational speeds. Thus, this experiment neatly shows the merging

of the two flow regimes.

Although extremely enlightening, this series of studies may be criticized

on three grounds:

- The blood is exposed to an air–liquid interface and to

materials other than the test materials. Thus, hemolysis may be associated with increased cell fragility and with contact with nontest surfaces. These effects are contained within the constant A; however, they prevent the derivation of an absolute hemolysis rate for a material.

- The results obtained are specific for the surfaces actually used and not representative to the general material classes from which they are selected. Specimen-specific features, such as type and degree of roughness, clearly affect the outcome (Monroe et al. 1981).

- The experiment is conducted in vitro and under conditions in which significant hemolysis rates will occur in brief periods; thus, it is very difficult to relate these results to those that might be obtained in vivo at more realistic low hemolysis rates.

9.5 Final Comments

It should be clear from the brief remarks in this chapter that understanding

and controlling the host response of materials exposed to blood represents

one of the great unsolved problems of biomaterials science. Valve and vas

cular replacements, left ventricular assist devices, and total artificial heart

replacements, as well as dialyzers and oxygenators used for shorter periods,

have become very sophisticated in design and control. However, their clinical

utility continues to be severely limited by unwanted interactions between

their materials of manufacture, the degradation products of those materials,

and circulating blood proteins and cells, especially those affected by shear

forces and foreign surface contact. Thus, it is difficult to overemphasize the

need for progress in developing materials that can function well in the

cardiovascular system for long periods of time. R C m C m t= ( ) ( ) ( ) = Δ Ω Δ , , sec 640 100 rpm

The problem is complicated by several factors:

• The phenomena of coagulation and hemolysis are complex and multifactorial.

• There seems to be a broad range of host response, particularly in temporal variations in response by individuals, unlike the less specific response to inflammation, with only quite modest responses tolerable chronically.

• Partly because of the first two points, as well as the rapidity of development of the coagulation cascade, adequate experimental models and techniques for research in this field are acutely lacking.

Fortunately, the search for improved “blood compatibility” as an attribute

of biomaterials continues to be vigorous. Harker et al. (1993) provide an

excellent overview of this difficult problem. Part III of this book will return

to the specific issue of deficiencies in testing and evaluation.

Baier, R.E., The role of surface energy in thrombogenesis, Bull. N.Y. Acad. Med., 48, 257, 1972.

Banerjee, R. et al., Hematological aspects of biocompatibility — review article, J. Biomater. Appl., 12, 57, 1997.

Harker, L.A., Ratner, B.D. and Didisheim, P. (Eds.), Cardiovascular Biomaterials and Biocompatibility. Cardio. Pathol., 2(3) (Suppl), 1993, 1.

Hayashi, K., In vivo thrombus formation induced by complement activation on polymer surfaces, J. Biomed. Mater. Res., 24, 1385, 1990.

Herzlinger, G.A. et al., Quantitative measurement of C3

activation at polymer surfaces, Blood, 57, 764, 1981.

Kiraly, R.J. and Nosé, Y., Natural tissue as a biomaterial, Biomat. Med. Dev. Art. Org., 2(3), 207, 1974.

Lampert, R.H. and Williams, M.C., Effect of surface materials on shear-induced hemolysis, J. Biomed. Mater. Res., 6, 499, 1972.

Levy, R.J. et al., Calcification of valved aortic allografts in rats: effects of age, crosslinking, and inhibitors, J. Biomed. Mater. Res., 29, 217, 1995.

Lindon, J.N. et al., Does the conformation of adsorbed fibrinogen dictate platelet interactions with artificial surfaces?, Blood, 68, 355, 1986.

Monroe, J.M. et al., Surface roughness and edge geometries in hemolysis with rotating disk flow, J. Biomed. Mater. Res., 15, 923, 1981.

Nosé, Y. et al., Surface characteristics of cardiac prostheses in vivo, J. Biomed. Mater. Res. Symp., 8, 85, 1977.

Salzman, E.W., Surface effects in hemostasis and thrombosis, in The Chemistry of Biosurfaces, Vol. II. Hair, M.L. (Ed.), Marcel Dekker, New York, 1972, 489.

Sawyer, P.N. and Kaplitt, M.J. (Eds.), Vascular Grafts, Appleton-Crofts, New York, 1978.

Sawyer, P.N. and Srinivasan, S., The role of electrochemical surface properties in thrombosis at vascular interfaces: cumulative experience of studies in animals and man, Bull. N.Y. Acad. Med., 48, 235, 1972.

Skarja, G.A. et al., A cone-and-plate device for the investigation of platelet biomaterial interactions, J. Biomed. Mater. Res., 34, 427, 1997.

Vogler, E.A., Structure and reactivity of water at biomaterial surfaces, Adv. Colloid Interface Sci., 74, 69, 1998.

Vroman, L., Summation: protein at the interface, Fed. Proc., 30, 1703, 1971.

Weinberg, C.B. and Bell, E., A blood vessel model constructed from collagen and cultured vascular cells,

Science, 231, 397, 1986.

Department of Health and Human Services, Guidelines for Blood-Material Interactions, NIH Publication 85-2185, Public Health Service, National Institutes of Health, U.S. Government Printing Office, Washington, D.C., 1986.

Bamford, C.H. (Ed.), The Vroman Effect, Coronet, Philadelphia, 1992.

Barbanel, J.C. et al., Blood Flow in Artificial Organs and Cardiovascular Prostheses, Clarendon Press, Oxford, 1989.

Basmadjian, D. et al., Coagulation on biomaterials in flowing blood: some theoretical considerations, Biomaterials, 18, 1511, 1972.

Bodnar, E. and Frater, R., Replacement Cardiac Valves, McGraw-Hill, New York, 1991.

Bruck, S.D., Blood Compatible Synthetic Polymers, Charles C Thomas, Springfield, IL, 1974.

Ellis, J.T. et al., Prosthesis-induced hemolysis: mechanism and quantification of shear stress, J. Heart Valve Dis., 7(4), 376, 1998.

Gott, V.L. and Furuse, A., Antithrombogenic surfaces, classification and in vivo evaluation, Fed. Proc., 30, 1679, 1971.

Hanson, S.R., Blood-material interactions, in Black, J. and Hastings, G. (Eds.), Handbook of Biomaterial Properties, Chapman & Hall, London, 1998, 545.

Hastings, G., Cardiovascular Biomaterials, Springer-Verlag, Berlin, 1991.

Hughes-Jones, N.C., Lecture Notes on Haematology, 7th ed., Blackwell Scientific, London, 2003.

Kambic, H.E., Kantrowitz, A. and Sung, P. (Eds.), Vascular Graft Update, Safety and Performance. ASTM STP 898. American Society for Testing and Materials, Philadelphia, 1986.

Lefrak, E.A. and Starr, A., Cardiac Valve Prostheses. Appleton-Century-Crofts, New York, 1979.

Leonard, E.F., Turitto, V.T. and Vroman, L. (Ed.), Blood in

Contact with Natural and Artificial Surfaces. Ann. N.Y. Acad. Sci., 516, 1988.

Magnani, A. and Barbucci, R., Hemocompatible materials, surface and interface aspects, in Encyclopedic Handbook of Biomaterials and Bioengineering, Part B, Applications, Vol. 2. Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, 1101.

Merrill, E.W., Properties of materials affecting the behavior of blood at their surfaces, Ann. N.Y. Acad. Sci., 283, 6, 1977.

Sawyer, P.N. et al., Physical chemistry of the vascular interface, in Vascular Grafts, Sawyer P.N. and Kaplitt M.J. (Eds.), Appleton-Crofts, New York, 1978, 53.

Smith, J.P. and Sawyer, P.N. (Eds.), Modern Vascular Grafts, McGraw-Hill, New York, 1986.

Schoen, F.J., Interventional and Surgical Cardiovascular Pathology, W.B. Saunders, Philadelphia, 1989.

Thubrikar, M. et al., Study of surface charge of the intima and artificial materials in relation to thrombogenicity, J. Biomech., 13, 663, 1980.

Van Kampen, C.L. et al., Effect of implant surface chemistry upon arterial thrombosis, J. Biomed. Mater. Res., 13, 517, 1979.

Vroman, L., Blood, American Museum Science Books, B26, Doubleday, New York, 1968.*

Wagner, W.R. et al., Blood biocompatibility analysis in the setting of ventricular assist devices, J. Biomater. Sci. Polym. Ed., 11(11), 1239, 2000.

* Blood, by Leo Vroman, is a marvelous, amusing, and witty account of blood biochemistry and

surface interactions by one of the leading blood physiologists of the 20th century. Although one

will enjoy it as recreational reading, one cannot avoid learning a great deal about blood. In addi

tion to being a researcher, Leo Vroman is an author of poetry and children’s books. Unfortu

nately, most have only been published in Dutch, his native language. Love, Greatly Enlarged (1991,

Cross-Cultural Communications) is a major poem in English and, given the author, is about

many things, not the least of which is blood. 183

10

Adaptation

10.1 Introduction

So far in Part II, acute host responses to singular events have been considered.

The insertion of an implant may evoke inflammation, with an acute course

and a longer chronic phase. Interruption of a blood vessel by injury or

insertion of an implant may trigger acute coagulation and, perhaps, chronic

hemolysis. Chapter 13 will take up the subject of neoplastic transformation:

abnormal tissue development and elaboration as a result of chemical or

foreign-body challenge.

Between these two types of events — acute response and abnormal devel

opment —is another class of tissue response; that is, the presence of an

implant, perhaps due to the implant’s chemical, physical, or electrical prop

erties, affects the organization and elaboration of tissue elements in the

vicinity. These events must be considered because of the well known ability

of many of the tissues to remodel adaptively, in response

to physical induc

tion factors, to reflect changes in demand and function. From the phrase

“adaptively remodel,” I shall purloin the term “adaptation” to describe such

events, especially as influenced by implants. The recognition and manage

ment of adaptation is an important aspect of the design, development, and

use of interactive (type 2) biomaterials.

10.2 Tissue Growth Strategies

10.2.1 General Principles

Goss (1978, p. 2) discusses the strategy of growth of tissue in terms of three

patterns previously recognized by Bizzozero (1894):

- Expanding tissues grow by mitosis to increase cell number (for instance, the liver).
- Static tissues retain essentially constant cell number but grow by individual hypertrophy (for instance, muscle).
- Renewing tissues retain essentially constant cell number by replacing losses from differentiation of proliferating stem cells (for instance, skin).

In the rapidly developing immature individual, all tissues expand by

mitosis. As maturation proceeds, the cells of some tissues lose their mitotic

ability and the tissues become static or renewing. It is also possible for tissues

to continue to display a combination of two of these patterns, varying their

response to the challenge.

The question of control of these processes is still to a

certain degree unre

solved. Because all of these processes tend towards limits, a variety of neg

ative-feedback control systems have been proposed (see Section 10.3.6 for

one example). However, a response is evoked in each cell type by death of

a portion of the tissue or by surgical removal. Less significant challenges,

such as blunt trauma or change in mechanical functional requirements, may

also evoke responses. These observations suggest the existence of a wide

variety of control processes regulating the quantity and, to some degree, the

type of tissue in any location in a mammalian body. It is altogether reasonable

to assume that the response of any such active biological control system

facing a challenge may be affected by the presence of an implant.

10.2.2 Fracture Healing

The process of fracture healing — the restoration of the integrity and conti

nuity of mineralized tissue after mechanical injury — includes an interesting

example of natural adaptation in the absence of implants. Successful fracture

healing can be considered most generally to entail four stages:

1. Hematoma: from injury to formation of a “soft” callus

2. Soft callus: from initiation of soft callus formation until its condensation into a “hard” callus

3. Hard callus: from initiation of hard callus until normal stiffness is restored

4. Remodeling: from restoration of normal stiffness to full restoration of normal structure

Stages 1 and 2 (see Figure 10.1) represent the acute or healing phase leading

to the formation of a natural splint or callus. This is a weak provisional tissue

consisting of fibrocartilage and fibrous bone with little internal organization.

However, when 50 to 75% of the normal stiffness is reached, the healing

fracture undergoes a very dramatic and fairly rapid transformation. The soft

callus rapidly condenses and shrinks to form a more organized hard callus,

then is slowly resorbed through a progressive remodeling process leading

to full restoration of normal structure (including reopening of the medullary

canal in long bones). These latter two stages appear to be mediated by

mechanical requirements through Wolff’s law (see Section 10.3.4) and lead

to an efficient structure with normal properties. Thus, stages 3 and 4 of

fracture healing can be thought of as a chronic phase and appear to represent

adaptive remodeling of a functionally healed bone (end of stage 2).

Note that normal stiffness is obtained first and, in fact, generally exceeded,

due to the combined presence of callus and healing cortical

bone in the

defect; normal strength is obtained only towards the end of the remodeling

phase.

In any particular bone, fracture healing, with a certain degree of injury,

can be expected to progress to completion in an average time characteristic

of the initial condition and, to some degree, the type of treatment (internal

fixation, external splinting, etc.). If there is a significant delay but eventual

complete healing and remodeling, the condition is termed delayed union.

However, it is possible for the process to be interrupted at any stage. If

this occurs in stages 1 and 2, before any degree of structural integrity is

obtained, and is permanent, the result is a nonunion, sometimes called a

“pseudarthrosis.”* Nonunions are frequently sites of active tissue turn

over but rarely heal without additional intervention, validating the dis

tinction made here between nonadaptive stages (1 and 2) and the adaptive

ones (3 and 4).

FIGURE 10.1

Stages of fracture healing.

* Black (1987) includes a more detailed discussion of these diagnostic distinctions. Stiffness (100%) Strength (100%) TimeInjury 1 2 3 4 (end)

10.3 Examples of Adaptation in Implant Applications

10.3.1 Introduction

Implant applications offer a wide variety of possible examples of adaptation.

Consideration here will be restricted to the following examples:

- Growth of the “neointima” in arterial prostheses
- Attachment of tendon prostheses to soft tissue
- Hard tissue remodeling in the presence of implants
- Bone response to electrified implants

Many other examples of adaptation to the presence of implants can be found.

In fact, it may be useful to consider that, when resolution to a stable situation

is possible (see Section 8.2.6), accommodation of the local host tissues to

implants consists most generally of two phases: an acute or healing phase

and a chronic or adaptive phase.

In all of the adaptive processes, the control mechanism invoked is phe

nomenologically described by a unifying principle. In hard tissue, this prin

ciple is termed Wolff’s law. Julius Wolff, a 19th century German anatomist,

suggested in 1892 that bone (and, by inference, other load-bearing tissues)

remodels in an attempt to maintain a constant (optimal) pressure or local

stress. Although he did not make such a specific statement, it is usual to say

that Wolff's law is: "The form being given, tissue adapts to best fulfill its

mechanical function."

Thus, as load increases over a period of time, bone mass would be expected

to increase to maintain a constant level of stress. Conversely, a reduction in

load should produce a loss of tissue. In a more sophisticated interpretation,

realignment of principal stresses should be reflected by a modification of

tissue structure. Observations in a variety of static and renewing tissues

suggest a considerable pragmatic generality for Wolff's law.

10.3.2 Vascular Adaptation

The growth of a new tissue layer, or neointima, on the internal surfaces of

knitted arterial prostheses is an interesting example of adaptation. Here, the

prosthesis is introduced to serve as a framework to support host tissue that

will serve as a long-term nonthrombogenic blood contact surface. The body

of the prosthesis, which is most commonly made of polyester or similar

polymeric fiber, provides the mechanical resistance to internal pressures that

was once provided by the original vessel.

Upon insertion of the prosthesis, the features of the clotting cascade

described in Section 9.2 take place. In fact, the surgeon usually preclots

the prosthesis using the patient’s blood in an effort to provide a smooth,

defect-free surface and to reduce blood loss. The fibrin surface, inside and

outside, matures and achieves stable dimensions within 24 hours. At this

point, healing is clearly initiated. Within a few weeks, the outside (tissue

side) of the prosthesis is covered by granulation tissue, and a capsule of

fibrous tissue matures with increasing organization. The resolution or heal

ing response of the internal surface facing flowing blood is a different matter.

Schoen (1989) distinguishes between two forms of vascular resolution:

pseudointimal formation, the mere coating of the implant’s surface with

proteins and cells other than endothelial cells, and neointimal formation, the

formation of an endothelial lined surface, usually overlying a layer of smooth

muscle cells. The choice of outcome is apparently governed by the nature of

the biomaterial surface and, as will be seen, can be considered as an

example of adaptation of the natural healing process to the properties of the

prosthesis.

During ideal or optimal healing, blood vessels penetrate to the lumen of

the prosthesis and “tufts” of tissue spread along the inner surface, merging

to form a smooth neointimal surface that functions like the natural arterial

lining. Some investigators (e.g., Annis et al. 1978) suggest that this process

of “through-growth” is not essential to the formation of the neointima and

that longitudinal growth from the ends inward is possible in impermeable

vascular prostheses. In a pig, this process is completed within a month, but

it takes up to a year in a human patient.

However, this healthy adaptive vascular maturation has been shown

(Wesolowski et al. 1968) to be critically dependent upon the prosthesis poros

ity. Figure 10.2a displays the relationship developed for a variety of porous

prosthetic materials tested as arterial grafts in the pig. The porosity is given

in units of liters/min/cm 2 of water expressed from the lumen through the

wall of an unclotted non-blood-exposed graft with a pressure differential of

120 mmHg. The calcification index is the product of the average calcification

(on a subjective scale of 1+ to 4+) of all animals implanted with a given

material and the percentage of all specimens of the same material that dis

play calcification. Here, high porosity above a value of 1 favors maturation

of the neointima; lower porosity leads to failure of microvascular ingrowth,

focal necrosis of the neointima, and possible calcification of the resulting

pseudointima, in many respects mirroring the events of arteriosclerosis in

natural tissue.

Attempts have been made to moderate this process by “seeding” the lumen

wall with autologous cells (Kahn and Burkel 1973), with cultured endothelial

cells (Mansfield et al. 1975), and by various pretreatments; however, the

relationship found by Wesolowski et al. (1968) appears to be well founded.

The generality of this relationship is suggested by Figure 10.2b. This dis

plays the relationship of a “net acceptability index” and the previously

discussed physical water porosity. It represents the results of the evaluation

of a variety of knit and velour polyester arterial prostheses (Sawyer et al.

1979). The net acceptability index is a transformation of the “net evaluation

index” used by the authors so that the low scores are satisfactory, as in Figure

10.2a. The net evaluation index is a combined score based upon in vivo

performance and postimplantation evaluation. It is clear that the same result

is obtained as that found by Wesolowski et al. (1968); high porosity favors

good in vivo performance. This is clearly an example of a structural attribute

of an implant strongly affecting tissue adaptation after surgery. Unlike the

case of Wolff’s law adaptation in bone, where the amount of tissue is affected

FIGURE 10.2

(a) Relationship between physical water porosity of arterial (woven) prostheses and calcification

in the pig. (b) Relationship between physical water porosity and net acceptability index of

arterial grafts (dashed lines indicate range). (Figure 10.2a adapted from Wesolowski, S.A. et al.,

Ann. N.Y. Acad. Sci., 146(1), 325, 1968; Figure 10.2b adapted from Sawyer, P.N. et al., J. Biomed.

Mater. Res., 13, 937, 1979.) 0 100 200 300 1 2 3 4 5 0 1 2 3 1 2 3 4 Calcification Index Net Acceptability Index (4 - Net Evaluation Index) P o r o s i t y P o r o s i t y (a) (b)

by the implant attribute, here the type of tissue is affected by the (nonchem

ical) implant attribute.

10.3.3 Prosthetic Replacement of Tendons

The second area of adaptation to be considered is in the area of tendon

prostheses. Here, the natural system provides a junction between the soft

tissue (tendon) and the hard tissue (bone) by a series of collagenous fibers

(Sharpey’s fibers) that pass into the bone. There has been considerable inter

est in reproducing such a system by inserting a porous material into the

bone or by providing a porous bridge between the end of the natural tendon

insertion and a tendon remnant or the muscle. In either case, a situation is

desired in which the natural tissue will grow into the prosthesis and provide

mechanical strength. The topic of bony ingrowth will be discussed later.

Homsy et al. (1972) performed an interesting study of this subject using a

porous graphite-reinforced poly (tetrafluoro) ethylene (Proplast™, Vitek,

Inc., Houston, TX).* Blocks of this material were inserted in the rabbit cal

caneal tendon, replacing segments of the natural structure, and sutured in

place to be load bearing immediately. At periods of up to 26 weeks, the

rabbits were sacrificed and the strength of the bond between natural and

prosthetic material was tested in tension. The results are shown in Figure

10.3. These results are reported to be the same for tendon/prosthesis and

muscle (gluteal)/prosthesis interfaces and to reach a plateau value of rupture

strength shortly after 8 weeks — about 5 weeks later than for collagenous

* I discussed this study in the first edition of this work (published in 1981). Since then, the sad story

of the misapplication of this material to load-bearing applications in bone, such as in the attempted

replacement of the human temperomandibular joint, has become well known. However, in prepar

ing this edition, I elected again to retain this study for two reasons: (1) it is, for its time, a well done

piece of work; and (2) it is an object lesson concerning the limits of animal studies and the reality

of the need to define biological performance in relationship to specific applications.

FIGURE 10.3

Prosthesis/tissue anastamosis strength. (From Homsy, C.A. et al., Clin. Orthop. Rel. Res., 89, 220,

1972.) 2 3 4 1 Time (weeks) 0 2 4 6 8 10 12 14 16 26 U n i t R u p t u r e S t r e s s (K g F / c m 2)

ingrowth in bony sites. Here the gradual development of strength, as con

trasted with the rapid (within 3 weeks) complete penetration of unorganized

collagen that the authors would have predicted from earlier studies suggests

that an organized structure is forming under control of the axial mechanical

load exerted by the muscle.

This picture is substantiated by studies of a different system in this appli

cation. Here, the system is a complete tendon prosthesis that gradually

disintegrates under use. Studies with a braided carbon ligament in rabbits

(Forster et al. 1978) and sheep (Jenkins et al. 1977) showed that, as the

prosthesis frayed and fatigued, it served as a scaffold for the growth of

fibrous tissue that took over the function of the prosthesis. Figure 10.4 shows

the breaking strength of the rabbit calcaneal tendon prostheses from this

study. The authors ascribe the rapid development of strength to a stimulation

effect of the carbon, but one might equally suggest that the gradual transfer

of stress to the ingrowing tissue evoked this adaptive response. The devel

opment of maximum strength at 6 weeks (somewhat earlier than in the study

of Homsy et al. in 1972) suggests that the disintegration of the prosthesis

served to transfer stress more rapidly than was the case with a more durable

material.

This experiment has been carried to a natural conclusion by incorporating

the carbon fibers in a matrix that is degradable in the internal environment

(Alexander et al. 1979). The matrix used here was polylactic acid, and the

implant was inserted as a replacement for the canine patellar tendon. A

gradual dynamic replacement of prosthesis with organized fibrous tissue

was reported as the prosthesis matrix disintegrated, with reasonable matu

rity and linear tissue arrangement after 2 months of implantation. However,

in neither of these experiments did the resulting tissue closely come to

resemble normal tendon. Thus, it should be best termed neotendon, in par

allel with Schoen’s (1989) terms for healing vascular endothelial tissue. In

more extreme cases when the new tissue more resembles a fibrous scar or

capsule, it is more appropriately termed pseudotendon and its long-term

durability under mechanical loads must surely be questioned. Balduini at

FIGURE 10.4

Breaking strength of pseudotendon. (Adapted from Jenkins, D.H.R. et al., J. Bone Joint Surg.,

59B, 53, 1977.) R u p t u r e S t r e n g t h (K g F) Normal range 0 2 4 6 8 10 12 4 8 12 16 20 Time (weeks)

al. (1986) have summarized further clinical developments that attempted to

build on these observations.

10.3.4 Adaptive Remodeling of Bone near Implants

10.3.4.1 Stress Shielding

Wolff’s law suggests that the introduction of a load-bearing implant coupled

to a previously load-bearing natural structure should result in some atrophy

or tissue loss. Because the assumption of a portion of the tensile load or

bending moment by the implant must necessarily reduce the local stress in

the adjacent tissue, this phenomenon has come to be called “stress shielding”

(Huiskes 1988). The most commonly cited example is that of the progressive

loss of bone material in the proximal medial femoral cortex (calcar) observed

in animals and humans after total replacement of the hip joint. However,

observation of the remodeling response is complicated by a simultaneous

presence of an osteolytic response mediated by the presence of wear debris

released from the articulating interface (Amstutz et al. 1992).

A more easily examined example is an unfortunate concomitant of the

use of metallic internal fracture fixation devices. These devices are usually

far more rigid than the bone to which they are attached, even if the bone

is intact (as in experimental situations). Although they provide excellent

support and maintain reduction and fixation during healing, a considerable

amount of osteoporosis,* or loss of bone mass without external change of

shape, occurs in the bone under the plate or adjacent to the rod. A study

of experimental fractures in rabbits (Brown and Mayor 1978) seems to

reinforce this point. Fractures were produced in the tibias of rabbits and

were internally fixed with rods made of a variety of metals and polymers.

The rods were a constant diameter to provide a range of stiffness relative

to the intact bone from 10 to 0.03×. The animals were sacrificed and studied

at 9 and 16 weeks after fracture and fixation. The results were confused by

an anomalous response to one metal alloy (Ti6Al4V); however, at 16 weeks,

fractures fixed with rods that were less stiff than the intact bone were

significantly stronger and tougher in torsion than those fixed with rods

that were stiffer than the intact bone. Additionally, in the weaker, less tough

bones (fixed with the stiffer rods), a greater degree of osteoporosis was

seen histologically.

This experiment is difficult to interpret solely in terms of an adaptive

response to implants because the changes in bone are presumably caused by

two factors: a healing response and an adaptive response. Moyen et al. (1978)

conducted an experiment in dogs in which no fracture was involved and

obtained somewhat similar results. In this experiment, metallic plates of two

* The term osteoporosis is more generally applied to metabolic rather than adaptive loss of bone.

(See NIH Consensus Statement, Vol. 17 (1)), Osteoporosis Prevention, Diagnosis and Therapy,

Washington, D.C., 2000.) However, the structural and mechanical consequences are essentially

the same as in adaptive remodeling, so the same term is used here.

different stiffnesses varying by a factor of approximately 5 were attached to

the midshaft of the femur in the dog. The bone mass under the plates was

compared with the control (unplated) side after 6 and 9 months implantation.

Interestingly, a small constant porosity of 1 to 3% was seen. However, after 6

months, the bone mass under the rigid plate had decreased 26.4% vs. only

16.4% under the more flexible plate. The decreases in bone mass continued to

develop more slowly up to 9 months and showed modest reversals in another

group implanted for 6 months and studied 3 months after plate removal. The

authors ascribed the failure to observe the greater porosity seen in other studies

(such as the one by Brown and Mayor in 1978) to the absence of the fracture

healing process accompanying the remodeling (adaptive) process.

Perren et al. (1988) further criticized the possible adaptive role in the

production of porosity near fracture fixation devices and suggested that the

physical presence of the device interferes with revascularization after frac

ture. He showed an inverse relationship between the area of plate-bone

contact and cortical porosity in a sheep tibial model. One may, in turn,

criticize this work because reducing the plate-bone contact area probably

reduces the coupling between plate and bone, thus rendering the plate

effectively less stiff — that is, less able to remove load (and thus reduce local

stress) from the bone.

Another study by Bradley et al. (1979) combined some of the aspects of

the studies of Brown and Mayor (1978) and Moyen et al. (1978). In this case,

a variety of fracture fixation plates, with stiffnesses between 4 and 40% of

the bone to be fixed, were used in a 16-week study of the healing of femoral

midshaft osteotomies in dogs. A definite relationship was seen between plate

rigidity and strength of the bony material and the femoral midshaft as a

structure. This is shown in Figure 10.5.

Two comments should be made about this study. In the first place, the

parameter examined was strength rather than rigidity, as in the case of the

previous two studies. Although rigidity may parallel strength, the correlation

is not exact, even in materials that are simpler in microstructure than bone.

Furthermore, restoration of rigidity is probably more important in the early

phases of fracture healing because it confers functional ability before adap

tation is complete. In the second place, porosity was not studied, as in the

work of Moyen et al. (1978). Porosity was suggested by Moyen to be a

concomitant of trauma rather than simply adaptation (my term) and by

Perren et al. (1988) as secondary to interference with revascularization; it

may severely affect material and structural strength due to stress concentra

tion effects, but have a modest volume-fraction effect upon modulus and

thus upon material and structural bending rigidity (see Section 6.3.2). It is

impossible to isolate this effect in this study.

One should not assume from these studies that large changes in stress are

necessary to modify bone growth — that is, to produce adaptive changes in

bone. Modest changes in stress, such as those that might be produced by

simple, soft polymeric caps of bone shafts after segmental excision, have

been shown to produce profound adaptive changes (Lusskin et al. 1972).

10.3.4.2 Ingrowth into Porous Biomaterials

It is an easy step from the earlier discussion of the ingrowth associated with

the prosthetic replacement of tendons to consideration of the more general

problem of ingrowth into porous bodies. One of the responses to implants

is the formation of a fibrous capsule, so it is no surprise that tissue will

invade the internal spaces of an implant with an open, connected pore

structure.

Extensive studies of this phenomenon have been conducted. Ingrowth

occurs into porous implants fabricated from a wide variety

of metals,

polymers, and ceramics. The nature of the ingrowing tissue in the presence

of sufficient interfacial mechanical stability* depends upon the size of the

FIGURE 10.5

Changes in bone material and structural strength with fixation plate rigidity. (Adapted from

Bradley, G.W. et al., J. Bone Joint Surg., 61A, 866, 1979.)

* The issue of the role of interfacial shear (producing the so-called “micromotion”) on tissue

ingrowth remains sufficiently confused that an analytical discussion of this point is not possible.

However, see Brunski (1988) and Prendergast et al. (1997) for fuller discussions of this topic. 2 4 6 8 10 12 14 16 18 2 4 6 8 10 12 14 16 18 N o r m a l i z e d S t r u c t u r a l S t r e n g t h | s / s c o n t r o l | N o r m a l i z e d M a t e r i a l S t r e n g t h | σ / σ c o n t r o l | beneath plate opposite plate beneath plate opposite plate Plate Flexural Rigidity (N - m 2) Plate Flexural Rigidity (N - m 2) 0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 0.2 0.4 0.6 0.8 1.0 1.2 1.4 0

pore (Friedenberg and Lawrence 1959) or, more properly, on the minimum

size of the interconnections between pores (Klawitter and Weinstein 1974).

Soft tissue elements will be found in interconnects as small as 1 to 5 μm;

at some minimum interconnect diameter between 50 and 100 μm, miner

alized tissue will be found and organized osteonal bone will grow into

interconnects as small as 250 μm. Maximum interfacial shear strengths

develop between 8 and 16 weeks after implantation,

depending upon

anatomical locations, species of animal, and type of tissue ingrowth. Veloc

ity of ingrowth appears to increase with pore sizes above 50 μm and to

reach a peak near pore sizes of 400 and 500 μm, as determined in a single

pore model (Howe et al. 1974).

The ability of tissue to mineralize and organize as interconnect size

increases is another clear example of adaptation. A study of Proplast™ (Vitek,

Inc., Houston, TX) by Spector et al. (1979) confirmed this finding and dem

onstrated that it is not a false conclusion based upon comparison of studies

with different materials and/or test conditions. If implanted directly, this

material exhibits a pore size near 76 μm with an interconnect size of 50 μm.

In a canine cortical bone site, only fibrous ingrowth was observed for periods

of up to 20 weeks. However, if the material was “teased” before implantation

to increase the size of interconnects, a variable degree of bony ingrowth

occurred.

There appears to be a difference of opinion over the interpretation of the

findings in this report (Homsy 1979; Spector 1979). This finding, combined

with earlier reports (Klawitter and Hulbert 1971), suggests a practical lower

interconnect limit of 100 μm for bone ingrowth. The mechanism of control

of ingrowth and the manner in which pore interconnect size controls min

eralization are unknown. Although Wolff's law arguments can be invoked

to explain tissue remodeling near the bone–implant interface, it is presumed

that tissue more than one pore diameter deep within the implant porosity

will be essentially load free if the modulus of the implant exceeds that of

bone to any significant degree. However, tissue maturation internal to porous

implants appears to have little dependence on implant material modulus,

but may be related more to electrical, chemical, and morphological effects

on the pericellular environment.

10.3.4.3 Adhesion

Tissue is not inherently "sticky." Cells adhere to each other and to their

extracellular matrices through the interaction of a variety of specific and

nonspecific adhesion molecules and specific cell surface receptors for por

tions of these molecules (see Section 11.3.3), in addition to more diffuse Van

der Waals bonding mechanisms. However, attempts to cause implants pur

posefully to adhere to tissue have aroused considerable interest.

When such adhesion is produced by the mere close (molecular-scale)

approximation of tissue and implant, without an intervening fibrous capsule

or other elements of an inflammatory response, it is termed most generally

tissue integration; in the case of bone, the more specific term is osseointe

gration (Albrektsson and Hansson 1986). In the latter case, the apparent

adhesion is produced by cellular binding to proteins adsorbed to the implant

surface. Originally thought to be a property of pure titanium alone, such

tissue integration has now been shown for a variety of metallic implant

surfaces (Linder 1989), including tantalum (Black 1994). In fact, Linder (1989)

has suggested that, in general, “osseointegration is a response of bone to a

tolerable implant material inserted under tolerable conditions” without spec

ifying the meaning of “tolerable” in either case.

When tissue adhesion to an implant is accompanied by a chemical alter

ation of the implant surface, a true bonding process with a continuous

gradation of structure and composition across the tissue–implant interface

may occur. Although there is no generally accepted term for this condition,

interactive biomaterials that produce it have been termed surface active

(Hench and Wilson 1984) in recognition of the necessity of chemical reaction

with the local host environment prior to bond formation.* A number of

ceramic and glassy materials have been produced that develop such bonds

to bone and soft tissue (Figure 10.6).

In the case of integration or of bonding, the implant becomes mechanically

coupled to the adjacent tissue. In the case of hard tissue, this results in a

strain incompatibility due to the differences in moduli between bone and

the implant. Several adaptive changes are possible. The most common situ

ations are:

* The term bioactive has also been used for such materials (see Section 1.4). However, this is an

apparent misnomer because it appears that the necessary surface modification is a consequence

of exposure to the physiological environment, rather than to life processes.

FIGURE 10.6

Ceramic and glassy tissue-bonding materials. (From Hench, L.L. and Wilson, J., Science, 226,

630, 1984. With permission: L.L. Hench.) SiO 2 Cervital ® (Leitz) A/W Glass Ceramic (Kyoto U.) Inert Adhesive Resorbable 45S5 Bioglass ® (U. of Florida) Bone bonding boundary CaO(MgO) + P 2 O 5 Na 2 O(K 2 O) Compositions where soft tissue adhesion occurs

• The implant is placed in cancellous bone and is of very significantly higher modulus than the surrounding tissue. The frequently observed response in this case is the formation of a bony “plate” much resembling a subchondral plate in an articular joint and a relative rarefaction of

the cancellous trabeculae behind the plate. This results in introducing a relatively compliant tissue zone adjacent to the implant and “shielding” the bone further away from the mechanical consequences of the stiff implant.

• The implant is placed in cortical bone and is of significantly higher modulus than surrounding tissue. In this case, bone near the implant becomes porous, much as in the stress-shielding examples previously discussed (Section 10.3.4.1). However, this porosity may increase and proceed to a remodeled condition resembling cancellous bone. Thus, this process is termed cancellization.

In either case, the tissue structure changes are a result of the change in

mechanical conditions near the newly formed interface and thus are true

examples of adaptive remodeling.

10.3.5 Bone Response to Electrified Implants

It has been frequently suggested that the mechanism of Wolff’s law in bone

is electrically controlled. Bone and other tissues produce potentials when

deformed; these potentials are called piezoelectric potentials or, more gener

ally, strain-related potentials. A variety of other potential sources also exists.

Bassett (1971) proposed a generalized, closed-loop control system (as

shown in Figure 10.7) to relate these signals to hard tissue remodeling. There

is a conceptual error in his scheme because, presumably, the structural

response (to adjust stress) results in a change in the osseous transducer (see

added dashed line), rather than in a modification of the extrinsic force as

proposed. Nevertheless, this general idea, first proposed some years before

this early review was published, has been a motivating factor in the inves

tigation of the effects of electrical phenomena on the modification of bony

growth and remodeling. Numerous studies have shown a correspondence

between endogenous electrical phenomena and growth, repair, and remod

eling processes; however, no critical experiments that show that these signals

are necessary and sufficient to serve as stimuli for the observed processes

have yet been performed.

Although it is not clear that electrical control of bone growth, remodeling,

and repair is an example of adaptive response to implants, it is worth noting

some general conclusions from research in this area for completeness of this

discussion (Black 1987). A physical electrode may be considered as a special

case of metallic implantation: one in which the electrode, instead of being

allowed to find its appropriate mixed corrosion potential (see Section 4.6),

is maintained under a controlled relative potential or current condition. The

responses to implantation of such a physical electrode in or near hard tissue

are summarized as:

- The presence of a metallic cathode, with a negative

potential, stimulates the conduct of cells involved in bone formation.

• In particular, bony repair in sites of trauma is accelerated, and cells in medullary sites may be induced to form bone in the absence of bony trauma or to maintain bone formed in response to transient trauma.

• In all cases, apparently a narrow stimulatory “window” is defined by limits on current and electrode potential.

• Finally, monophasic negative pulses of frequencies from 10 to 750 Hz, with duty cycles between 50 and 5%, provide stimulation that approaches but does not exceed that of direct uninterrupted current.

Although the relationship of this line of research to the more general problem

of adaptive growth is unclear, it does represent one of the more systematic

attempts to elucidate the phenomena involved.

10.4 A Final Comment on Adaptation

It now seems clear that one of the original goals of implantation — that is,

to produce minimal tissue (host) response — is an outmoded view that may

FIGURE 10.7

Negative feedback control system proposed as a basis for Wolff’s law. (Adapted from Bassett,

C.A.L., in Biochemistry and Physiology of Bone, Vol. 2, 2nd ed., Bourne, G.H., Ed., Academic Press,

New York, 1971, 1.) (Correct effect) STRUCTURAL RESPONSE TO RESIST FORCE OSSEOUS TRANSDUCER EXTRINSIC FORCE PROPORTIONAL ELECTRICAL CONTROL SIGNAL BIOLOGICAL TRANSDUCER

limit further development of implant materials and devices. It is proper to

ask that adverse host response be kept within bounds acceptable to the

application. This is the necessary condition of biocompatibility. It is essential

to rule out a priori certain classes of response, such as neoplastic transforma

tion, as unacceptable. Now it appears equally reasonable to pursue active

tissue response in the form of adaptation so that natural tissue can take over

the role of the implant as completely as possible.

One of the ways of viewing the research literature on local host response

is to note that it has three somewhat unconnected parts:

- The majority of the studies reported emphasize the chemical composition of the implant and its degradation products. The local host response is seen as a physiological response to soluble chemical species.

- A smaller body of work, primarily oriented to orthopaedic surgery, emphasizes the stiffness of the implant in relation to surrounding tissues, strains imposed by function, and, especially recently, the surface texture and configuration of the implant surface. The local host response is seen as a structural embodiment of consequences of Wolff’s law.

- A still smaller set of studies report the cellular and tissue response to imposed electrical fields and currents, especially in the context of biomaterials, by implanted electrodes. The local host response is seen, primarily, as mediated by information content of the electrical effects and secondarily by local electrochemically induced pericellular environmental changes.

Figure 10.8 illustrates the general schematic form of the proposition: physical

factors induce local host response through various mechanisms.

However, it may well be the case that these effects are not independent,

but interdependent and perhaps, in some cases, synergistic. Figure 10.9

summarizes the local host effects discussed in Chapter 8, Chapter 9, Chapter

12, and Chapter 13 and their relationships to the degree or intensity (“dose”)

FIGURE 10.8

Physical induction factors in local host response. PHYSICAL INDUCTION FACTORS CHEMICAL ELECTRICAL MECHANICAL LOCAL HOST RESPONSE IMPLANT

of physical induction factors. Here I distinguish between interfacial stress

and resulting shear displacement (motion): these are, in fact, coupled because

the latter depends upon the former and on the surface structure of the

implant. A “rough” implant permits far smaller interfacial displacements

than a “smooth” nonadhesive one under the same stress. Normal host

response, the quiescent state after full, acceptable resolution has occurred

(see Section 8.2.6), is most generally characterized by low chemical activity,

intermediate (near charge neutral) electrical activity, and intermediate inter

facial stress, accompanied by an appropriate physical configuration of the

implant surface. Particular cases, such as direct tissue adhesion, require other

combinations of levels of these factors.

Much work remains to be done until the principles of adaptation are fully

understood and harnessed to the solution of patient problems.

Albrektsson, T. and Hansson, H.-A., An ultrastructural characterization of the interface between bone and sputtered titanium or stainless steel surfaces, Biomaterials, 7, 201, 1986.

FIGURE 10.9

Adaptive responses to physical induction factors. (Adapted from Black, J., Orthopaedic Bio

materials in Research and Practice, Churchill-Livingstone, New York, 1988, 288.) IMPLANT TISSUE LOCAL HOST RESPONSE

ADHESION (?)

HYPERSENSITIVITY

CHEM. NEOPLASIA

CHRONIC, SEVERE

INFLAMMATION

ACUTE, MILD

INFLAMMATION

FB NEOPLASIA (?) (?): Possible effect

CHEMICAL ELECTRICAL
MECHANICAL

LOW
LOW STRESS “MOTION” GROWTH
and HEALING SUB-CHONDRAL ENCAPSULIZATION
CONDENSATION (?) NECROSIS CHRONIC
FRACTURE INFLAMMATION ADHESION (?)
INGROWTH ADAPTIVE REMODELING PHAGOCYTOSIS CLASIS
HYPERPLASIA HEALING ATROPHY CANCELLIZATION REMODELING
PHYSICAL INDUCTION FACTORS HIGH NECROSIS RESORPTION

HIGH

Alexander, H. et al., Ligament and tendon replacement with resorbable polymerfilamentous carbon tissue scaffolds, Trans. Orthop. Res. Soc., 4, 27, 1979.

Amstutz, H.C. et al., Mechanism and clinical significance of wear debris-induced osteolysis. Clin. Orthop. Rel. Res., 276, 7, 1992.

Annis, D. et al., An elastomeric vascular prosthesis, Trans. Am. Soc. Artif. Intern. Organs, XXIV, 209, 1978.

Balduini, F.C., Clemow, A.J.T. and Lehman, R.C., Synthetic Ligaments: Scaffolds, Stents, and Prostheses, Slack, Thorofare, NJ, 1986.

Bassett, C.A.L. Byophysical principles affecting bone structure, in Biochemistry and Physiology of Bone, Vol. 2, 2nd ed., Bourne, G.H. (Ed.), Academic Press, New York, 1971, 1.

Bizzozero, G., Brit. Med. J., 1, 728, 1894 (cited in Goss, 1978).

Black, J., Electrical Stimulation: Its Role in Growth, Repair, and Remodeling of the Musculoskeletal System, Praeger, New York, 1987.

Black, J., Orthopaedic Biomaterials in Research and Practice, Churchill-Livingstone, New York, 1988, 288.

Black, J., Biological performance of tantalum: a review, Clin. Mater., 16(3), 167, 1994.

Bradley, G.W. et al., Effects of flexural rigidity of plates on bone healing, J. Bone Joint Surg., 61A, 866, 1979.

Brown, S.A. and Mayor, M.B., The biocompatibility of materials for internal fixation of fractures, J. Biomed. Mater. Res., 12, 67, 1978.

Brunski, J.B., The influence of force, motion, and related quantities on the response of bone to implants, in Non-Cemented Total Hip Arthroplasty, Fitzgerald, R.H., Jr. (Ed.), Raven, New York, 1988, 7.

Forster, I.W. et al., Biological reaction to carbon fiber implants: the formation and structure of a carbon-induced “neotendon,” Clin. Orthop. Rel. Res., 131, 299, 1978.

Friedenberg, Z.B. and Lawrence, R., Bone growth in polyvinyl sponge, Surg. Gynecol. Obstet., 109, 291, 1959.

Goss, R.J., The Physiology of Growth, Academic Press, New

York, 1978.

Hench, L.L. and Wilson, J., Surface active biomaterials, Science, 226, 630, 1984.

Homsy, C.A., Comments on “characteristics of tissue growth into Proplast and porous polyethylene implants in bone,” J. Biomed. Mater. Res., 13, 987, 1979.

Homsy, C.A. et al., Porous implant systems for prosthesis stabilization, Clin. Orthop. Rel. Res., 89, 220, 1972.

Howe, D.F., Svare, C.W. and Tock, R.W., Some effects of pore diameter on single-pore bony ingression patterns in Teflon, J. Biomed. Mater. Res., 8, 399, 1974.

Huiskes, R., Stress patterns, failure modes, and bone remodeling, in Non-Cemented Total Hip Arthroplasty, Fitzgerald, R.H., Jr. (Ed.), Raven, New York, 1988, 283.

Jenkins, D.H.R. et al., Induction of tendon and ligament formation by carbon implants, J. Bone Joint Surg., 59B, 53, 1977.

Kahn, R.H. and Burkel, W.E., Propagation of pseudointimal linings of vascular prostheses, In Vitro, 8, 451, 1973.

Klawitter, J.J. and Hulbert, S.F., Application of porous ceramics for the attachment of load-bearing internal orthopedic applications, J. Biomed. Mater. Res. Symp., 2, 161, 1971.

Klawitter, J.J. and Weinstein, A.M., The status of porous materials to obtain direct skeletal attachment by tissue ingrowth, Acta Orthop. Belgica, 40, 755. 1974.

Linder, L., Osseintegration of metallic implants. I. Light microcopy in the rabbit, Acta Orthop. Scand., 60, 129, 1989.

Lusskin, R. et al., Bone contouring under silicone polymer implants, Clin. Orthop. Rel. Res., 83, 300, 1972.

Mansfield, P.B., Wechezak, A.R. and Sauvage, L.R., Preventing thrombus on artificial vascular surfaces: true endothelial cell linings, Trans. Am. Soc. Artif. Intern. Organs, XXI, 264, 1975.

Moyen, B.J.-L. et al., Effects on intact femora of dogs of the application and removal of metal plates, J. Bone Joint

Surg., 60A, 940, 1978.

Perren, S.M. et al., Early temporary porosis of bone induced by internal fixation implants. A reaction to necrosis, not stress protection? Clin. Orthop. Rel. Res., 232, 139, 1988.

Prendergast, P.J., Husikes, R. and Soballe, K., ESB research award 1996. Biophysical stimuli on cells during tissue differentiation at implant interfaces, J. Biomech., 30, 539, 1997.

Sawyer, P.N. et al., In vitro and in vivo evaluations of Dacron velour and knit prostheses, J. Biomed. Mater. Res., 13, 937, 1979.

Schoen, F.J., Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles, W.B. Saunders, Philadelphia, 1989, 36.

Spector, M., Reply to comments on “characteristics of tissue growth into Proplast and porous polyethylene implants in bone,” J. Biomed. Mater. Res., 13, 991, 1979.

Spector, M., Harmon, S.L. and Kreutner, A., Characteristics of tissue growth into proplast and porous polyethylene implants in bone, J. Biomed. Mater. Res., 13, 677, 1979.

Wesolowski, S.A. et al., Arterial prosthetic materials, Ann. N.Y. Acad. Sci., 146(1), 325, 1968.

Wolff, J., Das Gesetz der Transformation der Knochen, A. Hirschwald, Berlin, 1892.

Brighton, C.T., Black, J. and Pollack, S.R. (Eds.), Electrical Properties of Bone and Cartilage: Experimental Effects and Clinical Applications, Grune & Stratton, New York, 1979.

Burke, J.F. et al., Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury, Ann. Surg., 194, 413, 1981.

Chehroudi, B. and Brunette, D.M., in Encyclopedic Handbook of Biomaterials and Bioengineering, Part A, Vol. 1, Wise, D.L. et al. (Eds.), Marcel Dekker, New York, 1995, 813.

Dadsetan, M. et al., Surface chemistry mediates adhesive structure, cytoskeletal organization, and fusion of macrophages, J. Biomed. Mater. Res., 71A, 439, 2004.

Draenert, K.D. et al., Strain adaptive remodeling in total joint replacement, Clin. Orthop. Rel. Res., 430, 12, 2005.

Fitzgerald, R.H., Jr. (Ed.), Non-Cemented Total Hip Arthroplasty, Raven, New York, 1998.

Giavaresi, G. et al., Mechanical and histomorphometric evaluations of titanium implants with different surface treatments inserted in sheep cortical bone, Biomaterials, 24, 1583, 2003.

Homsy, C.A., Implant stabilization. Chemical and biomechanical considerations, Orthop. Clin. N. Am., 4, 295, 1973.

Huiskes, R. et al., A biomechanical regulatory model for periprosthetic fibrous-tissue differentiation, J. Mater. Sci. Mater. Med., 8, 785, 1997.

Lane, J.M. (Ed.), Fracture Healing, Churchill Livingstone, New York, 1987.

Lossdörfer, S. et al., Microrough implant surface topographies increase osteogenesis by reducing osteoclast formation and activity, J. Biomed. Mater. Res., 70A, 361, 2004.

Rubin, C.T. and Hausman, M.R., The cellular basis of Wolff's law. Transduction of physical stimuli to skeletal adaptation, Rhem. Clin. N. Am., 14, 503, 1988.

Smith, I.O., Baumann, M.J. and McCabe, L.R., Electrostatic interactions as a predictor for osteoblast attachment to biomaterials, J. Biomed. Mater. Res., 70A, 436, 2004.

Søballe, K. et al., Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions, J. Orthop. Res., 10, 285, 1992.

Thompson, D'A.W. On Growth and Form, Bonner, J.T. (Ed.), Cambridge University Press, Cambridge, 1977.

Vogel, S., Life's Devices, Princeton, NJ, Princeton University Press, 1988.

Wainwright, S.A. et al., Mechanical Design in Organisms, John Wiley & Sons, New York, 1976, 348.

Woo, S. L.-Y. et al., Less rigid internal fixation plates:

historical perspectives and new concepts, J. Orthop. Res., 1, 431, 1984. 203

11

In Vitro Tissue Growth and Replantation

11.1 General Considerations

In 1992, I defined the field of biomaterials (Section 1.4) as having four historic

phases and, in turn, identified four classes or types of biomaterials:

- Type 1: inert
- Type 2: interactive
- Type 3: viable ([bio]hybrid)
- Type 4: replant

The current increasing interest in tissue engineering (TE) represents a shift

in focus from types 1 and 2 to types 3 and 4 biomaterials. The earlier

biomaterials, especially type 2, are not passé; on the contrary, they will

continue to be represented in devices used in the bulk of conventional clinical

applications, will be incorporated in some phase 3 devices, and will serve

in devices intended as bridges to replantation* of phase 4 “devices” (organs).

In some applications, due to problems of cost, supply, etc., types 1 and 2 will

continue to be the biomaterials of choice indefinitely. Research and devel

opment of type 2 materials also continues very actively: in fact, the use of

such materials to produce adaptive affects in the host tissues (see Chapter

10) can be considered, in many cases, as in vivo precursors of tissue engi

neering. Nevertheless, tissue engineering is a rapidly growing area of bio

materials science and engineering (BSE). This chapter will begin to define

the field, explore its early progress, and foresee its near future.

* The surgical literature uses the term “replantation” to describe reattachment of severed body

parts (fingers, etc.). If the severed part is viable and circulation is restored, such procedures can

be highly successful. I retain the term (Section 1.4 and here) because, in each case, the inserted or

reattached portion is mature, autologous tissue.

11.2 What Is Tissue Engineering?

The clearest early definition of tissue engineering of which I am aware is:

“Tissue engineering is the application of principles and methods of engi

neering and life sciences toward fundamental understanding of structure

function relationships in normal and pathological mammalian tissues and

the development of biological substitutes to restore, maintain, or improve

tissue function” (Skalak et al. 1988). After providing this definition, Skalak

went on to remark that The basic point of the above definition is that tissue engineering involves the use of living cells.... The definition is intended to encompass procedures in which the replacements may consist of cells

in suspension, cells implanted on a scaffold such as collagen and in cases in which the replacement consists entirely of cells and their extracellular products.

Skalak was correct and prescient: the use of engineering principles and

techniques to elaborate and incorporate living cells into constructs for ther

apeutic use distinguishes tissue engineering from more conventional biom

aterials studies and from the concerns of other fields of physical and

biological science and medicine. However, his definition has not been gen

erally accepted and there are many interpretations of the scope and breadth

of tissue engineering today.

The best global discussion of this term is provided by Vacanti and col

leagues (2000): In essence, new functional living tissue is fabricated using living cells which are usually associated in one way or another to a matrix or scaffolding which can be natural, man-made, or a composite of both. The living cells can migrate into the implant after implantation or can be associated with the matrix in cell culture before implantation. Conceptually, the field (tissue engineering) differs from the field of cell transplantation insofar as organized three-dimensional tissue is desired and designed.

However, Vacanti et al. conflate types 2, 3, and 4 biomaterials as they have

been previously defined (Section 1.4):

- Type 2 consists of materials engineered in vitro to produce a desired host response in vivo, such as ingrowth into a porous surfaced medullary stem.

- Type 3 consists of composites of cells and matrix (natural, manmade, or a combination) produced in vitro for implantation, such as synthetic vascular grafts

incorporating one or several cell types in a resorbable matrix.

• Type 4 consists of cells, but more generally tissue and, eventually, organs, grown and/or modified in vitro for replantation. Carticel™ (autologous hyaline cartilage cells cultured and replanted) is a primitive type 4 biomaterial because, although it is fully viable, it lacks the (differentiated) three-dimensional aspect referred to by Vacanti.

I will not attempt a final definition of “tissue engineering” here: as is the

case for any emerging field, the definition will mature as the field does.

However, any widely adopted, successful definition (one that can clearly

delimit TE and distinguish it from other pre-existing efforts) must contain

four elements:

• TE must involve engineering — that is, the utilization of fundamental physical, chemical, and electromagnetic laws and principles as well as proven design and development methodology to produce practical solutions to clinical problems. Thus, merely renaming another research field “tissue engineering” will not contribute to progress. A sad example of this is the parallel emerging field of “genetic engineering,” which apparently involves neither an engineering design component nor any appeal to basic physical laws or principles.

• TE must involve engineering manipulation of live cells or tissue, not merely the preparation of interactive (type 2) biomaterials. Thus, there may be type 3 and 4 tissue-engineered materials, but type 1 or 2 materials cannot be reasonably said to be tissue engineered because they affect, attract, or incorporate viable cells and tissues only after being placed in vivo.

• The organic component of a tissue-engineered product must include viable cells (or, at the very least, functional genes). The use of processed natural products as type 1 and 2 biomaterials in medical devices (such as gluteraldehyde-treated porcine tissue) is very well established and, although it has considerable clinical

utility, it cannot be fairly said to constitute TE. Such products are probably better grouped with other "biologics": nonviable agents or materials of essentially natural (rather than synthetic) origin.

• The production of a tissue-engineered product must also involve some in vitro manipulation of viable tissue, cells, or organs. If this is not the case, it will be very difficult to distinguish, as Vacanti et al. (2000) try to do, between tissue engineering and transplantation of cells, tissue, and organs; the latter is a purely medical, not engineering, procedure.

Tissue engineering has a considerable overlap with the emerging field of

regenerative medicine. It is as yet unclear where one can draw the

line between the two; in fact, interdisciplinary academic programs already

combine the two. In general, one can distinguish tissue engineering as pri

marily comprising efforts to replace damaged or absent tissue, using engi

neering techniques as outlined earlier. Regenerative medicine currently

embodies more traditional therapeutic approaches, utilizing stem cells and

genetic transfection, to restore inadequate or lost function in situ, as in

treatment of diabetes, heart disease, spinal cord injury, and Parkinson's

disease (National Resource Council 2002).

11.3 The Cell–Receptor Paradigm

11.3.1 Early Ideas

The advent of the "unit cell" concept in materials science had a revolutionary

effect on understanding of materials properties and their

dependence on

structure. Thus, it was natural, as physical scientists and engineers moved

into interdisciplinary biological research, for them to seek a similar unifying,

simplifying paradigm. In early BSE studies, tissues were regarded as con

tinuous, largely homogenous materials possessing only limited anisotropy

of structure and properties. Because most early characterization studies were

performed on dead tissue, cells were viewed as imperfections in structure,

rather like defects or grain boundaries in polycrystalline materials, and were

largely overlooked. It was understood that cellular function defined the

living state, but that was not a concern for engineers and the general, usually

unspoken, nonvitalist assumption was that living and dead materials had

the same physical properties. This has turned out to be untrue in the general

case (Black 1984).

As BSE became more sophisticated, the biological cell came to be seen as

an equivalent, in tissues, of the unit cell in engineering materials. However,

much of the bulk of tissues is made up of water and of various molecules,

collectively termed extracellular matrix. This matrix, as well as the small

partial volume contributed by the cell walls of dead cells,

is, in fact, being

characterized when investigations of structure-property relations are per

formed on tissues. Only in particular hypercellular structures, such as the

epiphyseal growth plates of long bones or in the contents of the circulatory

system, do the physical structure and properties of biological cells dominate

in mechanical property determinations.

The cell wall, more generally termed the plasma membrane, was originally

described as a phospholipid bilayer, with a hydrophobic core, possessing

general permeability and numerous pores, some passive but others with

active ion-pumping mechanisms. The cell content was regarded as an amor

phous gel with specialized organelles, such as the nucleus and mitochondria,

simply floating in essentially random locations. This simple model has

proven inadequate to describe and explain the details of cell morphology

and function and, in particular, the association of cells with each other and

with their extracellular matrix, in all of the specialized profusion found in

mammalian as well as nonmammalian tissues. For instance, such a simple

model predicts that, through surface tension arguments, all cells should be

spherical in solution and sessile on surfaces. This is

clearly not the case.

Fortunately, in parallel with the development of BSE, mammalian cell

biology and physiology was making great strides. A new unifying paradigm

has emerged: receptor–ligand binding. Tissues are now seen as associations

of cells and matrix, connected by specific and nonspecific receptor–ligand

binding and receptors crossing the plasma membrane, providing bidirec

tional linkages capable of transducing information among the interior of the

cell, its nearest neighbors, and its environment. Furthermore, most cells are

now recognized to have well defined internal structures; active and passive

molecular scaffolding links many of the organelles. Thus, the recep

tor–ligand-binding model in normal tissues provides the key to understand

ing the elaboration of those tissues and therefore the association between

cells and synthetic matrices of types 1 through 3 biomaterials.

Tissues, as always, remain artifacts of the lives of cells. However, through

the receptor–ligand paradigm, how cells make tissue matrices and, in turn,

how these matrices influence the conduct of their lives can be understood.

11.3.2 The Membrane Receptor

In its most general form, a cellular receptor is a complex

of two molecular

chains traversing the cell membrane. The receptors are grouped together

into types, such as integrins, selectins, cadherins, etc., based upon similarity

of structure and of function. Within each type, the individual molecular

chains are grouped together into families, depending upon general features

of structure — primarily, the possession of a common subunit (see following).

The integrin type is perhaps of primary importance to TE studies because

these receptors play key roles in cell–cell and cell–matrix association. Inte

grins are heterodimers made up of one each from subunits or chains termed

“ α” and “β” (see Figure 11.1). There are large numbers of α- and β-chains

and thus very large numbers of possible different receptor structures and

functions. The α- and β-chains are distinguished by the use of numerical

subscripts: for example, the α 6 β 1 is a common receptor specialized for

binding to the matrix protein laminin (Wei et al. 1997). However, all integrins

share the following characteristics:

• The two chains, as combined, reside in the cell membrane so that they have three principal domains, or subsections: • An intracellular domain that can link with intracellular molecules and, in particular, can bind to the internal molecular skeleton of the cell • An intramembrane domain • An extracellular domain that forms the binding site for extracellular ligands, such as free molecules (cytokines,

peptides, etc.) or portions of the extracellular matrix

• The receptors are free to move along the surface of the membrane and, under certain conditions, such as phagocytosis, can be internalized, recycled, and reappear on the cell surface.

• Intracellular and extracellular binding is reversible and, as such, the bound state represents an equilibrium:

Thus, the action of a receptor depends upon its population concentration

on the cell membrane, the concentration of the ligand, and the energetics of

binding and dissociation, as represented by k b and k d , respectively. Further

more, divalent ions, such as Ca ++ , are also frequently involved in forming

or stabilizing receptor–ligand complexes. In addition, the population con

centration on the cell membrane depends upon equilibrium between the

assembled receptor and the intracellular concentrations of the respective α

and β-chains. Thus, receptor activity can be affected in many ways and

receptor–ligand association has the potential to exert well differentiated

effects on the cell.

11.3.3 Receptor–Matrix Interactions

The primary interest here is in the consequences of binding of receptors to

molecules in the extracellular matrix. Again, although this complex material

holds many molecules and the appearance and concentration of the spectrum

vary from tissue to tissue, certain motifs recur. Ligand binding by receptors

depends on recognizing short sequences of three or more amino acids. One

such sequence is (-arginine-glycine-aspartamine-) (abbreviated: RGD). The

FIGURE 11.1

Schematic arrangement of the integrin receptor. α β Cell Membrane INTRACELLULAR EXTRACELLULAR Ligand Binding Site Receptor+Ligand Receptor-ligan k k b d complex

α 5 β 1 integrin binds to the RGD sequence, which is found in the very common

extracellular matrix molecule fibronectin. Thus, the formation of α 5 β 1 RGD

complexes plays a strong role in association between cells and the extracel

lular matrix (MacDonald 1989). This observation has been utilized in the

fabrication of interactive substrates that will bind cells through recep

tor–ligand association rather than through nonspecific chemical affinity

(Massia and Hubbell 1990).

Once receptor–ligand binding takes place, several consequences can occur

(Lauffenburger and Lindermann 1993) (Figure 11.2):

- The extracellular receptor–ligand complex formation may change the nature and/or affinity of the intracellular domains for intracellular species. Such intracellular binding, in turn, may alter the behavior of the extracellular domain of the receptor.

- The complex may be internalized, as in phagocytosis, thus playing a role in transmembrane transport of the ligand.

- Changes in the extracellular domain may “transduce”

information, via the intracellular molecular skeleton (not shown in Figure 11.2 for clarity) to organelles such as the nucleus. In the short term, this may result in modification of cellular behavior (modulation), but in the longer term, it may produce activation of DNA, resulting in expression of new RNA and thus a possibly irreversible change in cell function (differentiation).

FIGURE 11.2

Possible consequences of extracellular receptor–ligand binding. α β Ligand Receptor Binding Consequences of extracellular ligand binding: transmembrane transport intracellular signaling coupling with membraneassociated molecules Dissociation Cell Membrane

The emerging understanding of the consequences of the receptor–ligand

paradigm is profound. In regard to BSE in general and TE in particular, the

following conclusions can be drawn:

• Cells are in constant communication with their external environment; therefore, maintenance and/or alteration of the pericellular conditions are important considerations in understanding host response to biomaterials.

• In their native habitat, cells depend upon signals received (transduced) from their extracellular matrix in order to develop normally and to maintain their appropriate phenotype. Thus, the design of synthetic matrices for type 3 biomaterials must focus not merely on avoiding cytotoxic or inhibitory responses but also on providing appropriate information so as to encourage cells to maintain their normal habit and function or stimulate specific behavior.

• The appropriate consideration of biomaterial–(local) host interactions must now move from the so-called “tissue–material” interface to the cell–material or, more properly, the receptor–ligand interaction realm.

11.4 Matrices and Cell Sources

11.4.1 Cells*

Whether consisting entirely of cells and their extracellular products, like

more traditional tissue grafts and organ transplants, or merely incorporating

living cells, tissue replacements come in three types: auto-, allo-, and xeno,

reflecting the original cell source (respectively, autobiopsy, allobiopsy, and

xenobiopsy). The issue of xenohybrids (type 3) or xenoreplants** (type 4)

will not be considered here because they represent special cases of xenografts

and, except in the minds of animal rights advocates, do not raise any of the

objections that will be discussed later. However, the success in transplanting

human immune systems to small rodents such as mice suggests that, in the

future, the availability of “pseudo” xenotissue and organ sources may help

to resolve some of my present concerns. It has even been proposed to use

genetically transformed larger animals such as pigs to grow immunologi

cally matched xeno-organs, which I would term xenoreplants (Fox 1997).

Of the two remaining tissue types, the autoreplant, or true replant, as

employed by Peterson (Brittberg et al. 1994) (see Section 11.5) in attempting

* Portions of this subsection, as well as Section 11.5, were published previously in different form

(Black 1997).

** Strictly speaking, such replants could only be into animals, such as seeing eye dogs, unless

transgenic hosts were used.

to repair articular cartilage, appears to raise the lesser concern. The avail

ability of true cultured autografts would certainly definitively dispel some

of the generic problems with transplants: each replant would exactly match

the donor genetically (especially immunologically), it would introduce no

additional infectious agents (if carefully handled in vitro and during replan

tation), and the supply would always match the demand. The downside

would be high cost, significant delay (which in the case of culturing a full

organ such as the kidney might be several years), and availability of support

technology. The commercial and legal issues are fairly straightforward: the

cost would reflect the processing (growth and handling) of tissue removed

from the ultimate user and then returned, as well as some amortization of

research and development costs.

However, the alloreplant seems to pose more problems. On the face of it,

the use of cells from a single, possibly fetal or newborn, human donor and

the elaboration of very large quantities of tissue appear attractive. This offers

the theoretical prospects of lower costs (through economy of scale), better

quality control, and a more manageable commercial

manufacturing process.

Early efforts in this area feature, in some cases, a self-contained cassette or

cartridge: a support enclosure in which the cells can be maintained, nour

ished, and kept sterile until delivered to the sterile field within the operating

room for implantation.

However, several areas of concern arise:

• The possible use of tissue from a single source — not for 15 to 25 recipients as is commonly the case for organ transplantation, but for perhaps as many as 25,000 recipients — raises the prospect of real clinical catastrophe if something goes wrong, such as inadvertent transmission of an undetected (possible previously unrecognized) slow virus. Unfortunately, one can only test for those viri and bacteria that have already been detected and even such tests have a significant rate of false negative findings.

• The use of an allobiopsy rather than autobiopsy cell source probably enables the future identification of the replant by karotyping, especially in the case of long lived tissue such as articular cartilage or cultured functional organs. This has potential implications for legal proceedings related to mal-outcome of the clinical procedure.

• In the U.S., the Uniform Anatomical Gift Act (1968) and the National Organ Transplant Act (1984) essentially forbid the sale or other commercial use of dead or live human body parts. The motivation for these laws is very clear and straightforward: they were intended to make human material available for teaching, research, and therapeutic purposes without creating a market in such materials. The concern about market forces stems from three bases: • A recognition that the human body is special; emboding the moral sense that human beings are ends in themselves and should not be used as means to achieve other purposes • A desire to prevent the poor and powerless from selling parts of their body, perhaps under duress • A more general need to prevent the creation of an analog of the autobody chop shop that converts stolen cars into far more valuable subassemblies and parts In the case of postmortuum organ

donation, the organ is donated by the next of kin, frequently carrying out the desires of the donor, and the charges to the recipient cover only “harvesting,” testing, transport, and implantation (although donor funeral expenses are also sometimes provided for). However, what about the donation of cells or portions of organs, perhaps by surviving donors, that could benefit thousands of recipients and are incorporated into “products” with significant value added by manufacturers? What would be sold then? Who should benefit financially? Can it be done legally and ethically?

• The need to obtain allogenic cells with pluripotentiality has turned interest first to human adult and then to fetal and embryonic stem cells. The former can be obtained with little or no injury to the donor, but harvesting the latter invariably results in death of the fetus or embryo. This latter situation has produced a wide range of national responses related, in large part, to local attitudes towards early-life issues such as abortion. In some countries, such cell sources may not be used and, in others, there is wide latitude, under ethical supervision. In the U.S., a hybrid approach is followed, permitting fetal stem cells to be used but limiting their sources narrowly to previously* established cell lines when public funding is involved.

Thus, one of the barriers to successful TE appears to be a need to under

stand and reach agreement concerning implications of choosing among var

ious cell sources. As I have suggested previously, some of these objections

may be overcome, potentially, by the use of transgenic xeno- (animal)

sources. In the near term, however, the issues raised by current practices

must be addressed and workable answers provided. Similar issues, particu

larly of ownership and its transfer, have already arisen in the commercial

preparation of biological products from human cell sources. The litigation

record, although instructive, does not resolve these questions definitively.

Furthermore, even if it did, one would still be constrained to consider the

ethical aspects of the questions. I will return to these points again in Section

11.5.

* Before August 9, 2001 (speech, 11/11/01, President G.W. Bush).

11.4.2 Matrices

There are also less ethically challenging but more pragmatic problems with

the choice of matrix material, in the case of design and fabrication of a type

3 biomaterial.

Matrices may be natural in origin, such as collagen, keratin, or chitosan.

Natural matrices are, to a lesser or greater degree, inherently “biodegrad

able,” depending upon the amount of molecular structure change during

processing, because mammalian systems possess a wide repertoire of deg

radative enzymes for self- and foreign organic molecules. A further attraction

of natural sources is that a matrix familiar to the selected cells can be chosen;

thus, type II collagen can be combined with chondrocytes in an attempt to

fabricate a tissue-engineered hyaline cartilage. Collagen is perhaps the most

widely used of such natural materials (Silver and Pins

1992; Bell 1995),

although concerns still remain about immune response to some types (Lynn

et al. 2004).

Matrices may also be prepared by deliberately modifying natural materials

through physical, chemical, and enzymatic treatment. This is a practice of

great antiquity, used in attempts to process natural structures, such as dem

ineralized bone or tendon segments, to reduce their antigenic properties and

improve their physical handling and postimplantation behavior. Many such

materials derived from allo- and xeno- sources are in clinical use as type 2

biomaterials.

However, both of these approaches, although still popular, seem too crude

today. A far more promising approach is the direct synthesis of polymers

with specific structures and properties, such as including receptor recogni

tion sequences, as the previously noted (-RGD-). Capello (1992) and his

coworkers have been pioneers in this approach, using recombinant tech

niques to select DNA sequences that code for specific molecular arrange

ments and then transfecting these pseudogenes into bacteria such as

Escherichia coli. They then induce them to synthesize large quantities of the

desired material, which can then be spun into fibers, coated onto surfaces,

etc. Such materials can be designed to be nonresorbable, partially resorbable,

or fully resorbable, depending upon the demands of the application. One of

the first achievements of this technique was the synthesis of spider silk

modified to include receptor recognition domains (Anderson et al. 1994).

11.4.3 Combining Cells and Matrices

The issue of combining cells with matrices will not, in the long run, be a

problem as the technology of TE moves increasingly towards type 4 or

replant materials. In the meantime, considerable concern and argument will

involve which combinations of cell and matrix sources are the most appro

priate. Although it is hard to generalize, I suggest that, at this moment, the

possible combinations can be grouped into three classes, in order of decreas

ing preference (Figure 11.3):

- Class 1: the most desirable from pragmatic and ethical points of view appears to be the use of autobiopsy cells with partially or fully resorbable, synthetic matrices.

- Class 2: this can be extended, with care and consideration, to include natural matrices such as collagen and chitosan, perhaps with some chemical modification, and allobiopsy cell sources, particularly primitive stem cells. This class is the one now enjoying the most attention from industrial developers.

- Class 3: finally, and likely to be least satisfactory in

the long run, is the use of xenobiopsy cell sources and the permanent incorporation of nonresorbable matrix elements. In some cases, such as in early studies using encapsulated xenobiotic cells for experimental human therapy, these approaches are unavoidable. It may continue to prove economically desirable in certain external applications, such as burn treatment. However, I hope that this approach will fall into disuse, due to permanent concerns about the possibility of unsought gene transfer and presence of undetected infectious agents.

11.5 Thinking Twice about Tissue Engineering

The dividing line between traditional biomaterials (in particular, the search

for the Philosopher's Stone), the truly inert (type 1) biomaterial, and the field

of tissue engineering was crossed on October 2, 1967 when Dr. Christiaan

Barnard transplanted a live human heart into a patient with heart failure

FIGURE 11.3

Possible combinations of matrices and cell sources (numbers identify classes; see text). MAN MADE NONRESORBABLE MAN MADE - RESORBABLE NATURAL MATRICES C E L L S O U R C E A U T O B I O P S Y A L L O B I O P S Y X E N O B I O P S Y 1 2 3

(Barnard 1967). Although his first patient succumbed to a variety of clinical

complications 18 days later, the possibility of routine transplantation of major

functioning organs drew worldwide attention. An immediate impact felt in

the U.S. was a radical curtailment of funds for the multicontractor federal

program directed towards the development of an implantable (permanent)

artificial heart. It is worth noting that this research and development program

never recovered from this setback; today, successor devices such as active

left ventricular assist devices (LVADs) are seen only as “bridges” to trans

plantation: as devices to sustain a patient’s life until a suitable donor organ

becomes available. In the same way, blood and peritoneal dialysis, which

were originally viewed as miraculous but last-stage interventions in kidney

disease and failure, are now widely employed for prolonged periods for

patients awaiting definitive treatment by allotransplantation.

The success of organ transplantation from cadavers or, in the case of

kidneys, from related or unrelated live donors cannot be denied. Perhaps as

many as 340,000* U.S. patients have received transplants of living organs,

including kidneys (the most commonly transplanted), heart, lung, liver, pan

creas, and intestinal segments. Many patients receive multiple organ trans

plants, such as ex-governor of Pennsylvania Robert Casey, who received a

combined heart and liver transplant in 1993 (Alexander and Baker 1993).

Casey’s situation illustrates some popular concerns about organ donation

and transplantation:

• Organs for transplantation are rare in comparison to need and waiting times may be long. In 1995, it was estimated

that 38,000 U.S. patients were on waiting lists as possible organ recipients; a new name was added very 30 minutes and at least 8 patients per day died while awaiting transplants. Nevertheless, a match was fortuitously found for Casey within 1 day of the decision to perform his transplant. Today, some 88,500 people await transplants.

• The donor involved was young and relatively disenfranchised: a 34 year old murder victim. This had been the situation in Dr. Barnard's initial heart transplantation; the donor was a young man killed in a vehicular accident (Barnard 1967).

• The recipient was older and, to a considerable degree, privileged. This issue was also highlighted by Barnard's first transplant: in a country still in the coils of apartheid, the donor was black and the recipient was a retired white civil servant. This issue of status privilege was also raised when the legendary baseball star Mickey Mantle received an unsuccessful liver transplant (Meyerson 1995).

Without question, organ transplantation is difficult and expensive. It is

extremely difficult to screen donors for transmissible disease and accurately

match donor organs to recipients so that the best possible blood and tissue

∗ http://www.optn.org/latestData/rptData.asp.

compatibility, as well as appropriate size, can be obtained. It must be done

in a very short time span because organs generally become available on short

notice and deteriorate rapidly with time, even when the donor is maintained

on life support. Thus, statewide and regional networks and a national net

work, the United Network for Organ Sharing (UNOS),∗ have sprung up in

the U.S. in response to the National Organ Transplant Act (1986) to facilitate

optimal usage of organs. As a result, it is now possible for organs and tissues

from a single donor to be given to many geographically widely separated

recipients. Extensive publicity drives have been conducted to encourage

individuals, especially people obtaining driver’s licenses, to register as pro

spective organ donors. However, the fundamental problems remain: demand

far exceeds supply and costs of the procedures involved tend pragmatically

to reduce access by less well off and disenfranchised patients; as a result,

nagging questions of social justice remain.

It is fair to state that these moral, ethical, and pragmatic considerations

have also played strong roles in the development of TE so far. Early efforts

in TE, although surrounded by high enthusiasm and attracting large quan

tities of venture capital, were relatively noncontroversial. These included,

primarily in animal experimental studies and, in some cases, early human

clinical trials, the encapsulation of Langerhans’ islet cells for the treatment

of diabetes (Scharp et al. 1994); the separation, culturing, and reinfusion of

specific lymphocyte subpopulations for cancer therapy (Chen 2000); and the

fabrication of a variety of hybrid skin replacements for use in burn treatment

(Yannas and Burke 1980; Yannas 1997). In each case, the goal was transient

therapy rather than definitive replacement, the conditions addressed were

severe and life threatening, and an easy distinction could be maintained

between “implant” and recipient.

However, in 1994, another phase began. Dr. Peterson and coworkers from

the University of Göteborg, Sweden (Brittberg et al. 1994), reported early

clinical trials of growth and replantation of articular chondrocytes in a pro

cedure to replace full thickness focal defects in the tibial plateau. Autologous

cells were removed from non-load-bearing areas of articular cartilage, sep

arated from their matrix, cultured in vitro for 14 to 21 days, and then

replanted in articular cartilage defects in the tibial plateaus of each donor;

autologous periosteal membrane was used to retain the replant. In this

application, the therapy is expected to be definitive (in the same way that

implanting a metal and plastic total joint “replacement” is), the disease

treated is not life threatening, and the replant is expected to become fully

integrated with the patient’s tissues.

This technique was introduced into the U.S. on an experimental basis and

received FDA approval for some medical indications in August 1997. The

“product,” as commercialized by Genzyme Tissue Repair (GTR) (a division

of Genzyme Inc.) and now distributed by U.S. Biosciences, is called Carticel™

(autologous replant chrondrocytes). The technique of Brittberg et al. (1994)

* http://www.unos.org.

is generally followed, with a 3- to 6-week interval between autobiopsy and

replantation. The culture process currently costs (nominally) $19,750 of an

estimated average total treatment cost, including surgeon’s fees, of $40,000.*

The general technique, now termed articular cartilage implantation or ACI,

has been essentially duplicated by several other companies and is in use in

a number of countries.

This development requires taking a second look at the entire concept of

TE. Before going too far down this path, it is worthwhile to think twice —

to consider the implications and ask whether some things should not be

done even when they appear to be possible. Section 11.4 discussed some

of the trade-offs necessary between benefit and risk in the selection of

matrices and cell sources for type 3 and 4 biomaterials. It is still too early

to do more than muse about which of the risks will emerge

as true clinical

and legal problems and, as a result, which of the conflicting viewpoints

among TE researchers and developers will come to dominate clinical prac

tice in replantation.

I would like to note a more fundamental concern about TE. This concern

was raised a half a century ago by Jack Vance (1956) in a novel entitled To

Live Forever. Vance imagined a city society, Clarges, on a remote world in the

last stages of societal decay. On one hand, its citizens possess an obsession

about immortality, but, on the other, they submit to an agreement for State

limitation of life span through the use of public assassins, with postponement

of “termination” based upon a continual measurement of one’s individual

contribution to the public good. However, as one would suspect, in Clarges

some people are more equal than others and society, in Vance’s account, has

evolved into five social classes: Brood, Wedge, Third, Verge, and Amaranth.

It is the privileged Amaranth, the social and economic elite, who have solved

the problem of immortality. Those few judged to have achieved the most

and contributed the most to Clarges’ society are admitted into the Amaranth

class and undergo the following procedure: ...Five cells

were extracted from [the] body. After such modification of genes as might be desired, they were immersed in a solution of nutrients, hormones and various special stimulants, where they rapidly evolved through the stages of embryo, infant, child and adolescent.... When invested with the prototype's memory-bank, they became the identity of the original: full-fledged surrogates (Vance 1965).

Amaranths zealously keep their memory-bank recordings up to date and

their surrogates are carefully guarded against the day that the original (the

prototype) might have a fatal accident, develop an incurable disease, or be

irrecoverably injured or killed by violence.

Vance's novel centers on a problematic situation: one of the surrogates

escapes and tries to lead a life independently of its prototype. Issues con

cerning the meaning of self, the value of life, involuntary servitude, and

* http://www.firstdatabank.com; Dr. T. Minas (personal communication).

manipulation of the fundamental elements of human existence are raised.

In this prescient novel, the logical, although perhaps impossible, conse

quence of the promise of Dolly, the first successful report of cloning a sheep

by nuclear transfer (Campbell et al. 1996), can be recognized. A dark reflec

tion of the "baby factories" of an earlier visionary novel, Brave New World

(Huxley 1932), in which all fetal development occurs in vitro (rather than in

utero) and chemical manipulation is employed to fit each

individual to his

or her predestined place in society can also be seen. Rather than rejecting

such disturbing visions out of hand as incredible, one should be aware of

the widespread current efforts in therapeutic gene implantation and of anec

dotal rumors of conception of babies to serve as marrow donors for older

siblings.

The question that ought to be raised by Vance, Huxley, and visionaries is

essentially, “When is enough, enough?” That is to say, where is the line

between legitimate therapeutic intervention and a morbid preoccupation

with life enhancement at all costs, and who shall judge its location? This is

not a problem unique to the fields of BSE and TE. It can be recognized in

the use of life support for the terminally ill, in radical interventional surgery,

including multiple organ transplants in the elderly, in fetal (in utero) surgery,

and so forth.

In his work, Enough: Staying Human in an Engineered Age (2003), McKibben

wrote: …[T]hese new technologies show us that human meaning dangles by a far thinner thread than we thought. What if the ending to our story has already been written, our compass set? What if we have been programmed, or at least must suspect each time we choose a path that we have been nudged in that direction by our engineered cells. Who then are we?

One can properly object that my suggesting connections between TE and,

on one hand, the fictional visions of Huxley and Vance and, on the other,

biotechnological research into gene transplantation and mammalian cloning

is extreme and far fetched. In principle, I agree. However, this is a situation

in which one can only see the extreme ends of a spectrum: at one end are

research and medical procedures, which are simple and raise no ethical

issues; at the other are dark dreams of clearly morally objectionable acts.

The reason for creating this spectrum, or linkage, is to raise the questions:

how will the boundary between the acceptable and the unacceptable be

recognized? What are the moral mileposts that should warn one to slow

down and, perhaps, to stop when, in McKibben’s view, enough has been

achieved?

Consider an illustrative example of such a spectrum, one relating to kidney

transplantation. The implantation of cadaveric kidneys can be placed at one

end; at the other, assume Vance’s hypothesis but suggest only that the cloned

human surrogate be maintained as an “organ bank” for the prototype.

Clearly, the former situation is found to be acceptable and the latter rejected

as unthinkable.*

Now consider some possible intermediate points on this spectrum of pos

sible organ sources, in no particular order:

• Live organ transplantation: • From a parent • From a child • From a sibling • From a sibling expressly conceived for the purpose • From a late term aborted fetus • From a transgenic anima • From a paid donor • From an executed criminal • From a condemned criminal • From a criminal seeking reduction or remission of sentence

• Implantation of artificial constructs (hybrid artificial organs) with cells from one or more of such sources or from a cloned surrogate

The potential use of each of these organ or cell sources raises interesting,

different, and, in some cases, morally complex problems. Their rank order

of moral acceptability is not obvious and a marker or threshold of unaccept

ability is not clear.

Traditionally, such questions have been referred to philosophers, ethicists,

and religious leaders while scientists, engineers, and physicians have gone

on with their studies and clinical treatment. I have no simple answers to the

questions raised here. However, I am sufficiently disturbed by long-term

implications of TE to suggest that engineers and scientists need to open a

broad and deep dialogue with a cross-section of interested parties rather

than simply going ahead with a narrow focus on possible technological

solutions to human problems. The road to hell is, as Ambrose Bierce com

mented, paved with good intentions (1906).

Finally, I want to suggest a simple functional test for engineers and scien

tists in these (or, for that matter, other related) fields of investigation. Even

if one can personally resolve the issues raised, as one must, it is worthwhile

considering this question: will this work ultimately benefit refugees in

Rwanda** or in the other parts of the world mired in desperate, apparently

chronic, poverty and deprivation?

* If one has any doubt of this statement, simply replace “kidney” with “heart” or “pancreas” in

the first sentence of this paragraph.

** As this is written (in 2005), more than three-fourths of a million refugees still are unable or

afraid to return home, despite the best efforts of international organizations, more than a decade

after the massive intertribal massacres that occurred in Rwanda.

I have come to call this question the “Rwanda test.” I offer it to readers,

experienced professionals, and students alike — not with the suggestion that

a negative response is a necessary “show stopper,” but rather with the hope

that, among all the good and promising questions that can be asked, increas

ingly often those that have the potential to bring the greatest good to the

most with the least risk of catastrophe will be selected. To fail to apply such

a test to future investigations runs the risk of losing oneself and one's society.

11.6 Some Final Comments

Tissue engineering, with its hints of Frankenstein's monster and the seduc

tion of dealing with the very substance of life — living tissue — is enor

mously alluring to beginning and long-time investigators in BSE, as well as

in many other more traditional fields. Beyond the ethical concerns raised in

the previous section, I want to close this discussion with a few practical

concerns.

Without question, TE will continue to grow and flourish, although many

of the early extravagant visions of the pioneers may be long delayed or prove

unattainable. In the meantime, it is important not to lose sight of these points:

- Like the larger field of BSE, TE has three primary aspects: it is a materials science, a biological science, and a clinical science. Thus, TE cannot be expected to be successful unless it is moved forward by integrated multidisciplinary teams of physical and biological scientists, engineers, and clinicians and physicians. It would be easy for newer TE workers (such as materials specialists beginning to work in TE) to become second-rate biochemists, biophysicists, cell biologists, etc. This is a bad idea; it is far better to leave these more fundamental fields to their traditional practitioners, harvest their intellectual product, and focus on being broad integrators and innovators, as workers in BSE have always been.

- Interdisciplinary or innovative studies are no excuse for

mediocrity. TE should not be allowed to become a refuge for workers who cannot compete successfully elsewhere in BSE or in its foundation fields of biological and physical sciences and engineering. On the contrary, difficult interdisciplinary fields such as TE have little room for the otherwise blameless but merely average investigator.

• Nothing is really new: many challenging problems faced in TE have been investigated in other contexts and, in many cases, practical solutions already exist. The emergence of online publications, new journals, and fledgling scientific societies are welcome as signs of intellectual vigor; however, abandoning the traditional literature and forums of biological and physical science and engineering and, particularly, of BSE will only handicap students and advanced workers alike in TE.

• TE products will continue to need a supporting superstructure of types 1 and 2 biomaterials for their fabrication, evaluation, preservation, handling, implantation, and clinical monitoring. Care must be taken that older, successful biomaterials technologies are not neglected in the haste to move ahead. Otherwise, future workers will repeat old mistakes and be faced with continually “reinventing the wheel.”

• Clinical success of TE products will require a much more sophisticated understanding of the physical property differences between normal and diseased tissues than is currently available. I have long argued this point in the broader field of BSE, saying that, in particular, tissue mechanics is an essential prerequisite to and should be a component of any research effort directed towards support or replacement of natural tissues or organs with structural attributes. With the emergence of TE, I hope for an accompanying revival of tissue mechanics and morphometrics, with an increased focus on changes associated with medical and surgical procedures, disease, age, and interaction with implants.

• In any newer aspect of research such as TE, traditional methods and procedures continue to have a place. Vision is no excuse for abandonment of rigorous process: good science will always require the sequence of conception of new ideas; hypothesis formulation; careful observation; replication of experiments; critical, skeptical statistical analysis of outcomes; and testing and retesting of earlier hypotheses. Good engineering practice requires clear statements of problems; examination, development, and perfection of alternate approaches; and exhaustive testing*

and verification of numerical, process, and hardware solutions. With regard to outcomes in science or engineering, if something seems too good to be true, it probably is, whether it is a laboratory result or a vacation travel offer.

Nevertheless, I have significant enthusiasm for TE; I only hope that the field

and its workers are able to fulfill its great promise in responsible and ethical

ways.

* Many years ago, to my amusement and dismay, I heard a podium presentation about an

implant study in which two dogs had been used to examine local host response to a wide variety

of candidate biomaterials. When I questioned the presenter, I suffered a lapsus lingua and asked

why two dogs were used (rather than why only two were used!). The answer, after much reflec

tion, was, “Well, I suppose I could have used just one.” Since then, at each meeting I have

attended, I have mentally bestowed the “one dog” award to the presentation containing the

greatest amount of data gained from the smallest number of test subjects, animal or human.

Regretfully, there has been a continuing need to make this award at TE as well as BSE meetings.

(See also Chapter 18, Appendix 1.)

Alexander, K.L. and Baker, S., Governor Casey’s timely transplant, Bus. Week, June 28, 1993.

Anderson, J.P. et al., Structural evolution of genetically engineered silk like protein polymers, in Silk Polymers: Materials Science and Biotechnology (ACS Symposium Series #544). Kaplan, D., Adams, W.W., Farmer, B. and Viney, C. (Eds.), American Chemical Society, Washington, D.C., 1994, p. 137.

Barnard, C.N., The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town, S. Afr. Med. J., 41(48), 1271, 1967.

Bell, E., Strategy for the selection of scaffolds for tissue engineering, Tissue Eng., 1(2), 163, 1995.

Black, J., Tissue properties: relationship of in vitro studies to in vivo behavior, in Natural and Living Biomaterials, Hastings, G.W. and Ducheyne, P. (Eds.), CRC Press, Boca Raton, FL, 1984, 5.

Black, J., Thinking twice about tissue engineering, IEEE Eng. Biol. Med., 16(4), 102, 1997.

Brittberg, M. et al., Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation, New Engl. J. Med., 331(14), 889, 1994.

Campbell, K.H. et al., Implications of cloning, Nature, 6573, 383, 1996.

Capello, J., Genetic production of synthetic protein polymers, Mater. Res. Soc. Bull., 17, 48, 1992.

Chen, U., Lymphoid cells, in Lanza, R.P., Langer, R. and Chick, W.L. (Eds.), Principles of Tissue Engineering, 2nd ed., Elsevier Science, New York, 2000, 611.

Fox, M., Sheep-cloners PPL to breed for transplants, Reuters News Service, 3/24/97, 1997.

Huxley, A.L., Brave New World, Doubleday, Doran & Co., Garden City, NJ, 1932.

Lauffenburger, D.A. and Linderman, J.J., Receptors: Models for Binding, Trafficking, and Signaling, Oxford University Press, New York, 1993.

Lynn, A.K. et al., Antigenicity and immunogenicity of collagen, J. Biomed. Mater. Res., Part B: Appl. Biomater., 71B, 343, 2004.

MacDonald, J.A., Receptors for extracellular matrix components, J. Physiol., 257, L331, 1989.

Massia, S.P. and Hubbell, J.A., Covalent surface immobilization of Arg-Gly-Asp- and Tyr-Ile-Gly-Ser-Arg-containing peptides to obtain

well-defined cell-adhesive substrates, Anal. Biochem., 187(2), 292, 1990.

McKibben, B., Enough: Staying Human in an Engineered Age, Henry Holt, New York, 2003, 65.

Meyerson, A.R., Final stats: Mantle's last medical bills, NY Times, 8/20/95.

National Organ Transplant Act, Public Law No: 98-507, 1984.

National Research Council, Stem Cells and the Future of Regenerative Medicine, National Academy Press: Washington, D.C., 2002, 4.

Scharp, D.W. et al., Protection of encapsulated human islets implanted without immunosuppression in patients with type I or type II diabetes and in nondiabetic control subjects, Diabetes, 43, 1167, 1994.

Silver, F.H. and Pins, G., Cell growth on collagen: a review of tissue engineering using scaffolds containing extracellular matrix, J. Long-Term Eff. Med. Impl., 2(1), 67, 1992.

Skalak, R. et al., Preface, in Skalak, R. and Fox, C.F. (Eds), Tissue Engineering, Alan R. Liss, Inc., New York, 1988, 1.

Uniform Anatomical Gift Act (1968, as amended 1987), National Conference of Commissioners on Uniform State Laws, C. 1:12A-8 (subsequently adopted by individual states (U.S.)).

Vacanti, J.P. and Vacanti, C.A., History and scope of tissue engineering, in Lanza, R.P., Langer, R. and Chick, W.L. (Eds.), Principles of Tissue Engineering, 2nd ed., Elsevier Science, New York, 2000, 3.

Vance, J., To Live Forever, Ballantine Books, New York, 1965.

Wei, J. et al., Integrin signaling in leukocytes: lessons from the α 6 β 1 integrin, J. Leukocyte Biol., 61, 397, 1997.

Yannas, I.V. and Burke, J.F., Design of an artificial skin. I. Basic design principles, J. Biomed. Mater. Res., 14, 65, 1980.

Yannas, I.V., In vivo synthesis of tissues and organs, in Lanza, R.P., Langer, R. and Chick, W.L. (Eds.), Principles of Tissue Engineering, 1st ed., Elsevier Science, New York, 1997, 167.

Atala, A. and Lanza, R.P., Methods of Tissue Engineering, Academic Press, New York, 2001.

Beauchamp, T.L. and Childress, J.F., Principles of Biomedical Ethics, 5th ed., Oxford University Press, New York, 2001.

Bierce, A., The Cynic's Word Book, 1906. (Reprinted as: The Devil's Dictionary, Castle Books: New York, 1967).

Brodt, P. (Ed.), Cell Adhesion and Invasion in Cancer Metastasis, Chapman & Hall, London, 1996.

Germain, L. et al., Engineering human tissues for in vivo applications, Ann. N.Y. Acad. Sci., 961, 268, 2002.

Gold, E.R., Body Parts: Property Rights and the Ownership of Human Biological Materials, Georgetown University Press, Washington, D.C., 1996.

Fox, R.C. and Swazey, J.P., Spare Parts. Organ Replacement in American Society, Oxford University Press (Acadia Institute), New York, 1992.

Hardie, D.G., Biochemical Messengers: Hormones, Neurotransmitters, and Growth Factors, Chapman & Hall, London, 1991.

Katz, B.Z. and Yamada, K.M., Integrins in morphogenesis and signaling, Biochimie, 79(8), 467, 1997.

Langer, R. and Vacanti, J.P., Tissue engineering, Science, 260, 920, 1993.

Lanza, R.P., Langer, R. and Chick, W.L. (Eds.), Principles of Tissue Engineering, 2nd ed., Elsevier Science, New York, 2000.

Lysaght, M.J. and Hazelhurst, A.L., Tissue engineering: The end of the beginning, Tissue Eng., 10(1/2), 309, 2004.

Palsson, B., Hubbell, J.A., Plonsey, R. and Bronzino, J.D. (Eds.), Tissue Engineering, CRC Press, Boca Raton, 2003.

Ratner, B.D. and Bryant, S.J., Biomaterials: Where we have

been and where we are going, Annu. Rev. Biomed. Eng., 6, 41, 2004.

Schwartz, M.A. et al., Integrins: emerging paradigms of signal transduction, Annu. Rev. Cell Dev. Biol., 11, 549, 1995.

Shelly, M., Frankenstein, 1818 (reprinted by J.M. Dent, Everyman's Library, London, 1994.)

Skalak, R. and Fox, C.F. (Eds.), Tissue Engineering, proceedings for a workshop held at Granlibakken, Lake Tahoe, California, February 26–29, 1988, Alan R. Liss, Inc., New York, 1988.

Younger, S.J. et al., (Eds.), Organ Transplantation, University of Wisconsin Press, Madison, 1996. 225

12

Allergic Foreign Body Response

12.1 Specific vs. Nonspecific Response

In earlier consideration of the inflammatory response (Chapter 8), the actions

of neutrophils and macrophages in response to a foreign material are

described as a nonspecific defense mechanism. That is, their response is

universal in nature and only slightly affected by the structure and chemical

composition of the foreign material. This chapter will discuss a second type

of response to foreign materials, the specific or immune response.

The aspects of specific response to foreign or nonself materials are grouped

together and collectively ascribed to a system of cells and mediating agents,

collectively termed the immune system. Immunity is usually understood as

the property of being secure or nonsusceptible to the adverse effects of a

particular bacterium or foreign material. Conversely, allergy is the property

of being especially sensitive (or hypersensitive) to such agents. Figure 12.1

shows the overall system and its general features in mammals.

The immune system is configured or adapts to distinguish between self

(things that are part of the natural, intact physiological system) and nonself

(all other things). It normally ignores all aspects of self; however, if it mistakes

self for nonself, adverse reactions, collectively termed autoimmunity, may

occur. Introduction of foreign tissue, also recognized as nonself, produces

an inflammatory response termed rejection. Resistance may be conferred by

genetic inheritance of a “memory” for certain nonself materials such as

proteins in bacterial cell walls, thus producing a natural resistance to certain

infections. Perhaps the most important aspect of the system is its ability to

adapt by developing a specific memory for particular foreign materials. This

may be produced by deliberate exposure to a partial or attenuated organism

or material under nonpathogenic conditions (vaccination) or by prior expo

sure under sensitizing conditions (high dosage, physical

stress, presence of

an adjuvant material, etc.). The result of this specific memory may be desir

able, as in affording acquired (vs. natural) resistance to infection, or unde

sirable, as in producing a form of adverse reaction to antigens or implants,

termed hypersensitivity.

12.2 Mechanisms of Immune Response

12.2.1 Antigen–Antibody Complex Formation

Specific or immune responses depend upon the exact details of the chemical

composition and conformation or structure (see Section 5.2) of the foreign

material. This class of response is directed primarily towards recognition of

foreign proteins such as toxins, viri, and bacterial cell wall components. The

response to these foreign materials takes place through two mechanisms:

humoral and cellular (also termed cell-mediated) response. In each case, the

foreign body is referred to as an antigen and the body responds by producing

an antibody. Antibody is a generic name for a macromolecular complex formed

by the association of large immunoglobulins present in serum into a Y-shaped

molecule with a molecular weight exceeding 1×10^{6}. The stem of the Y is

essentially the same for all antibodies, permitting it to bind to cell surfaces;

regions in the arms are variable in structure, producing the specificity, or ability

to bind with a particular antigen, characteristic of an antibody.

The humoral mechanism is based upon the production of freely circulating

antibodies. These antibodies are designed to unite with the foreign material

and “denature” or neutralize it. That is, the antibody-antigen complex lacks

the undesirable or destructive activity of the free antigen. The complex may

accumulate locally in tissue, be carried to lymph nodes by phagocytes, or

FIGURE 12.1

The immune system. (Adapted from Playfair, J.H., Immunology at a Glance, 3rd ed., Blackwell

Scientific Publications, Oxford, 1979.) Desirable Consequences of Immunity Natural Resistance Acquired Resistance N O N S E L F V a c c i n a t i o n G r a f t i n g I n f e c t i o n I m p l a n t a t i o n R e i n f e c t i o n / r e i m p l a n t a t i o n A D A P T I V E I M M U N E R E S P O N S E SPECIFIC MEMORY Autoimmunity Rejection Hypersensitivity Undesirable Consequences of Immunity S E L F

be more easily catabolized than the free antigen. Circulating antibody pro

duction is mediated by a class of lymphocytes called B-cells that arise from

primitive mesenchymal cells in the bone marrow. Antibody production is

initiated by introduction of an antigen consisting in part or whole of a foreign

(nonself) material. Whether biological, organic, or inorganic in constitution,

such material may be able to act as an antigen; it may combine with native

proteins, especially complement fragments of C3 and C5 (see Section 12.2.2),

to form an antigen; or it may undergo metabolic processing by a phagocytic

cell, usually a macrophage, to become an antigen.

Once antibodies are produced and released into the blood stream, they

may persist for long periods of time. This is the principle of immunization

to bacterial and viral infection: administering a small provocative dose of a

specific antigen or one that produces antibodies specific to the infectious

organism of interest. Then, when a later challenge is encountered, immediate

antibody–antigen complexing occurs without the delay necessary for new

antibody production. The antibody production response is quite variable,

depending upon the initiating agent, its concentration, the general state of

health of the immune system, and the presence of sensitizing agents such

as corticosteroids. Finally, a subpopulation of B-lymphocytes, memory B

cells, are then capable of rapidly synthesizing additional amounts of the

specific antibody (which it “remembers”) upon stimulus by a later exposure

to the same foreign body.

Cell-mediated response depends upon the action of another

class of lym

phocytes, the T-cells. These cells also arise in bone marrow, but pass through

the thymus gland where they undergo a conversion that improves their

ability to differentiate. They then collect in lymph nodes and associated

tissue. Their activity continues to be affected by a hormone secreted by

epithelial cells in the thymus gland. The T-cells cannot be distinguished from

B-cells morphologically until challenged by an antigen. As in the case of

humoral response, a foreign material or one of its degradation products may

be able to act as an antigen; it may combine with native proteins, especially

complement molecule C5 (which may be activated to C5a [see Shepard et

al. 1984]), to form an antigen or it may undergo metabolic processing by a

phagocytic cell, usually a macrophage, to become an antigen.

T-cells may then be distinguished by morphological changes that include

the appearance of many polyribosomes and scant rough endoplasmic retic

ulum. They produce and store a different class of antibodies, primarily

bound to the cell membrane surface. These antibodies are highly specific

and cannot survive with appreciable activity outside or separate from the

T-cell. T-cell antibodies act against intracellular

infections, cancer, and foreign

materials of nonbiological origin. However, T-cells must be present and

aggregate in the region of antigen concentration to be effective because they

must externalize and directly present the antibody to the antigen.

In addition to direct neutralization of undesired effects of foreign materials,

the formation of antibody–antigen complexes acts to enhance inflammatory

response. This can happen directly through a nonspecific phagocytic

response because the complexes can grow to microscopic size by accretion

of additional antibody and antigen molecules, or it can occur indirectly

through complement activation (Chenoweth 1986; Tang et al. 1998).

Because particulate foreign materials such as wear debris from a joint

replacement (Urban et al. 1994, 2004) may be distributed widely in the host

and lymphocytes and circulating antibodies are also widespread, local

response to antibody–antigen complexing may occur anywhere. This results

in the wide variety of physiological effects popularly termed “allergic”:

swelling of the membranes in the respiratory system (hay fever, asthma,

etc.), rash or reddening (arthus, etc.), hives (swelling related to local kinin

activation), and so forth.

12.2.2 Complement System Activation

The formation of antigen–antibody complexes will interfere with the chem

ical function of the antigen. However, if the antigen is a surface feature,

perhaps a receptor, on the surface of an invading bacteria, then the mere

formation of such a complex may not be enough to prevent the bacteria from

multiplying, producing toxins, etc. Thus, a humoral system of immune

defense exists that has been termed the complement system because it sup

ports and extends the immune system. The complement system consists of

approximately 40 proteins of various molecular weights found in serum and

interstitial fluid. When activated, its main function is to produce a product

(the membrane attack complex [MAC]) that renders bacterial cell wall mem

branes porous, leading to cell death. Thus, the MAC is directly bactericidal.

The principal molecular elements of the complement system are labeled

C1 though C9 and, in a motif similar to the coagulation cascade (see Figure

9.1), they participate in a cleavage and amplification process leading to the

formation of MACs. There are two primary pathways: the classical pathway

is initiated by the formation of antigen–antibody complexes

and thus can

become active as a concomitant of humoral or cellular immune responses;

an alternate pathway can be triggered in the absence of a specific immune

response by certain foreign molecules, such as repeating sugars or proteins

(Figure 12.2).

The role of complement activation in immune response to implants is

controversial, but has been recognized by some researchers (Chenoweth

1987; Tegnander et al. 1994). It is clearly implicated in the case of T- or B

cell activation. However, the types of materials that may be able to activate

the alternate pathway are still not well recognized. Complement activation

has several consequences:

- The MAC can attack native cells and foreign cells (as in transplants), as well as bacteria, causing undesirable cellular necrosis.

- In sufficient concentration, several of the activated intermediates, such as C5a, are capable of producing an inflammatory process (see Section 8.2).

- Some intermediates, such as C3b, inhibit the growth of antigen–antibody complexes.

- Some intermediates, such as C3b and C5a, serve as opsonins (see Section 8.2.3) and encourage phagocytosis.

The consequences of complement activation are not necessarily adverse.

Although cellular necrosis and inflammation are unwanted effects, reduction

in antigen–antibody complex size and improvement of phagocytosis through

more efficient opsonization may be beneficial in certain settings. The role of

complement activation in local (and systemic) host response to implants is

still largely unexplored and further investigations may yield new insights

in the future.

FIGURE 12.2

Classical and alternative pathways for complement activation. (Adapted from Elgert, K.D.,

Immunology. Understanding the Immune System, Wiley–Liss, New York, 1996.)

different structures; same enzymatic activity Surface Contact Antigen-Antibody Complex Classical Pathway Alternative Pathway C3 convertase C3 convertase Membrane attack complex C5a, C5bC5 C5 convertase C5 convertase* C6, C7, C8, C9 C3 C3a, C3b

D, B, C3

C1, C4, C2 C3 C3a, C3b

12.3 Classes of Hypersensitivity Reactions

Allergic responses are more properly categorized collectively as hypersen

sitivity reactions (Merritt 1998). These may be separated into immediate

hypersensitivity, which is mediated by direct antibody–antigen combination,

and delayed hypersensitivity, which is cell mediated. Immediate hypersen

sitivity is further subdivided into three types:

- Anaphylactic or immediate shock response

- Cytolytic/cytotoxic reactions
- Toxic complex syndrome

Delayed hypersensitivity responses are usually called type 4 reactions. If a

challenge evokes an immediate reaction (type 1, 2, or 3) and then a further,

delayed reaction, the net reaction is termed “mixed” and referred to as type

5. (Note: these responses are frequently designated by Roman numerals.)

The nature of supposed responses to implants (to be discussed later) sug

gests that they are, collectively, examples of delayed hypersensitivity, or type

4 reactions. The type 4 reaction is clinically similar to a chronic inflammatory

response, except that lymphocytes as well as neutrophils are seen in foci of

antigen–antibody complex accumulation and additional concomitant symp

toms, as discussed in Section 12.4, may occur.

12.4 Hypersensitivity Reactions Associated with Implants

12.4.1 Polymers

Although humoral and cell-mediated immune responses are usually directed

toward materials of natural origin, it is of interest to inquire concerning the

response to implants. As of now, few responses to polymers used as biom

aterials are recognized, except for the special case of implants made from

processed natural tissue. The use of such materials,

including processed

allografts (tissue from human donors) and xenografts (tissue from other

species, such as porcine heart valves, etc.) is finally limited by the ability to

denature or chemically mask the foreign materials so as to suppress their

antigenic activity (Bajpai 1983). Some natural materials used in medicine,

but fortunately not as implants (such as latex rubber), are widely recognized

to evoke responses (Emans 1992).

Attempts to produce immune responses to bulk polymers (Maurin 1995;

Stern et al. 1972) have produced very mild effects. They are most suggestive

of immune response to native proteins denatured by adsorption (see Section

5.5) sufficiently so that they are no longer recognized as self and are able to

serve as antigens, rather than direct antibody production or T-cell activation

by polymer molecules. Clinically, cell-mediated responses have been

reported to poly methyl methacrylate “bone cement” (Haddad et al. 1995;

Clementi et al. 1980) and to silicone elastomers (Kossovsky et al. 1987).

This latter topic has attracted a wide interest in recent years. Silica (SiO_2)

has long been recognized as an antigenic adjuvant; that is, when adminis

tered in conjunction with an antigen, in animal models, it

produces a height

ened immune response. Some animal studies suggest that silicone gel may

be an adjuvant (Nicholson et al. 1996; Naim et al. 1995). Thus, scattered

reports of apparent autoimmune diseases in patients with silicone elastomer

breast augmentation devices raised the question of whether a causal con

nection might be possible. Kossovsky has been the primary proponent of

this view (Kossovsky and Freiman 1994). However, despite continued animal

studies and extended human epidemiological studies, no association has

been demonstrated between the use of silicone implants and a wide range

of connective tissue disorders, many of which are known or suspected to be

autoimmunity diseases (Gabriel et al. 1994).*

Despite these isolated reports implicating polymers, concerns about

immune or allergic responses to biomaterials have centered primarily on

metallic materials on the skin and as implants.**

12.4.2 Metals

12.4.2.1 General

The action of metals on the immune system is a bit of a puzzle. It is generally

recognized that they must be dissolved to be active but the low molecular

weight and simplicity of structure of the resulting ions

argue against their

being capable of directly inducing humoral or cell-mediated response. It is

thought that they combine with organic molecules such as albumin to form

complexes termed haptens, which possess antigenic qualities. It has also

been suggested that increases in concentrations of naturally occurring

metal–carrier protein complexes, such as Fe–transferrin or thioneins, can

render them effective haptens. Details of metal–protein complexing affecting

molecular shape changes are complex (Friedberg 1974).

However, Yang and Merritt (1994, 1996) have been able to demonstrate

the presence of antibodies to albumin–metal complexes in patients with well

functioning cobalt-base alloy joint replacement components and to produce

specific monoclonal antibodies to these complexes in a rabbit model. In the

presence of excessive wear, these findings may possibly be clinically signif

icant. Nakamura et al. (1997) reported a case of autoimmune hemolytic

* The reader may wish to consult Angel (1997) for an account of the practical consequences of

this controversy.

** Note: immune responses to ceramic biomaterials have apparently not been reported.

anemia associated with abnormal wear of a cobalt-base femoral head by

screw impingement.

Metal sensitivity among the general population is not rare; sensitivity to

nickel is the most common, followed by cobalt and chromium. The incidence

of sensitivity is estimated to be between 1 and 5%, with as much as 10% of

the population sensitive to at least one of these metals (Table 12.1). Incidence

rates are different for men and women, reflecting differences in home and

workplace exposure, and are higher for individuals involved in certain

industries, including mining, metal refining, electroplating, printing, etc.

In addition to acting as antigens through hapten formation, some metals

of interest for use in implants have been shown to affect directly the response

of the host immune system to other antigens. Chromium (Shrivastava et al.

2002) and nickel have been shown to suppress antibody production; the roles

of cobalt and manganese are anomalous. Iron, chromium, and nickel also

have been shown in vitro to bind with T-cell surface antigens (Bravo et al.

1990); this binding may change the specificity of the previously formed

antigens.

12.4.2.2 Dermatitis

Only two aspects of immune response to metals will be

discussed. The first

of these is dermatitis as a direct response to metallic contact. This is important

for a number of reasons. It may be a direct and unacceptable side effect of

the use of external metallic support devices such as braces or dentures. It

has come to be recognized as a general indicator of systemic challenge in

the mechanism of hypersensitivity of metals.

A classic account of metallic dermatitis is that of Fisher (1986), who rec

ognizes sensitization by nickel, chromium, cobalt, gold, and platinum among

the metals of implant interest (the last two have extensive dental applica

tions). With the exception of nickel, these do not provoke an initial sensitivity

in the solid state due to their low solubility. However, in a previously sen

sitized individual, all can evoke skin inflammations (that is, dermatitis)

of various types and degrees of severity. Fisher suggests that little TABLE 12.1 Incidence of Metal Sensitivity Patients Presenting with Skin Problems (%) Normals (%) Allergen Male Female Total Male Female Total Nickel 3.1 12.9 9.6 1.5 8.9 4.2 Chromium 12.7 7.1 9.3 2.0 1.5 1.7 Cobalt 4.7 5.3 6.0 nr nr nr Note: nr: not reported. Source: Adapted from Hildebrand, H.F. et al., in Biocompatibility of Co-Cr-Ni Alloys, Hildebrand, H.F. and Champy, M. (Eds.), Plenum Press, New York, 1988, 201.

cross-sensitivity occurs — that is, metal “A” causing a response in a patient

sensitized to metal “B” — although nickel sensitivity is often accompanied

by cobalt sensitivity.* Chromium appears to cause a response primarily when

present as a chromate [Cr +6]; the other metals are active in divalent and

trivalent ionic forms. Fisher's chapter is especially valuable for its catalogs

of metal-bearing articles and environmental (exposure) settings. It also pro

vides excellent clinical descriptions of the various dermatitides and of tech

niques for skin testing for sensitivity.

Wahlberg (1973) tested a number of patients with identified clinical sensi

tivity to metals and determined threshold concentrations for topical appli

cation of metal salts. Of interest is his finding that the carrier used in the

patch test affects the threshold in many cases. That is, if the carrier aids

penetration of the metallic ions, a lower threshold is found. Table 12.2 pre

sents these data for water-based solutions only. At variance with Fisher's

conclusion, a subtle pattern of cross-sensitivity, at least with respect to the

minimum dose required for response, can be seen. These data should be

regarded with some care because individual patients showed a response to

concentrations one to two orders of magnitude below mean threshold values

for these experimental groups.

Wahlberg also looked for relationships between clinical

severity of

responses and threshold values for particular patients and found poor cor

relations except in the case of cobalt, where the correlation coefficient r =

0.61. He concluded that “…renewed contact with cobalt plays a greater role

in recurrence [of allergenic response] than [with] allergens such as chromium

and nickel, where other factors, such as infections, heat, moisture, cold,

stress, etc.…contribute to the recurrence.”

At a more subtle level, Hallab et al. (2004) found a positive correlation

between chromium and cobalt serum concentrations in nonsymptomatic TABLE 12.2 Sensitivity Thresholds for Metals Clinical Sensitivity Challenge Compound Threshold Conc. (mean, wt%) Co CoCl 2 0.27 Co, Ni CoCl 2 0.25 Co, Ni, Cr CoCl 2 0.51 Co, Cr CoCl 2 0.30 Cr K 2 CrO 4 0.21 Cr, Co K 2 CrO 4 0.08 Cr, Co, Ni K 2 CrO 4 0.14 Cr K 2 Cr 2 O 7 0.22 Cr, Co K 2 Cr 2 O 7 0.22 Source: Adapted from Wahlberg, J.E., Berufsdermatosen, 21, 22, 1973.

* Note that this latter finding may be due simply to the close association of these two metals in

alloys, etc. and not to a true cross-sensitivity.

patients with high release rate (metal-on-metal) hip replacements and the

responses of their lymphocytes to dissolved cobalt or nickel challenge in vitro.

It should be noted here that clinical practice is to use 1 to 5 wt% solutions

for skin patch testing (McGillis et al. 1989) for metallic allergenic response.

Comparing these concentrations with the threshold data in Table 12.1 lends

real weight to the concern that patch testing in the presence of a sensitizing

agent or condition may contribute to a later immune response in a previously

insensitive individual.

Many clinical reports detail local as well as remote skin response to metallic

devices. One that is reported completely (Brendlinger and Tarsitano 1970)

will suffice as an example. The patient, a 25-year-old woman, appeared with

generalized eruptions on her trunk, arms, and legs. Treatment with topical

corticosteroids provided some relief. She sought treatment for dermatitis on

her ring finger 8 months later. Despite treatment, she continued to experience

a spread and increase in intensity of symptoms. A rash appeared on her feet.

She began to experience pain and soreness in her mouth 2 months later —

that is, 11 months after her first symptoms appeared. On examination, she

was found to have a cobalt-chromium partial denture that she had acquired

several months before her initial skin problems and had worn intermittently

thereafter. Replacement of the metal denture with an acrylic one resulted in

prompt remission of symptoms. Reinsertion of the metal denture resulted

in a return of symptoms within 24 hours. At that time, skin testing showed

that she was sensitive to chromium as well as nickel in pure solid metallic

form.

Sensitivity to chromium, cobalt, and nickel is now well recognized in

dental applications in which contact between the device and the oral mucosa

occurs. Hildebrand et al. (1988) report a compilation of 149 cases that fulfill

three strict criteria:

• Presence of one or more clinical features suggestive of immune response, such as eczema, redness, ulceration, etc.

• Healing (resolution of the clinical features) after removal of the device

• Positive skin (epicutaneous) response to a metallic component of the device

Of particular interest in this report is the observation that only 28 patients

(~20%) reported a prior history of symptoms referable to an established

metal sensitivity. Thus, it is probable that the use of stainless-steel and cobalt

base alloys in dental applications can result in sensitizing previously non

sensitive patients.

It should not be concluded that skin or mucosal contact by the implant is

necessary to produce dermatitis. A report (Cramers and Lucht 1977) docu

ments the cases of three patients with 316L stainless steel and screw implants

who developed dermatitis 3 to 3.5 months after surgery. Two

patients were

found to be sensitive to chromium and cobalt by patch test and one was

sensitive to nickel. On surgical exploration, no infection could be cultured

in any case, and all immune response symptoms resolved promptly after

the devices were removed.

12.4.2.3 Implant Site Inflammation

The second aspect of immune response to metals to be considered is the

direct implant site inflammation. Hicks (1958) was probably the first to report

this effect. Initially, it was thought to be a simple inflammatory response

associated with the relatively high corrosion rates of alloys in use in the

1940s and 1950s. In the 1970s, interest in the problems of loosening of total

joint replacements, especially of the hip, reawakened interest in this problem,

especially in relation to possible immune response to metals.

An initial study of the possible relationship between sensitivity to metal

and problems with total joint replacement conducted by Evans et al. (1974)

aroused considerable interest. These researchers reported the results shown

in Table 12.3. They also found an apparently greater effect associated with

metal-on-metal devices. Several of their conclusions are:

1. Evidence is presented which suggests that after replacement, bone necrosis and consequent loosening of the prosthesis may be due to the development of sensitivity to the metals used.

4. Examination of this material [tissue of joints from sensitive patients] showed necrosis of bone and soft tissue following obliterative changes in the vascular supply.

7. We conclude that prostheses in which metal articulates with polyethylene should be preferred; that any patient in whom loosening or fragmentation occurs should be patch tested and that if sensitivity is found the implant should be removed.

This study suggests a linkage between loosening, perhaps secondary to

inflammation, and sensitivity, especially for metal-on-metal devices.

Although they have overall lower wear rates, such devices would be TABLE 12.3 Relationship between THR Loosening and Metal Sensitivity a Patients Total (#) Sensitive (#, %) Insensitive (#, %) Loose 14 9 b (64) 5 (36) Not loose 24 — 24 (100) a By skin test. b 11 loose prostheses. Source: Adapted from Evans, E.M. et al., J. Bone Joint Surg., 56B, 626, 1974.

expected to shed larger amounts of metallic products than metal-on-polymer

ones and appear to be involved more often in the supposed linkage than do

metal-on-polymer devices. The study was poorly controlled, as was a smaller

one later by Elves et al. (1975), who reported the following results: Sensitivity to chromium, cobalt, nickel, molybdenum, vanadium and titanium was studied by patch tests in 50 patients who had received total joint replacements. Nineteen (38%) were sensitive to one or more metals, primarily cobalt and nickel. In 23 patients, nontraumatic failure of the prosthesis had occurred and 15 of these failures were sensitive to metal. Out of 27 patients with no evidence of prosthesis loosening, four were sensitive to nickel and cobalt or nickel alone. Dermatological reactions occurred in 13 patients after surgery; however, only eight of these showed evidence of

metal sensitivity.

However, several questions remain unanswered. One of particular interest

is whether sensitization occurs from an implant or if it is a pre-existing

condition. No accurate incidence rates for metal sensitivity in the general

population are available. Large-scale studies, yielding the rates quoted in

the previous section, have been done only on populations that appear at

dermatological clinics — that is, patients with active skin problems — with

small control groups. A report published with that of Elves et al. (Benson et

al. 1975) favored the presensitization position. Groups of patients awaiting

total hip joint replacement were compared with those who had received the

devices already and were, in some cases, already symptomatic (device loos

ening). Although “high” rates were found in both groups, no differential

was seen.

A subsequent study of 212 patients awaiting total hip replacement (Deut

man et al. 1977) produced more definite data. These patients could be divided

into four groups, as shown in Table 12.4. This study showed a modest TABLE 12.4 Metal Sensitivity a and Associated Complications Total Number Sensitive a Patient Classification Preoperative Postoperative I: no previous bone operation 173 10 14 b II: previous metal implant 17 2 2 III: loose THR (to be revised) 16 2 2 IV: normal THR (contralateral) 6 — — Note: THR = total hip replacement. a

Sensitive to at least one: Co^{+2}, Ni^{+2}, CrO_4^{-2} (by skin test). b From retest, 6 months postoperatively of 66/168 patients with no preoperative sensitivity. Source: Adapted from Deutman, R. et al., J. Bone Joint Surg., 59A, 862, 1977.

possibility of association between sensitivity and device loosening and a

small possibility of sensitization or activation of previous sensitization by

metallic implantation.

Another clinical report (Brown et al. 1977) casts further doubt on an easy

interpretation. This study reported a group of 20 American patients with 23

hip implants of the metal-on-metal type. At least one implant was loose in

each patient. No patients were found to be sensitive to cobalt, nickel, or

chromium. This difference in incidence rates of metal sensitivity has been

ascribed to different environmental exposure between Brown's American

patients and Elves' and Benson's British patients.

The questions of the relationship between immune sensitivity and device

loosening and of possible sensitization by implanted device components

have remained of interest to the clinical and research communities. Carlsson

et al. (1980) examined a group of 112 patients before and 134 patients after

metal-on-polymer hip replacement and concluded that little or no relation

ship existed between previous sensitivity and loosening.

They also felt that

it was doubtful that devices could induce sensitivity. Waterman and Schrik

(1985) studied 85 patients before and after metal-on-polymer hip replace

ment and, although finding definite evidence of postoperative sensitization

to Cr +6 , Co +2 , Ni +2 , and methyl methacrylate, also concluded that no relation

ship was present between these findings and device loosening.

These latter studies suggest that probably more than one mechanism is

involved in device loosening. The results of Brown et al. (1977) would be

explained by some, such as Willert and Semlitsch (1977), as being secondary

to accumulations of wear debris and response to that accumulation. In small

amounts, wear particles are encapsulated or removed to regional lymph

nodes. When this system is overwhelmed, a foreign body response with

accumulation of giant cells may invade the tissues surrounding the joint,

causing resorption of soft and hard tissue. In such cases, device loosening

might be secondary to cellular attack of the interface between implant and

tissue (Harris 1995) or, as it were, it might be a biological analog of crevice

corrosion. However, multiple processes may occur in the same implant site

(Santavirta et al. 1990).

There has been continuing interest in the question of a possible relationship

between immune sensitivity to metal implants and bone damage in the

absence of infection (aseptic loosening) or wear debris. Leynadier and Lang

lais (1988) reviewed the studies cited here, as well as others, and summarized

the outcome of 300 patients. In these studies, they found an overall 7.4%

incidence of sensitivity (to Ni, Cr, and/or Co in some valence state) in

patients with a good clinical outcome (N = 163) vs. a 46% incidence of

sensitivity in patients with aseptic loosening (N = 137). They further noted

an unexpectedly high rate of sensitivity to cobalt (30%) that was more than

ten times that expected from their control population. On the basis of this

review, they concluded that, except in exceptional cases, loosening was more

likely to promote development of sensitivity rather than vice versa.

This view is contradicted by Hierholzer (1990) in a study of patients with

nickel-bearing (steel) fracture fixation implants. He found that, although

tissue nickel concentrations around fracture fixation hardware were as much

as 100 times greater in infected than noninfected sites (Hierholzer et al. 1984),

a positive correlation could be found between incidence of all prosthetic

loosening (whether associated with delayed union or infection) and metal

sensitivity. His results are summarized in Table 12.5.

A major criticism of this entire line of clinical investigation of possible

immune responses to implants is the relative crudity of the skin test. Merritt

and Brown (1980) have adapted a test termed the leukocyte migration inhi

bition factor (MIF) test to determine sensitivity to metallic ions more accu

rately. This test is an in vitro measure of the ability of metal ions (incorporated

into haptens) to inhibit migration of human leucocytes towards a chemotactic

attractant. Inhibition of migration is taken as a measure of production of a

leukocyte migration inhibition factor by T-lymphocytes presumably acti

vated by the specific metal-bearing hapten involved. In a later report, Merritt

and Brown (1985) reviewed a study of 283 patients who underwent routine

or cause-related device removal. Their data (summarized in Table 12.6) sug

gest a far higher incidence of metal sensitivity in patients with metallic

devices than in any other study previously cited. In a parallel test of 629

patients coming to surgery (without prior history of metal implantation),

they found, again by the MIF test, that 25% were sensitive to at least one

metal among nickel, cobalt, and chromium.

Using a somewhat different approach, Wooley et al. (1997) demonstrated

an association between sensitivity to poly (methyl) methacrylate or cobalt

base alloy particles and clinical diagnosis in patients receiving primary total

joint replacement or presenting for revision for component loosening and

pain, suggesting as expected a role for other health factors in determining

immune response to foreign materials.

More recently, using MIF testing, Merritt and Rodrigo (1996) screened a

carefully selected group of 22 patients, without metallic implants, who were

coming to primary total joint replacement surgery. All were insensitive to TABLE 12.5 Relationship of Metal Sensitivity a to Loosening in Internal Fixation of Fractures Postoperative Complications Number Sensitive Sensitive to (#) b M (#) F (#) Total (%) Ni Cr Co None 208 — 8 8 (3.9) 7 3 — Delayed union 230 10 14 24 (10.4) 21 4 3 Infected 267 14 13 27 (10.1) 26 2 4 a By skin test. b Some sensitive to more than one metal; no cobalt in alloy used. Source: Hierholzer, personal communication, 1990.

the metals for which they were screened (see Table 12.7) but 3 to 12 months

later, seven (31.8%) had developed sensitivities to one or more metals and

one developed a total nonmigration response characterized as a “severe

response.” See Hallab et al. (2001) for a full review of this complex topic.

12.4.2.4 Summary

It appears possible to draw the following conclusions concerning specific

immune sensitivity to metallic biomaterials:

• A significant level of immune sensitivity to metals is present in the general population.

• Groups of patients who have had nickel-, chromium-, and cobaltbearing implants display higher than expected incidences of sensitivity. TABLE 12.6 Metal Sensitivity a at Device Removal Alloy Number Insensitive (%) Sensitive (%) Reacting (%) b Stainless steel 187 43 37 20 Cobalt base 55 26 36 38 a Sensitive to one or more of Ni +2 , Co +2 , Cr +6 (by MIF test). b “Nonmigrators” (all chemotaxis suppressed); reverted to sensitive on retest 30 to 60 days after implant removal. Source: Adapted from Merritt, K. and Brown, S.A., in Corrosion and Degradation of Implant Materials: Second Symposium. ASTM STP 859, Fraker, A.C. and Griffin, C.D. (Eds.), American Society of Testing and Materials, Philadelphia, 1985, 195. TABLE 12.7 Metal Sensitivity Associated with Primary Total Joint Replacement Postimplantation a Element Insensitive (%) Sensitive (%) b Reacting (%) c Titanium 17 (77.3) 4 (18.2) 1 (4.5) Cobalt 19 (86.4) 2 (9.1) 1 (4.5) Chromium 17 (77.3) 4 (18.2) 1 (4.5) Nickel 20 (91.0) 1 (4.5) 1 (4.5) a 3 to 12 months postoperative. b Seven patients showed sensitivity to one or more element. c One patient. Source: Adapted from Merritt, K. and Rodrigo, J.J., Clin. Orthop. Rel. Res., 326, 71, 1996.

• Specific instances of symptoms consistent with a type 4 delayed hypersensitivity reaction being specifically related to the presence of a metallic implant have been documented.*

• Sensitivity to metal and sensitivity to other clinical symptoms, especially device loosening, are generally correlated; however, which is cause and which is effect is unclear at this time.

12.5 Final Comment

The lack of basic knowledge and reliable statistics on clinical outcomes

associated with hypersensitivity responses to biomaterials has had severe

consequences, most notably in the debate over possible immune or autoim

mune responses associated with the use of silicone gel-filled breast implant

prostheses. Although immune responses associated with implants may well

have a low incidence, the consequences for individual patients remain

severe. In the present medical treatment environment, in which the possi

bility of such effects is usually ignored, some patients no doubt experience

a high level of frustration and prolonged periods of inappropriate therapy.

These possibly include patients with suspected infections that prove impos

sible to culture from clinical specimens and who receive the working diag

nosis of “sterile abscess” without appropriate subsequent testing for delayed

hypersensitivity to implanted materials (Hallab et al. 2000).

The entire issue of the role of specific (i.e., immune) vs. general response

to implants should remain an exciting one, particularly as biomaterials tech

nology advances. For example, newer total joint replacements with hard-on

hard (metal/metal or ceramic/ceramic) bearings are known to yield very

large numbers of submicron (1 to 100 nm)-sized metal oxide particles during

locomotion. Recent concerns have been raised (Gatti et al.

2004; Lomer et al.

2002) as to whether such particles may be antigens or adjuvants. Basic and

clinical research results can be expected to continue to shed more light on

these as well as more traditional concerns in the future. However, it would

be fair to say that study of effects of biomaterials on the human immune

system is one of the most neglected areas of host response research.

* This story may still have additional chapters: current interest in the use of metal/metal

articulations in total hip replacements is producing a number of clinical failures of fixation of

components to bone with adjacent soft tissues characterized as showing "…necrosis, lym

phocyte infiltration, elevated mast cell counts and tissue fibrosis" (Lintner et al. 2005.) This is

interpreted as a type 3 toxic or arthus response to cobalt-bearing particles (Lintner, personal

communication).

Angel, M., Science on Trial, W.W. Norton and Co., New York, 1997.

Bajpai, P.K., Antigenicity of glutaraldehyde-stabilized biological materials, in Biomaterials in Reconstructive Surgery, Rubin, L.R. (Ed.), C.V. Mosby, St. Louis, 1983, 243.

Benson, M.K.D. et al., Metal sensitivity in patients with joint replacement arthroplasties, Br. Med. J., 4, 374, 1975.

Bravo, I. et al., Differential effects of eight metal ions on lymphocyte differentiation antigens in vitro, J. Biomed. Mater. Res., 24, 1059, 1990.

Brendlinger, D.L. and Tarsitano, J.J., Generalized dermatitis due to sensitivity to a chrome cobalt removable partial denture, J. Am. Dent. Assoc., 81, 392, 1970.

Brown, G.C. et al., Sensitivity to metal as a possible cause of sterile loosening after cobalt-chromium total hip-replacement arthroplasty, J. Bone Joint Surg., 59A, 164, 1977.

Carlsson, Å.S. et al., Metal sensitivity in patients with metal-to-plastic total hip arthroplasties, Acta Orthop. Scand., 51, 57, 1980.

Chenoweth, D.E., Complement activation produced by biomaterials, Trans. Am. Soc. Artif. Intern. Organs, 32, 226, 1986.

Chenoweth, D.E., Complement activation in extracorporeal circuits, Ann. N.Y. Acad. Sci., 516, 306, 1987.

Clementi, D. et al., Clinical investigations of tolerance to materials and acrylic cement in patients with hip prostheses, Ital. J. Orthop. Traumatol., 6, 97, 1980.

Cramers, M. and Lucht, U., Metal sensitivity in patients treated for tibial fractures with plates of stainless steel, Acta Orthop. Scand., 48, 245, 1977.

Deutman, R. et al., Metal sensitivity before and after total hip arthroplasty, J. Bone Joint Surg., 59A, 862, 1977.

Elgert, K.D., Immunology. Understanding the Immune System, Wiley-Liss, New York, 1996.

Elves, M.W. et al., Incidence of metal sensitivity in patients with total joint replacements, Brit. Med. J., 4(Nov. 15), 376, 1975.

Emans, J.B., Current concepts review: allergy to latex in patients with myelodysplasia, J. Bone Joint Surg., 74A, 1103, 1992.

Evans, E.M. et al., Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement, J. Bone Joint Surg., 56B, 626, 1974.

Fisher, A.A., Dermatitis and discolorations from metals, in, Contact Dermatitis, 3rd ed., Fisher, A.A. (Ed.), Lea & Febiger, Philadelphia, 1986, 710.

Friedberg, F., Effects of metal binding on protein structure, Q. Rev. Biophys., 7(1), 1, 1974.

Gabriel, S.E. et al., Risk of connective-tissue diseases and other disorders after breast implantation, N. Engl. J. Med., 330(24), 1697, 1994.

Gatti, A.M., Biocompatibility of micro- and nanoparticles in the colon. Part II., Biomaterials, 25, 2004.

Haddad, F.S. et al., Cement hypersensitivity: a cause of aseptic loosening? J. Bone Joint Surg., 77B, 329, 1995.

Hallab, N.J. et al., Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty, J. Arthrop. (Suppl 3), 19, 88, 2004.

Hallab, N. et al., Metal sensitivity in patients with orthopaedic implants, J. Bone Joint Surg., 83A, 428, 2001.

Hallab, N. et al., Hypersensitivity to metallic biomaterials: a review of leukocyte migration inhibition assays, Biomaterials, 21, 1301, 2000.

Harris, W.H., The problem is osteolysis, Clin. Orthop. Rel. Res., 311, 46, 1995.

Hicks, J.H., Pathological effects from surgical metal, in Modern Trends in Surgical Materials, Gillis, L. (Ed.), Butterworth, London, 1958, 29.

Hierholzer, S., Local tissue reactions and sensibilitization in the presence of stainless steel implants, personal communication, 1990.

Hierholzer, S. et al., Increased corrosion of stainless steel implants in infected plated fractures, Arch. Orthop. Trauma Surg., 102, 198, 1984.

Hildebrand, H.F. et al., Nickel, chromium, cobalt dental alloys, and allergic reactions: an overview, in Biocompatibility of Co-Cr-Ni Alloys, Hildebrand, H.F. and Champy, M. (Eds.), Plenum Press, New York, 1988, 201.

Kossovsky, N. and Freiman, C.J., Silicone breast implant pathology. Clinical data and immunologic consequences, Arch. Pathol. Lab. Med., 118, 686, 1994.

Kossovsky, N. et al., The bioreactivity of silicone, CRC

Crit. Rev. Biocompat., 3, 53, 1987.

Leynadier, F. and Langlais, F., Total hip arthroplasties and allergy to metals, in Biocompatibility of Co-Cr-Ni Alloys, Hildebrand, H.F. and Champy, M. (Eds.), Plenum Press, New York, 1988, 193.

Lintner, F. et al., Are multinucleated giant cells indicative of cobalt-related tissue damage after metal-on-metal THR? (Ger.; author's trans), Osteologie, 14, 117, 2005.

Lomer, M.C.E. et al., Fine and ultrafine particles of the diet: influence on the muscosal immune response and association with Crohn's disease, Proc. Nutr. Soc., 61, 123, 2002.

Maurin, N., Delayed in vitro immune response to long-term intraperitoneal polymer implant in mice, J. Biomed. Mater. Res., 29, 1493, 1995.

McGillis, S.T. et al., Patch testing, Clin. Rev. Allergy, 7, 441, 1989.

Merritt, K., Immune response, in Handbook of Biomaterial Properties, Black, J. and Hastings, G. (Eds.), Chapman & Hall, London, 1998, 513.

Merritt, K. and Brown. S.A., Tissue reaction and metal sensitivity. An animal study, Acta Orthop. Scand., 51, 403, 1980.

Merritt, K. and Brown, S.A., Biological effects of corrosion products from metals, in Corrosion and Degradation of Implant Materials: Second Symposium. ASTM STP 859, Fraker, A.C. and Griffin, C.D. (Eds.), American Society of Testing and Materials, Philadelphia, 1985, 195.

Merritt, K. and Rodrigo, J.J., Immune response to synthetic materials, Clin. Orthop. Rel. Res., 326, 71, 1996.

Naim, J.O. et al., The effect of molecular weight and gel preparation on humoral adjuvancy of silicone oils and silicone gels, Immunol. Invest., 24(3), 537, 1995.

Nakamura, S. et al., Autoantibodies to red cells associated with metallosis — a case report, Acta Orthop. Scand., 68, 495, 1997.

Nicholson, J.J., III et al., Silicone gel and

octamethylcyclotetrasiloxane (D4) enhances antibody production to bovine serum albumin in mice, J. Biomed. Mater. Res., 31, 345, 1996.

Playfair, J.H., Immunology at a Glance, 3rd ed., Blackwell Scientific Publications, Oxford, 1979.

Santavirta, S. et al., Aggressive granulomatous lesions associated with hip arthroplasty, J. Bone Joint Surg., 72A, 252, 1990.

Shepard, A.D. et al., Complement activation by synthetic vascular prostheses, J. Vasc. Surg., 1(6), 829, 1984.

Shrivastava, R. et al., Mini review: effects of chromium on the immune system, FEMS Immunol. Med. Microbiol., 34, 1, 2002.

Stern, I.J. et al., Immunogenic effects of foreign materials on plasma proteins, Nature, 238, 151, 1972.

Tang, L. et al., Complement activation and inflammation triggered by model biomaterial surfaces, J. Biomed. Mater. Res., 41, 333, 1998.

Tegnander, A. et al., Activation of the complement system and adverse effects of biodegradable pins of polylactic acid (Biofix®)) in osteochondritis dissecans, Acta Orthop. Scand., 65, 472, 1994.

Urban, R.M. et al., Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty, J. Arthrop., 19(8 Suppl 3), 94, 2004.

Urban, R.M. et al., Migration of corrosion products from modular hip prostheses. Particle microanalysis and histopathological findings, J. Bone Joint Surg., 76A, 1345, 1994.

Wahlberg, J.E., Thresholds of sensitivity in metal contact allergy. 1. Isolated and simultaneous allergy to chromium, cobalt, mercury, and/or nickel, Berufsdermatosen, 21, 22, 1973.

Waterman, A.H. and Schrik, J.J., Allergy in hip arthroplasty, Contact Derm., 13, 294, 1985.

Willert, H.-G. and Semlitsch, M., Reactions of the articular capsule to wear products of artificial joint prostheses, J. Biomed. Mater. Res., 11, 157, 1977.

Wooley, P.H. et al., Cellular immune responses to orthopedic implant materials following cemented total joint replacement, J. Orthop. Res., 15, 874, 1997.

Yang, J. and Merritt, K., Detection of antibodies against corrosion products in patients after Co-Cr total joint replacements, J. Biomed. Mater. Res., 28, 1249, 1994.

Yang, J. and Merritt, K., Production of monoclonal antibodies to study corrosion products of Co-Cr biomaterials, J. Biomed. Mater. Res., 31, 71, 1996.

Abbas, A.K. et al., Cellular and Molecular Immunology, 5th ed., W.B. Saunders, Philadelphia, 2003.

DeLustro, F. et al., Immune responses to allogenic and xenogenic implants of collagen and collagen derivatives, Clin. Orthop. Rel. Res., 260, 263, 1990.

Ellingsen, J.E., A study on the mechanism of protein adsorption to TiO 2 , Biomaterials, 12, 593, 1991.

Gabriel, S.E., Soft tissue responses to silicones, in Handbook of Biomaterial Properties, Black, J. and Hastings, G. (Eds.), Chapman & Hall, London, 1998, 556.

Guyton, A.C., Resistance of the body to infection: II. Immunity and allergy, in Textbook of Medical Physiology, 6th ed., W.B. Saunders, Philadelphia, 1991.

Hennekens, C.H. et al., Self-reported breast implants and connective-tissue diseases in female health professionals, JAMA, 275(8), 616, 1996.

Hildebrand, H.F., Veron, C. and Martin, P., Nickel, chromium, cobalt dental alloys, and allergic reactions: an overview, Biomaterials, 10, 545, 1989.

Klippel, J.H. (Ed.), Primer on the Rheumatic Diseases, 12th ed., Arthritis Foundation, Atlanta, 2001.

Kossovsky, N. and Freiman, C.J., Immunology of silicone breast implants, J. Appl. Biomater., 8(3), 237, 1994.

Kossovsky, N. et al., Self-reported signs and symptoms in breast implant patients with novel antibodies to silicone surface associated antigens [anti-SSAA(x)], J. Appl. Biomater., 6, 153, 1995.

Kumar, P. et al., Metal hypersensitivity in total joint replacement, Orthopedics, 6, 1455, 1983.

Merritt, K. and Brown, S.A., Hypersensitivity to metallic biomaterials, in Systemic Aspects of Biocompatibility, Vol. II, Williams, D.F. Ed., CRC Press, Boca Raton, FL, 1981, 33.

Merritt, K., Role of medical materials, both in implant and surface applications, in immune response and in resistance to infection, Biomaterials, 5, 47, 1984.

Niki, Y. et al., Screening or symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty, Biomaterials, 26, 1019, 2005.

Playfair, J.H.L. and Chain, B.M., Immunology at a Glance, 7th ed., Blackwell Scientific Publications, Oxford, 2000.

Rostocker, G. et al., Dermatitis due to orthopedic implants, J. Bone Joint Surg., 69A, 1408, 1987.

Wang, J.Y. et al., Prosthetic metals impair immune response and cytokine release in vivo and in vitro, J. Orthop. Res., 15, 688, 1997.

Weir, D.M. and Stewart, J., Immunology, 8th ed. Churchill-Livingstone, Edinburgh, 1997.

Wooley, P.H. et al., The immune response to implant materials in humans, Clin. Orthop. Rel. Res., 326, 63, 1996. 245

13

Chemical and Foreign-Body Carcinogenesis

13.1 Definitions

This chapter will consider the role of implants in carcinogenesis. Some def

initions are needed to make the arguments clear and unambiguous:

Benign Possessing controlled self-limiting growth without invasiveness or ability to metastasize.

Cancer Perhaps the best definition is that of Roe (1966): “Cancer is a disease of multicellular organisms which is

characterized by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism's own cells." Roe further states that the three key characteristics of cancer are cellular multiplication, autonomy, and invasiveness.

Carcinogen An agent capable of causing cancer.

Carcinogenesis The production of cancer (more properly but less commonly termed cancerogenesis).

Carcinogenic/tumorigenic Used interchangeably to connote agents capable of causing cancer.

Carcinoma A malignant neoplasm arising from cells of epithelial origin.

Leukemia or lymphoma A malignant neoplastic transformation of cells of the circulatory system.

Malignant Possessing uncontrolled growth, invasiveness, and ability to metastasize.

Metastasis A neoplasm arising by "seeding" from a primary malignant neoplasm to a remote site. Also called a secondary neoplasm.

Mutagenesis The production of inheritable (genotypic) changes in cells.

Neoplasm A tissue mass arising from an abnormal, uncoordinated proliferation of cells.

Primary neoplasm A locally arising neoplasm.

Sarcoma A malignant neoplasm arising from cells of connective tissue.

Tumor Literally, a swelling; used to refer to neoplasms.

With these terms in mind, first, chemically induced and promoted carcino

genesis as it relates to implants will be examined. Initially, all neoplasms

associated with implants in experimental animals and in patients were

thought to be chemical in origin. It is now recognized that

these tumors can

arise, at least in animals, from chemical and nonchemical origins. The

nonchemical or so-called “solid-state” mechanism will be taken up in the

later parts of this chapter.

13.2 Chemical Carcinogenesis

13.2.1 Introduction

Chemical carcinogens have many different forms, affect a variety of cell

types, and produce a variety of neoplasms. The nature of their action leads

to neoplastic transformation being possible near implants by direct solution

or diffusion; at a distance by transport and concentration; or in the absence

of implants by contact, ingestion, or inhalation. It is not within the scope of

this book to discuss the details of these processes. However, it should be

recognized that there is more than one transformation effect. Neoplastic

growth may be initiated by alteration of metabolic processes, by alteration

of replication processes (by growth stimulation or by reduction of contact

inhibition), or by mutagenesis. Although all carcinogens are now thought to

be mutagens, not all mutagenic agents are carcinogenic. A mutation may be

lethal (to a cell), prevent cellular replication, or simply not affect metabolic

or growth processes sufficiently to produce malignant behavior.

13.2.2 What "Everybody Knows" about Cancer

Before proceeding to a discussion of classes and types of chemical carcinogens,

it would be a good idea to discuss some popular misunderstandings about

carcinogenesis in general and chemical carcinogenesis in particular. "Every

body knows" at least three things about cancer that probably are not so:

• "Cancer is increasing." Figure 13.1 presents a summary of cancer death rates in the U.S. for the period of 1930 to 2000, adjusted for age (American Cancer Society, 2004). The adjustment for age is necessary because, as life expectancy and thus age at death increase, a fixed annual incidence rate of mortality from one source will produce an increase in actual deaths from that source. Today, most death

FIGURE 13.1

Cancer death rates, by site, U.S., 1930–2000. Rates adjusted to 1970 standard U.S. population;

*cervix and endometrium combined. (Adapted from American Cancer Society, 2004 Cancer Facts

and Figures, American Cancer Society, Atlanta, 2004.) 1930 1940 1950 1960 1970 1980 1990 2000 80 60 40 20 0 1930 1940 1950 1960 1970 1980 1990 2000 80 60 40 20 0 Lung R a t e p e r 1 0 0 , 0 0 0 f e m a l e p o p u l a t i o n R a t e p e r 1 0 0 , 0 0 0 m a l e p o p u l a t i o n Stomach Colon and Rectum Colon and Rectum Prostate Pancreas Liver Uterus* Breast Lung Stomach Ovary Pancreas rates due to particular types of cancer are decreasing. Furthermore, excluding lung cancer, which is related primarily to tobacco smoking and secondarily to environmental effects, death rates due to cancer have been constant or have decreased since 1945 for men and since 1930 for women. Note that, although the rate of death due to prostate cancer appeared to be increasing in the 1980s, this was likely due to better, earlier diagnosis rather than to an actual increase in incidence. Today, although nearly 30% of Americans alive will develop cancer and 25% will die from cancer, the overall 5-year

survival rate, despite an aging population, has increased to 63% compared with 33% in the 1960s and 25% in the 1930s. This increased survival rate is due in part to earlier detection, permitting a longer normal course until death and earlier medical intervention, and to improved therapies, especially for some specific cancers.

• “Everything causes cancer.” In fact, the contrary seems to be true. Chemical carcinogenesis seems to be the exception rather than the rule. The statistical estimates are as follow. Approximately 1.5 to 2 million compounds and substances are now individually chemically identifiable. An exhaustive literature search concerning the 6000 most likely candidates uncovered evidence that only 17%, or approximately 1000, were possible carcinogens. A survey by the National Institute of Occupational Safety and Health (Christensen 1972) of 2415 suspected carcinogens produced evidence of 1905 reported as carcinogenic effects but only 1000 thought to be carcinogenic in animals. In the most recent compilation available, only 58 substances or groups of related substances or occupational exposures are listed as known to cause cancer in humans; 188 additional ones can reasonably be anticipated to be carcinogenic in humans (U.S. Department of Health and Human Services 2004).

• “Toxic materials cause cancer.” The classic study is that of Innes et al. (1969) in which 120 pesticides and toxic industrial chemicals were selected for evaluation. These materials were fed to two strains of mice in the maximum tolerable doses. The animals were sacrificed after a standard period and evaluated for tumor incidence. The results were that 11 compounds (including five insecticides) were significantly carcinogenic; 20 compounds were equivocal — that is, did not show significant elevation of cancer incidence rates in this study; and 89 compounds produced no elevation of cancer incidence rates. Thus, in this study of compounds specifically selected for their toxicity and given in maximum possible doses, fewer than 10% proved to be carcinogenic. Furthermore, these findings have come under increasing criticism as being too pessimistic. It has been suggested that testing toxic potential carcinogens at high dosages may artificially accentuate their activity by inducing increased rates of cell division (Ames and Gold 1990).

13.2.3 Types of Carcinogens

In the classification of materials that are carcinogens, three types of agents

are recognized:

• The complete carcinogen that produces neoplastic transformation by itself

• The procarcinogen, or carcinogen precursor, that is not a carcinogen but is converted to one by metabolic processes in the body of the test animal or man

• The cocarcinogen, which is a weak carcinogen or has no inherent carcinogenic activity but increases the activity of complete carcinogens or procarcinogens when it appears in their company

The exact roles and functions of pro- and cocarcinogens remain unclear. It

was suggested early that neoplastic transformation is a two-step process

(Friedewald and Rous 1944):

1. Initiation produces the primary cellular transformation. The cells enter a latent period and do not ordinarily develop into a tumor.

2. Promotion is characterized by the development of previously transformed cells into an active visible tumor.

However, this process is now viewed as having at least three steps, with

specific conditions necessary during the latent period if subsequent expres

sion (development of a tumor) is to occur.

Thus, a complete carcinogen is one that is an initiator as well as a promoter,

and a cocarcinogen may be promoter or initiator but probably not both.

Similarly, a procarcinogen may not be a complete carcinogen after metabolic

conversion but its action may depend upon the presence of other initiators

and promoters (Berenblum 1969). It is clear that potential

chemical carcino

gens must be considered in their roles as complete or incomplete agents as

well as possible promoters of previously initiated processes of neoplastic

transformation.

13.2.4 Chemical Carcinogens

An excellent and still useful review of these three types of agents among

organic compounds is that of Weisburger and Williams (1975). Figure 13.2

and Figure 13.3 and Table 13.1 are drawn from this study. Figure 13.2 lists

some of the typical stronger, pure organic carcinogens with their chemical

structures. Table 13.1 lists some of the better known procarcinogens. The

details of metabolic conversion are still unclear for many of these agents.

Table 13.1 suggests the form of the converted carcinogen and Figure 13.3

provides examples of possible intermediates and structures. Of particular

interest is the inclusion of vinyl halide or acetate in the procarcinogen list

and a variety of epoxides in the activated list in Table 13.1. Polyvinyl chloride

(PVC) and polyvinyl acetate (PVA) have some popularity in medical appli

cations and epoxide conversion is possible for many polymeric implant

materials.

FIGURE 13.2

Typical direct-acting chemical carcinogens. (From Weisburger, J.H. and Williams, G.M., in Can

cer: A Comprehensive Treatise, Vol. 1, Becker, F.F. (Ed.), Plenum Press, New York, 1975, 185. With

permission.) β-Propiolactone 1,2,3,4-Diepoxybutane Ethyleneimine Propane sulfone Dimethyl sulfate Methyl methanesulfonate Bis(2-chloroethyl) sulfide (mustard gas or yperite) Nitrogen mustard (HN 2) Bis(chloromethyl) ether Benzyl chloride Dimethylcarbamyl chloride O CO CH 2 CH 2 CH 2 CH 2 CH 2 CH 2 CH 2 CH 3 OSO 2 OCH 3 CH 3 SO 2 OCH 3 CI CH 2 CH 2 CI CH 2 CH 2 CI CH 2 CH 2 CI CH 2 CH 2 CICH 2 OCH 2 CI C 6 H 6 CH 2 CI (CH 3) 2 NCOCI SO 2 CH 2 CH 2 CH CH O O NH O S N CH 3

Testing for possible agents, especially of the pro- or co-type, is quite

difficult due to the necessity of following the products through the various

steps of the metabolic chain. Also, many of the small animals used for these

tests have significant and not inconsiderable rates of spontaneous neoplastic

transformation. Although many agents that produce neoplastic transforma

tion in test animals have not been definitely shown to be carcinogenic in

man, it is essentially correct to assume that all human carcinogens also

produce neoplastic transformation in animals. All known (specifically iden

tified or associated with occupational exposure) chemical carcinogens in

humans have been shown to have carcinogenic activity in at least one test

animal species. However, the neoplasms may vary widely in location, dose

dependency, malignancy, etc. between species.

The vast majority of recognized chemical carcinogens are organic com

pounds. Ceramic-body induction of carcinogenesis through a chemical route

FIGURE 13.3

Typical procarcinogen activation reactions. (From Weisburger, J.H. and Williams, G.M., in Can

cer: A Comprehensive Treatise, Vol. 1, Becker, F.F. (Ed.), Plenum Press, New York, 1975, 185. With

permission.) Procarcinogen --> (proximate carcinogen) --> Ultimate Carcinogen O 5,6 - EPOXIDEBENZO (a) ANTHRACENE (BENZO (a) PYRENE WITH ADDITIONAL RING) NHCOCH 3 N-2-FLUORENYLACETAMIDE ACTIVE ESTER (SULFATE, ACETATE) R= -H or -COCH 3 NCOCH 3 OH CCl 3 + O H 2 C - CHCIH 2 C - CHCI EPOXIDE CARBON TETRACHLORIDE VINYL CHLORIDE CCI 4 N-HYDROXY DERIVATIVE N - R O - ESTER

has not been reliably identified in animals at this time. This is probably due

to the low solubility of ceramics used in implants and the paucity of testing.

The role of metals as possible chemical carcinogens will be examined in the

next section.

13.2.5 Metals as Chemical Carcinogens

The status of metals as carcinogens is less clear. One of the difficulties in

determining this is the problem of distinguishing between chemical and

foreign-body (FB) action (see Section 13.3). Mechanical implantation or inha

lation of metal dust may proceed to neoplastic transformation by a chemical

route after corrosion, by an FB route by the presence of the residual metal,

or perhaps due to aggregation of corrosion products at the implant or at a

remote site. Furthermore, unlike most organic molecules, metals can display

a wide range of electronic valences.

Metals may be placed in a classification system as given in the earlier

discussion. They may be directly (or completely) carcinogenic (pure action)

or they may potentiate other agents and their compounds. Reaction products

or organometallic complexes may be carcinogenic, thus classing the original

form as a procarcinogen. Potentiation (classing metals as cocarcinogens) is

a very broad, nonspecific activity because many forms of neoplasms tend to

concentrate metallic ions and complexes. It is difficult to distinguish cause

and effect here: the concentration of metals may be causal or merely the

consequence of the higher level of metabolic activity of the neoplastic cells. TABLE 13.1 Principal Procarcinogens and Key Derived Active Metabolites Procarcinogen Proximate or Ultimate Actual or Proposed Carcinogen Polycyclic aromatic hydrocarbons Epoxide; radical ion? Aflatoxin Epoxide Arylamine or amide; azo dyes N-Hydroxylamino-O-esters; radical ion (?); epoxide (special case: cutaneous cancers) Nitro aryl or heterocyclic compounds N-Hydroxylamino-O-esters 3-Hydroxyxanthine, related purines O-Esters Safrole 1′-Hydroxy-O-Esters Urethane, alkylcarbamates Active esters Pyrrolizidine alkaloids Pyrrolic esters Alkynitrosamines or -amides, alkyhydrazines or -triazenes Alkyl carbonium ion Halogenated hydrocarbons Haloalkyl carbonium ions Vinyl halide or acetate Epoxide? Source: Adapted from Weisburger,

J.H. and Williams, G.M., in Cancer: A Comprehensive Treatise, Vol. 1., Becker, F.F. (Ed.), Plenum Press, New York, 1975, 185.

Summarizing a broad range of early animal studies, Sunderman (1971)

has made a strong case for carcinogenic roles for chromium, cobalt, iron,

nickel, titanium, and for some metals not found in implant alloys. Environ

mental and industrial workplace studies support the presumed carcinoge

nicity of chromium, cobalt, nickel, and, perhaps, iron.

Furst (1978) has extensively reviewed the status of metals as carcinogenic

agents. This review is noteworthy because the author had previously (Furst

and Haro 1969) proposed strict criteria that a material should meet before it

could be considered carcinogenic: Tumors must appear both at the site and at a distance from the point of application; more than one route [of application] must be effective; more than one species must respond; the growth should be transplantable; and, if malignant, invasion and/or metastasis must be noted. Most important, all histological slides must be evaluated by a pathologist knowledgeable in animal tumors.

These criteria, although more than 35 years old, are still applicable and very

relevant today. Of importance are Furst’s conclusions drawn from then avail

able in vitro and animal studies subject to the preceding criteria:

- Metals for which pure metal and compounds are carcinogenic: Ni

- Metals for which pure metal is carcinogenic but no carcinogenic compound is known: Co

• Metals for which pure metal is not a carcinogen but that have carcinogenic compounds (given in parentheses): Cr (CrO_4^{-2}), Fe (dextran, dextrin), Ti (titanocene?), Mn ($MnCl_2$?) ("?" = there is some doubt)

Only metals of interest in implant applications are included here. Furst (1978)

lists several others, including cadmium, lead, and beryllium, that fall into

one of these categories. However, it is fair to state that Furst regards metallic

carcinogenesis as a well-established, real effect.

The complexity of the problem presented by potentially carcinogenic

metallic implants is shown in a study by Gaechter et al. (1977). These inves

tigators implanted polished rods of seven common implant alloys, including

common stainless steel and cobalt- and titanium-base implant alloys, in rats

and followed them for 2 years. Each of these alloys contained at least one

element recognized by Furst as carcinogenic. Neoplasms of a wide variety

of types were found, but no statistical elevation above the control (nonim

planted) group incidence rates was seen. This study was possibly suggested

by an earlier one by Heath et al. (1971) in which wear-produced particles

from a Co-Cr metal-on-metal total joint replacement were shown to be

carcinogenic in rat muscle 4 to 15 months after implantation.

There are two possible arguments to explain these conflicting findings. In

the first place, the rods used by Gaechter et al. (1977) may have released

metal at a slower rate than seen in the works referenced by Sunderman (1971)

or in the study of Heath et al. (1971). Thus, dilution may have prevented

direct chemical carcinogenesis or indirect (pro-) carcinogenesis by maintain

ing pool concentrations below critical levels. This possibility is supported

by a later, much larger and somewhat longer rat implant study using rods

and powder (Memoli et al. 1986), which demonstrated a small but significant

increase in incidence of sarcomas and lymphomas in animals with implants

containing cobalt, chromium, or nickel.

The possibility that dilution may reduce the risk of neoplastic transforma

tion leads directly to the question of whether a “threshold” of effect exists.

That is, is there a concentration of a carcinogenic agent below which it looses

its effectiveness? This is a matter of considerable importance in the implant

field because corrosion rates of successful alloys are relatively quite low. A

high-corrosion-rate alloy would probably be rejected for implant applica

tions because of an acute tissue response. These low corrosion rates result

in modest serum and tissue concentration increases, except in instances of

local concentration, as will be discussed in Chapter 15.

A great deal of attention has been paid to this possibility of threshold levels

by legislators and administrators concerned with food purity and workplace

safety. The common view is that no threshold exists; that is, the transforming

effect is like a molecular “trigger” and reduced concentration simply reduces

the likelihood that the critical event will take place. Therefore, given random

chance enhanced by continued exposure, any concentration of a carcinogen

can eventually evoke a neoplastic response. This view was the precipitating

factor in the adoption in 1958 of the now famous Delaney Amendment to

the Pure Food, Drug, and Cosmetic Act. This amendment imposed a zero

(!) permissible level of carcinogenic agents as deliberate food additives,

stating that “…no additive shall be deemed to be safe if it is found to induce

cancer when ingested by man or animal, or if it is found, after tests which

are appropriate for the evaluation of the safety of food additives, to induce

cancer in man or animals…”.* Contrast this with the discussion in Chapter

1 on value judgments inherent in definitions and the carefully enunciated

position of Furst (1978) on the carcinogenic status of metals and their com

pounds.

It is clear that, if one were to apply the Delaney criteria to medical devices,

none of the metals listed by Furst (1978) could be judged satisfactory, even

for short-term implantation. However, the wide utility of probably carcino

genic food substances, such as certain dyes and saccharin, has resulted in a

case-by-case relaxation of the Delaney criteria for deliberate food additives.

These decisions have been made by balancing risk against benefit with,

admittedly, a portion of political judgment added in some cases. In 1996, the

issue of residual materials, such as pesticides, was dealt with by the enact

ment of the Food Quality Protection Act.** Administered by the U.S.

* Cited in Federal Register 42(192), Tuesday Oct. 4, 1977, Part VI, page 54166.

** PL 104-170.

Environmental Protection Agency, this law establishes a system of scientific

review to establish (and review on a 10-year cycle) tolerable limits for the

presence of such materials in food stuffs.

The same careful judgments will probably need to be made concerning

metallic implants. To do so, it is necessary to know the dose-response rela

tionship for carcinogenesis accurately in the various animal models, how to

project this to low-dose–long-response-time conditions (in which animal

experiments become prohibitively expensive), and, most importantly, how

to translate the animal projections to rate predictions in humans. Very little

of the required information is now available.

The difficulty of doing such studies was illustrated by Bouchard et al.

(1996) in a large-scale, essentially lifetime study also performed in rats. In

this study, nearly cylindrical metal implants were fabricated from Ti6Al4V

(F138) or CoCrMo (F-75) in solid form and the latter in a fully porous form

with approximately 20 times the total surface area of the nonporous implants.

Groups of approximately 100 rats, with equal numbers of males and females,

had an implant placed on the lateral surface of one femur; an additional

group received a quantity of 50- to 80-μm F-75 microspheres implanted

subcutaneously. Animals were autopsied as they died of apparently natural

causes during the experiment and all remaining animals were sacrificed 24

months after implantation. No overall differences in tumor incidence or

death rates were found among the groups; however, 55 implant site tumors

of various types were observed (Table 13.2).

The data in Table 13.2 show a very significant association between implant

fixation ($p < 0.001$) with no apparent association between local dose (presumed

to be proportional to implant surface area) of potential carcinogens released

by CoCrMo alloys, with the possible expectation of a higher incidence in the

highest exposure group (IV) in which the implants might be considered to be

fixed due to individual encapsulation. Here, only one complication (implant

fixation) was studied closely; others known to affect cancer incidence and

prevalence include environmental, dietary, and hereditary factors. TABLE 13.2 Implant-Associated Tumors Implant Fixation Status a Group No. Tumors I II III IV Solid Ti6Al4V 23 22 0 0 1 Solid CoCrMo 14 12 0 0 2 Porous CoCrMo 3 0 0 3 0 CoCrMo microspheres 15 n/a a Key: I — loose in soft tissue; II — loose, but in contact with bone; III — fixed to bone (ingrown); IV — unclassified; n/a — not applicable (all microspheres encapsulated in soft fibrous tissue). Source: Adapted from Bouchard, P.R. et al., J. Biomed. Mater. Res., 32, 37, 1996.

Moreover, one disappointing factor is emerging. It appears that linear

projections of response rates to low dose rates, even when the dose-response

curve is linear, provide underestimates of the effect. One reason for this is

discussed briefly in the following section.

13.2.6 The Latent Period

A second argument that may shed light on the results of Gaechter et al.

(1977) is based on the issue of latency. It is common in animal and human

neoplastic transformation for a period of time to pass between exposure

(initiation) and manifestation of neoplastic transformation. This waiting or

latent period differs from species to species and is different for each agent.

In humans, latency periods are typically 15 to 20 years and may be as long

as 40 years (Schottenfeld and Haas 1979). Furthermore, no simple way to

“scale” the effect — that is, to predict the latent period for an agent in one

species from that observed in another species — is known. Thus, one may

argue that the latent period in Gaechter’s experiment exceeded the test

period, despite the fact that 2 years is more than half the life span of most

laboratory rats.

The latency argument is particularly important in the generalization of

conclusions such as those of Sunderman (1971) to expectations of implant

site tumor incidences in patients. The vast majority of implants have been

in patients for only 15 or fewer years because of the advanced age of the

average implant patient and the relatively recent advances in total joint

replacement. For instance, Table 13.3 suggests that patients 65 years or

older at time of surgery have less than a 50% chance of outliving a 20

year latency period, although some 2.5% will live to age 100 or more

(Arias 2004). Thus, the appearance of metal carcinogenesis in humans may

be awaiting the passage of an unelapsed latency period in the younger

patients who have received implants in large numbers in the last decade

(however, see Section 13.4). The differences in life expectancy at any age

between men and women depend upon a number of factors, including

occupational exposure, recreational pursuits, etc., and may not be related

merely to gender difference.

Excellent reviews of metal-associated chemical neoplastic transformation

have been provided by Sky-Peck (1986), Vahey et al. (1995), Rock (1998),

and Adams et al. (2003); the latter three reviews are directed primarily

towards human clinical experience.

13.3 Foreign Body Carcinogenesis

13.3.1 Early Observations of Foreign Body Carcinogenesis

So far the various classes of chemical carcinogens have been considered and

the available information concerning their metabolism and ability to produce

neoplastic transformation has been summarized. Across all the classes of

pro-, co-, and complete chemical cocarcinogens, it may be stated that the risk

of neoplastic transformation increases at least linearly with the concentration

and period of exposure.

Studies of chemical carcinogenesis show interesting differences in action

depending upon the manner and form of administration of the agent. Such

differences led early investigators to study the influence of the physical form

of the carcinogenic agent on its ability to induce transformation. A startling

finding was that many agents not previously thought to be carcinogens

produced dramatic neoplasm incidence rates in rodents when implanted in

a solid form rather than injected or fed in soluble or dispersed form. This TABLE 13.3 Life Expectancy a by Age in the U.S. Age (years) Male Female At birth 74.5 79.9 5 70.2 75.4 10 65.3 70.5 15 60.3 65.5 20 55.6 60.7 30 46.3 51.0 40 37.0 41.4 50 28.3 32.2 60 20.2 23.5 65 16.6 19.5 70 13.2 15.8 75 10.3 12.2 80 7.8 9.4 85 5.7 6.9 90 4.2 5.0 95 3.2 3.7 100 2.5 2.8 a Mean; all races; alive in 2002. Source: Arias, E., United States Life Tables, 2002, National Vital Statistic Reports, 53(6), National Center for Health Statistics, U.S. Government Printing Office, Washington, D.C., November 10, 2004.

effect was called foreign body (FB) carcinogenesis and is known more

recently as solid state* carcinogenesis.

Among the early investigators of FB carcinogenesis were E. and B.S.

Oppenheimer who, in conjunction with a number of co-investigators, pub

lished a long series of papers in the 1940s and 1950s (see Oppenheimer et

al. 1955). Their studies and those of other investigators of the period estab

lished the following points:

• Solid materials without chemical carcinogenic activity can induce a variety of neoplasms in several small rodent species.

• Induction activity generally increases with the size of the implant.

• Induction activity varies inversely as the inflammatory response; that is, in the long run, well-tolerated materials are more effective FB carcinogens.

• Porosity with an average diameter above 0.22 μm (the smallest size studied) reduces the risk of transformation.

13.3.2 Mechanisms of Foreign Body Carcinogenesis

An excellent contemporary summary of these early investigations, primarily

using plastic films as challenge agents, is that of Alexander and Horning

(1959), who proposed that “the most likely process [of neoplasm induction]

would appear to be that the film alters the normal environment of the

neighboring cells in such a way as to favor the induction (or selection) of

discontinuous variations leading to malignancy.” That is, the survival of

viable products of normally occurring cell damage or mutation are somehow

favored by the presence of the solid body and protected from physiological

processes until they are ready to enter the rapid growth phase characteristic

of malignancy.

Two considerations appear to favor this argument. The first is geometric

and was discussed briefly in Chapter 8 when the role of implants in infection

was examined. A cell is normally surrounded by a volume of tissue sub

tending a 4π solid angle. As an implant is approached, the solid angle

decreases to 2π. Furthermore, if the implant is invaginated with a surface

roughness that has a characteristic dimension on the order of cell sizes (2 to

20 μm), the solid angle might even be less than 2π for some selected cells.

The results would be less access to microvasculature, poorer diffusional

supply, and reduced cell contact inhibition. The flaw in this general line of

argument is, of course, the observation that materials with distributed poros

ity of cellular dimensions are less carcinogenic in rodents than smooth non

porous materials. Perhaps one of these geometric factors is dominant or

* I dislike this phrase due to its confusion with semiconducting materials and thus the implica

tion of electronic causality.

perhaps the improved diffusion and cellular activity associated with

microporous surfaces offsets the other aspects of the near-surface geometry.

The second consideration that favors the argument proposed by Alexander

and Horning (1959) is that chemical and electrical conditions near an

implant-tissue interface are different from those at a distance; this has been

discussed extensively in previous chapters. The question remains, however,

of which field and concentration effects might favor protection of deviant

cells. Russian investigators (cited by Bischoff and Bryson 1964) felt that

piezoelectric materials with sharp points and asperities were more tumori

genic than the same materials in smooth or colloidal form. This suggested

a role for very high gradient electric fields in FB carcinogenesis. A study by

Andrews et al. (1979) attempted to investigate this question by subcutaneous

implantation of plates of polystyrene resin in mice. The resin was implanted

in neutral condition or as poled (polarized) electrets of various strengths.

Tumors associated with the control plates were evenly distributed on both

sides, and those associated with the electrets were found predominantly on

the electronegative side.* The investigators felt that the trend was to higher

incidence rates and shorter latency periods for electrets with higher fields.

A more complete review (Bischoff and Bryson 1964) expanded this critique.

The authors posed and answered three questions:

• Question 1: “Is the concept of nonspecific (rather than by a specific chemical agent) solid state carcinogenesis justified?” Answer: After considerable criticism of experimental method and test subject, Bischoff and Bryson conclude that “on the basis of the responses to rather stable, unrelated substances, there is a type of nonspecific carcinogenesis in rodents that is dependent upon a minimum surface requirement.”

• Question 2: “Does solid state carcinogenesis occur in humans?” Answer: For humans, the authors note the low reported incidence of neoplasms associated with implants, natural deposits (cholesterol plaques, gall stones, etc.), and chronic low-level inflammatory processes (leading to acellular fibrotic tissue, which has FB attributes). They admit an exception to this basic pattern in the observation of carcinoma associated with silicosis and asbestosis. (Note, however, that in 1964 the very high correlation between a specific type of asbestos [chrysotile] and mesothelioma was not yet known.) They also recognize the problem of the latency period and of the relatively smaller implants (with respect to body weight) used clinically as compared with those in the experiments of Oppenheimer and others. Thus, they concluded that “the incidence of sarcoma [in humans] arising from subcutaneous FB granuloma is minimal.”

∗ However, this difference, as well as all other conclusions reported for this study, was not sta

tistically significant.

• Question 3: “Is the subcutaneous site in rodents valid for testing for carcinogenic hazards?” Answer: This question reflects their observation of a “widespread disenchantment” with subcutaneous studies in rodents. Their arguments are rather vague, but essentially arrive at the point of view that, through nonspecific irritation, FB carcinogenesis and chemical carcinogenesis may occur together and, without adequate controls, cannot be easily distinguished in the subcutaneous site. They suggest, however, that the determining factor is the difference between response to irritation in the chemical case and transformation after noninflammatory isolation of the foreign body in the FB case. In this latter comment, they presage the more modern studies of FB carcinogenesis.

13.3.3 Additional Studies of Foreign Body Carcinogenesis

Further studies by Ott and by Brand and their students have focused upon

the mechanisms of neoplastic transformation in rodents in order to distin

guish FB from chemical carcinogenesis. Brand (1975) has more fully sum

marized his research and theoretical ideas. He made extensive use of related

species of mice that will accept tissue transplants without immune response,

but in which cells and their daughters can be identified, by species, through

an examination of chromosomes (karyotyping). I will paraphrase two sec

tions of his paper dealing with the mechanism of the tumorigenic process

and hypotheses concerning initiation and promulgation of the process.

Brand reached the following conclusions, which were documented by

thorough and ingenious research:

- The most probable target cell in FB carcinogenesis is the pericyte, a small cell type associated with microvasculature.

- After implantation, the transformation needed to produce a preneoplastic parent cell, with all the genetic information for later expression in the active neoplasm, occurs quite rapidly. In Brand's mice populations, this occurs within 4 to 8 weeks after implantation.

- Although the transformation occurs "near" the FB-tissue interface, actual close contact with the FB is not required.

- Transformation is quite uncommon; thus, neoplasms appear to develop from single parent cells representing one in the

several million affected by the presence of the implant.

• Although neoplasm production will occur in a capsule after FB removal, a significant period of implantation after the initial transformation event is required.

• A latent period always occurs between transformation and neoplastic expression. However, this period is characterized more by inactivity of microphages than of the transformed parent cell that may be cloning (undergoing mitosis without inheritable change) at a slow rate. In the presence of active macrophages, as in moderate to severe chronic inflammation, later neoplastic expression is suppressed.

• When the latent period is over and rapid malignant growth begins, all daughter cells, even if transplanted, appear to act in synchrony.

Boone and coworkers' (1979) set of in vitro tissue culture experiments have

partially verified Brand's in vivo studies. These researchers studied the effects

of attachment of mouse fibroblasts to polycarbonate plates in an in vitro

tissue culture system. Cells implanted after in vitro exposure produced trans

plantable, undifferentiated sarcomas. Notwithstanding a decrease in latent

period with increased time in tissue culture, the authors concluded, as had

Brand, that the smooth surfaces of the plates acted as an FB carcinogen, for

at least initiation, independently of chemical composition.

Brand (1975) cited six proposed mechanistic origins of FB carcinogenesis

(with accompanying criticisms):

• Chemical activity of components of the FB. Brand suggested a moderating or modifying role for chemical agents; however, he felt that the nonchemical mechanism for

FB carcinogenesis was well established.

• Physiochemical surface properties of the FB. Again, Brand recognized a possible role for interface physical effects but suggested that they are overpowered in importance by other physical factors, such as porosity.

• Interruption of cellular contact or communication. Brand felt that this is an open question, but indicates that it would be expected to play a more important role in neoplasm expression and maturation than in induction.

• Tissue anoxia and insufficient exchange of metabolites. Brand rejected this hypothesis based upon comparison of cell distances from vascular processes in normal and neoplastic tissue and upon induction studies with vascularized microporous surfaces.

• Virus (as an unseen contaminant of FBs). Although some viri are now recognized as mammalian carcinogens, the evidence is still weak for viri playing a role in FB transformation; Brand evidently did not favor it.

• Disturbance of cellular growth regulation. Brand clearly favored this mechanism, based on the heritability of neoplastic behavior in the growing cell population. He suggested a wide variety of possible aberrations in growth control and communication processes in cells. Thus, his view is that the nonspecific surface effect, whatever its origins, acts in a mutagenic fashion on cell populations.

This discussion of FB carcinogenesis has focused on nonchemical neoplas

tic transformation effects produced by materials external to cells. However,

solid materials in a form that can penetrate cells can also produce FB trans

formation. The best known example is crysotile asbestos, which was recog

nized as a human carcinogen only because it produced a relatively rare lung

tumor (mesothelioma) (U.S. Department of Health and Human Services,

2004). Studies of asbestos and other fibers in animal

models has led to the

Stanton hypothesis: mesothelioma can be induced by fibers less than 0.5 to

1 μm in diameter and more than 8 μm in length,* regardless of fiber com

position (Lipkin 1980). Lipkin has also shown that in vitro fiber cytotoxicity

correlates well with these dimensions rather than with fiber composition.

Thus, slender stiff fibers, such as mineral whiskers, that are apparently able

to penetrate cells and produce direct mechanical damage, presumably to the

nucleus, appear to be undesirable components of biomaterials.

Perhaps the best place to end this discussion is with a quotation from

Brand (1975, p. 487): Despite the rarity of FB tumors in man, it would be irresponsible to look at the situation with complacency. Several measures are at our disposal which would minimize the probability of FB tumors in man…. These include (1) a more restrictive approach to artificial implantations, especially the exclusion of medically unnecessary cosmetic procedures, unless they are indicated for psychiatric reasons; (2) smallest possible size of implants; (3) reexamination of implant carriers at frequent intervals; (4) a centralized registry for gathering information on general complications as well as instances of neoplasia; (5) continued research (a) on implant materials regarding their suitability for specific surgical purposes and (b) on etiological questions concerning this type of neoplasia.

This passage certainly contains food for thought for the bioengineer.

13.4 Nonspecific Carcinogenesis

A final form of neoplastic stimulation is also recognized. Neoplasms can

arise in response to chronic irritation (leading to chronic inflammation).

Chemicals (as well as foreign bodies), infection, and mechanical trauma have

all been recognized as leading to this type of neoplastic transformation. This

was possibly a feature in the large, lifetime rodent implantation study

* That is, with an aspect ratio (L/D) > 8 to 16. However, other factors, such as fiber stiffness, may

play a role.

discussed previously (Section 13.2.5; Bouchard et al. 1996). It is characterized

by an infidelity of replication (producing a daughter cell not identical to its

parent). The formation of keloids (hyperplastic, expansive scars) is a non

malignant example of this effect. The occasional, apparently spontaneous,

malignant transformation of benign lesions such as fibrous histiocytomas is

a somewhat more ominous example (Heselson et al. 1983).

13.5 Evidence for Implant Carcinogenesis in Humans

In light of the long use of metallic implants in clinical orthopaedics and other

surgical specialties, it is fair to ask whether any evidence indicates chemical

or FB carcinogenesis associated with implants. The number of reports of

tumors at implant sites in animals is mounting. Sinibaldi et al. (1976) reported

sarcomas in animals (seven dogs and one cat) occurring 6 months to 4 years

after implantation of stainless steel devices. Of interest is the fact that five

of the eight cases accompanied the use of the Jonas telescoping splint. With

its integral deep “crevice” between parts, this device would be expected to

display an abnormally high rate of corrosion (see Chapter 4). Harrison et al.

(1976) had earlier reported two cases in dogs, one 6 years and one 12 years

after stainless steel implantation during clinical treatment of fractures. An

additional case of sarcoma occurring 12 years after Jonas splint implantation

in a dog has been reported recently (Madewell et al. 1977). A survey by

Stevenson et al. (1982), including these cases, reported 35 fracture-associated

sarcomas in animals with an average of 5.8 years between injury (and inter

nal fixation) and diagnosis.

Finally, these tumors in animals are apparently associated with implant

site infection. Such infection may be expected to produce elevated rates of

corrosion and thus elevated concentrations of metal-bearing species near

implants, due to the resulting local acidosis. However, a large-scale case

control study of possible association between tumors and the use of metallic

fracture fixation devices in 222 dogs with tumors (Li et al. 1993) failed to

show a significant relationship between the incidence of bone and soft-tissue

sarcomas and the use of implants predominantly fabricated from stainless

steel.

The early human orthopaedic literature reports only three cases of fracture

related implant site tumors: Delgado (1958), sarcoma after fracture of tibia,

internally fixed; Dube and Fisher (1972), hemangioendothelioma after frac

ture of tibia, internally fixed; and McDougall (1956), sarcoma (Ewing's type)

in fractured humerus, after internal fixation. The last case is the best known

and occurred more than 30 years after the initial injury and metallic implan

tation. Additional cases continue to be reported, typically occurring more

than 5 years after implantation. Although fracture fixation hardware should

be removed routinely within 2 years after implantation, if the patient's health

permits, less than half is currently removed. Therefore, although such cases

are expected to continue to be rare, some concern remains, especially for

younger individuals.

More than two dozen cases of tumors associated with partial or total joint

replacements in humans have now been published;* the average postoper

ative period before diagnosis is 7 years. The early reports have been dis

cussed previously (Black 1988); more recent reports are reviewed by Rock

(1998) and Adams et al. (2003). These tumors fall into two general groups:

- Tumors of various etiologies occurring in fairly short periods after implantation

- Primarily malignant fibrous histiocytomas occurring 10 to 15 years after implantation

To date, all of these tumors have been associated with stainless-steel or

cobalt-base alloy devices. The origin of the former group is somewhat

obscure; however, the latter group may reflect direct chemical carcinogenesis

(associated with elevated tissue concentrations of metals near the implant;

see Chapter 15) or possibly malignant transformation of the previously

benign implant capsule.

Orthopaedic devices are placed in soft and hard connective tissues, which

are not especially sensitive to primary neoplastic transformation in humans

(Black 1984, 1985). Until recently, no evidence had suggested remote site

tumors possibly resulting from concentrations of suspected carcinogens,

such as chromates, because no large epidemiological study had been done

to detect their presence or absence. However, due in part to my suggestions

(Black 1984), at least three epidemiological studies have now been com

pleted, the first by Gillespie et al. (1988).

Gillespie and colleagues identified 1358 patients who had received total

hip replacements in New Zealand between 1967 and 1978. They investigated

the health status of over 1000 of these patients who could be followed for

more than 10 years postimplantation and found a highly significant 70%

elevated incidence of tumors of lymphatic and hemopoietic origin (Table

13.4). In addition, they observed a significant suppression of soft tissue

(colon, bowel, and breast) tumor incidence up to 10 years postimplantation

followed by an apparent but nonsignificant increase in incidence. Even 10

year follow-up may be insufficient for expression of primary (chemical)

tumors at the low doses encountered at remote sites in implant-bearing

human patients. These results may simply reflect an effect of corrosion

products producing a chronic immune system stress — that is, playing the

part of indirect promoters of soft tissue neoplasias produced by other causes.

* The word “published” is operative here: during a career of more than three decades of lectur

ing on this topic to clinical audiences, almost without fail, after the formal program, I would be

approached by a surgeon who knew of someone who had such a case — but as yet unpublished!

Longer term follow-ups and larger, better defined study groups will be

required to explore these preliminary results.

Since this study, two additional ones have been done to explore the same

question (Table 13.4). The work by Visuri et al. (1991) appears to support the

earlier study, but that of Nyrén et al. (1995) appears to contradict it. However,

when viewed in light of the apparent prevalence of metal-on-metal devices,

which have been shown to produce perhaps as much as a 10- to 15-fold

elevation in circulating serum chromium concentration (Jacobs et al. 1996),

one might well conclude that a positive relationship exists between metal

release and the incidence of lymphoma and leukemia in patients. This con

clusion should be viewed with some caution because it has been known for

some time that patients with rheumatoid arthritis are at greater risk than the

overall population for developing lymphoma and leukemia (Isomäki et al.

1978). Studies such as those reported in Table 13.5 are based upon compar

isons to overall population statistics; in total hip replacement recipient

TABLE 13.4

Risks of Cancer in Patients with Total Hip Replacement

Study Feature Gillespie et al. (1988) a Visuri et al. (1991) Nyrén et al. (1995) b

Total patients 1358 433 39,154

Site New Zealand Finland Sweden

Total THRs unk. (>1358) 511 46,547

Total patient years 14,286 5729 327,922

Average duration,

years 10.5 9.6 8.4

Type of THR Many; mostly McKee-Farrar McKee-Farrar Many; no McKee-Farrar

Increased cancer

risk c Lymphoma/leukemia (1.38) (total period: 1.68 d) Lymphoma/ leukemia (3.01 d); intra-abdominal (2.78) Bone (2.08); melanoma (1.44 d); connective tissue (1.42); kidney (1.33 d); prostate (1.18 d)

Decreased cancer

risk c Colon/rectum (0.52 d); bronchus/lung (0.54); breast (0.30 d) Respiratory (0.86); female reproductive system (0.56) Gastric (0.74); lymphoma (0.89)

Overall risk c Decreased (0.77 d) Unchanged (1.02) Increased (1.05 d)

Comment Patients followed > 10 years; SIR = 1.60 e

Note: McKee-Farrar is a metal/metal articulating THR device.

a SIRs for 5- to 10-year follow-up.

b SIRs for 5- to 9-year follow-up.

c Standard incidence ratio (SIR).

d Significant change in SIR($p < 0.05$).

e Significant change in SIR($p < 0.01$).

Source: Adapted from Black, J., Clin. Orthop. Rel. Res., 329S, S244, 1996.

populations, individuals with rheumatoid arthritis are probably over-repre

sented in comparison to the overall population in the country of the study.

In reviewing this growing body of conflicting information, Rock (1998)

concludes that “[although] the incidence of primary tumors in close prox

imity to implants appears consistent with that expected in the general pop

ulation…the frequency of occurrence and associated individual and group

risks of systemic and remote site malignancy remains unresolved.”

The question of the occurrence of FB tumors in patients also remains a

mystery. Brand (1983) reviewed 43 tumors occurring in humans at implant

sites, at up to 53 years after implantation; 25% occurred within 15 years and

50% within 25 years of implantation. In light of the large upsurge in medical

and cosmetic implant use in the 1950s and 1960s, he would have expected

to find orders of magnitude for more cases if causation in humans was the

same as for mice. Thus, although continuing to express concern about the

possibilities for FB carcinogenesis in humans, Brand concluded that little

clinical evidence for its occurrence existed.

Similarly, Berkel and colleagues (1992) studied a group of 11,676 women

with silicone elastomer breast implants, at an average of 10.2 years after

implantation, and concluded that they experienced 52% fewer primary

breast tumors than expected. Thus, although longer term data still are

required, it is beginning to appear likely that the Oppenheimer effect is a

consequence of the relatively primitive immune system of rodents in com

parison to that in humans.

Perhaps the best overview is provided by a study published by the Inter

national Agency for Research on Cancer (IARC 1999). The IARC has classi

fied agents suspected of being carcinogens in a well-defined system based

upon balancing animal- and clinically-derived evidence. This system estab

lishes five groups of agents and exposures as carcinogenic, probably or TABLE 13.5 IARC Classification of Evidence for Human Carcinogenicity Risk Degree of Evidence for Carcinogenicity Group Classification in Humans In Humans In Animals 1: Carcinogenic < Sufficient but Sufficient 2a: Probably carcinogenic Limited and Sufficient Or inadequate and Sufficient 2b: Possibly carcinogenic Limited and < Sufficient Or inadequate and Sufficient 3: Not classifiable Inadequate and Limited or inadequate Or inadequate and Sufficient a 4: Not carcinogenic Suggested lack ?? Inadequate but Suggested lack a However, mechanism of causation inoperative in humans. Source: IARC, Evaluation Carcinogenic Risks Hum., Vol. 74, WHO, IARC, Lyon, France, 1999.

possibly carcinogenic, not classifiable, or not carcinogenic (Table 13.5). Based

upon an exhaustive study of animal data and human clinical results, the

IARC concluded that the following overall evaluation could be made con

cerning the carcinogenic risk of clinical implants:

- Group 1(carcinogenic): none
- Group 2A (probably carcinogenic): none
- Group 2B (possibly carcinogenic): smooth metallic and polymeric films, solid bodies of metallic cobalt, nickel, and a nickel alloy (66 to 67% Ni, 13 to 16% Cr, 7% Fe)
- Group 3 (not classifiable): orthopaedic implants of complex composition, cardiac pacemakers, silicone breast implants, metallic chromium, titanium, Co-, Cr-, and Ti-based alloys, stainless steels and depleted uranium, as well as dental materials and solid ceramic bodies
- Group 4 (noncarcinogenic): none

It is of interest that, despite the extensive clinical use of biomaterials as

human implants, the IARC could not conclude that any are actually carci

nogenic (group 1) or totally lacking in risk (group 4).

Two additional ways of approaching this issue parallel Furst's (1978)

analysis of metal carcinogenesis in animals. The U.S. Department of Health

and Human Services is required by statute* to publish a list of agents (A)

known to be human carcinogens or (B) reasonably anticipated to be human

carcinogens. These correspond to the IARC groups 1 and 2A, and 2B and

3, respectively (see Table 13.5). The most recent of these lists (U.S. Depart

ment of Health and Human Services 2004) contains the following agents,

which could be elements of metallic implants or be released by implant

degradation:

- Known (A): chromium hexavalent compounds, nickel compounds and metallic nickel

- Reasonably anticipated (B): cobalt sulfate

Additionally, the state of California adopted Proposition 65, the Safe Drink

ing Water and Toxic Enforcement Act of 1986, by ballot initiative. This act

requires the periodic publication of a list of chemicals known (to the state)

to cause cancer or reproductive toxicity. This list draws from many sources,

including IARC analyses; because it is precautionary, it is somewhat conser

vative. It also provides for labeling requirements for any product known to

contain such chemicals, unless the release (dose) rate can reasonably be

expected to be below a previously determined acceptable level.

* Section 301(b)(4) of the Public Health Service Act as amended by Section 262, PL, 95-622.

The most recent version of the Proposition 65 list (12/31/04)* contains the

following carcinogenic agents, which could be elements of metallic implants

or be released by implant degradation:

- Chromium (hexavalent compounds)

- Cobalt (metal powder; [II] oxide, sulfate heptahydrate)

• Nickel (metallic, acetate, carbonate, carbonyl, oxide, refinery dust, subsulfide), nickelocene

It remains clear that the traditional problem of projecting animal experi

ence to human occupational and clinical situations applies in the consider

ation of carcinogenesis as a possible consequence of biomaterial

implantation. In particular, it should be noted that, despite Brand's com

ments in his 1983 study, it is only now that significant human populations

with implants in place for more than 15 to 20 years are coming into existence.

Survivors of these large modern cohorts are now beginning to pass the

average latency period for low-concentration chemical carcinogenesis. There

are no animal experiments to guide one accurately in what expectations

should be. Perhaps Brand's previous remarks might be paraphrased:

"despite the rarity of [implant-associated] tumors in [hu]man[s]…" — and

more careful attention should be given in the future to the challenging and

difficult issues of possible chemical and FB carcinogenesis by clinical

implants.

Adams, J.E. et al., Prosthetic implant associated sarcomas: a case report emphasizing surface evaluation and spectroscopic trace meta analysis, Ann. Diagn. Pathol., 7(1), 35, 2003.

Alexander, P. and Horning, E.S., Observations on the

Oppenheimer method of inducing tumors by subcutaneous implantation of plastic films, in Carcinogenesis: Mechanisms of Action, Ciba Foundation Symposium, Wolstenholme, G.E.W. and O'Connor, M. (Eds.), Little, Brown, Boston, 1959, 12.

American Cancer Society, 2004 Cancer Facts and Figures, American Cancer Society, Atlanta, 2004.

Ames, B.N. and Gold, L.S., Too many rodent carcinogens: mitogenesis increases mutagenesis, Science, 249, 970, 1990.

Andrews, E.J. et al., Surface charge in foreign body carcinogenesis, J. Biomed. Mater. Res., 13, 173, 1979.

Arias, E., United States Life Tables, 2002, National Vital Statistic Reports, 53(6), National Center for Health Statistics, U.S. Government Printing Office, Washington, D.C., November 10, 2004.

* http://www.oehha.ca.gov/prop65/prop65_list/Newlist.html.

Berenblum, I., A re-evaluation of the concept of co-carcinogenesis, Prog. Exp. Tumor Res., 11, 21, 1969.

Berkel, H., Birdsell, D.C. and Jenkins, H., Breast augmentation: a risk factor for breast cancer? New Engl. J. Med., 326(25), 1649, 1992.

Bischoff, F. and Bryson, G., Carcinogenesis through solid state surfaces, Prog. Exp. Tumor Res., 5, 85, 1964.

Black, J., Systemic effects of biomaterials, Biomaterials, 5, 11, 1984.

Black, J., Metallic ion release and its relationship to oncogenesis, in Fitzgerald, R.H., Jr. (Ed.), The Hip, Vol. 13, C.V. Mosby, St. Louis, 1985, 199.

Black, J., Orthopedic Biomaterials in Research and Practice, Churchill Livingstone, New York, 1988, 292.

Black, J., Metal on metal bearings: a practical alternative to metal on polyethylene bearings? Clin. Orthop. Rel. Res., 329S, S244, 1996.

Boone, C.W. et al. "Spontaneous" neoplastic transformation in vitro: a form of foreign body (smooth surface) tumorigenesis, Science, 204, 177, 1979.

Bouchard, P.R et al., Carcinogenicity of CoCrMo (F-75) implants in the rat, J. Biomed. Mater. Res., 32, 37, 1996.

Brand, K.G., Foreign body induced sarcomas, in Cancer: A Comprehensive Treatise, Vol. 1, Becker, F.F. (Ed.), Plenum, New York, 485, 1975.

Brand, K.G., Human foreign-body carcinogenesis in the light of animal experiments and assessment of cancer risk at implant sites, in Biomaterials in Reconstructive Surgery, Rubin, L.R. (Ed.), C. V. Mosby, St. Louis, 36, 1983.

Christensen, H.E. and Fairchild, E.J. (Eds.), Suspected Carcinogens, 2nd ed., CDC, National Institute for Occupational Safety and Health, Cincinnati, OH, 1972.

Delgado, E.R., Sarcoma following surgically treated fractured tibia, Clin. Orthop., 12, 315, 1958.

Dube, V.E. and Fisher, D.E., Hemangioendothelioma of the leg following metallic fixation of the tibia, Cancer, 30, 1260, 1972.

Friedewald, W.F. and Rous, P., The initiating and promoting elements in tumor formation, J. Exp. Med., 80, 101, 1944.

Furst, A. and Haro, R.T., A survey of metal carcinogenesis, Progr. Exp. Tumor Res., 12, 102, 1969.

Furst, A., An overview of metal carcinogenesis, Adv. Exp. Med. Biol., 91, 1, 1978.

Gaechter, A. et al., Metal carcinogenesis, J. Bone Joint Surg., 59A, 622, 1977.

Gillespie, W.J. et al., The incidence of cancer following total hip replacement, J. Bone Joint Surg., 70B, 539, 1988.

Harrison, J.W. et al., Osteosarcoma associated with metallic implants, Clin. Orthop. Rel. Res., 116, 253, 1976.

Heath, J.C. et al., Carcinogenic properties of wear particles from prostheses made in cobalt-chromium alloy, Lancet (March 20), 564, 1971.

Heselson, N.G. et al., Two malignant fibrous histiocytomas in bone infracts, J. Bone Joint Surg., 65A, 1166,1983.

IARC, Surgical implants and other foreign bodies, IARC Monogr. Evaluation Carcinogenic Risks Hum., Vol. 74, WHO,

IARC, Lyon, France, 1999.

Innes, J.R.M. et al., Bioassay of pesticides and industrial chemicals for tumorgenicity in mice: a preliminary note, J. Natl. Cancer Inst., 42, 1101, 1969.

Isomäki, H.A. et al., Excess risk of lymphomas, leukemia, and myeloma in patients with rheumatoid arthritis, J. Chron. Dis., 31, 691, 1978.

Jacobs, J.J. et al., Cobalt and chromium concentrations in patients with metal-onmetal total hip replacements, Clin. Orthop. Rel. Res., 329S, S256, 1996.

Li, X.Q. et al., Relationship between metallic implants and cancer: a case-control study in a canine population, Vet. Clin. Orthop. Trauma, 6, 70, 1993.

Lipkin, L.E., Cellular effects of asbestos and other fibers: correlations with in vivo induction of pleural sarcoma, Environ. Health Persp., 34, 91, 1980.

Madewell, B.R. et al., Osteogenic sarcoma at the site of a chronic nonunion and internal fixation device in a dog, J. Am. Vet. Med. Assoc., 171, 187, 1977.

McDougall, A., Malignant tumor at site of bone plating, J. Bone Joint Surg., 38B, 709, 1956.

Memoli, V.A. et al., Malignant neoplasms associated with orthopedic implant materials in rats, J. Orthop. Res., 4, 346, 1986.

Nyrén, O. et al., Cancer risk after hip replacement with metal implants: a populationbased cohort study in Sweden, J. Natl. Cancer Inst., 87(1), 28, 1995.

Oppenheimer, B.S. et al., Further studies of polymers as carcinogenic agents in animals, Cancer Res., 15, 333, 1955.

Rock, M., Cancer, in Handbook of Biomaterial Properties, Black, J. and Hastings, G. (Eds.), Chapman & Hall, London, 1998, 529.

Schottenfeld, D. and Haas, J.F., Carcinogens in the workplace, CA, 29, 144, 1979.

Sinibaldi, K. et al., Tumors associated with metallic implants in animals, Clin. Orthop. Rel. Res., 118, 257, 1976.

Sky-Peck, H.H., Trace metals and neoplasia, Clin. Physiol. Biochem., 4, 99, 1986.

Stevenson, S. et al., Fracture-associated sarcoma in the dog, J. Am. Vet. Med. Assoc., 180, 1189, 1982.

Sunderman, F.W., Jr., Metal carcinogenesis in experimental animals, Food Cosmet. Toxicol., 9, 105, 1971.

U.S. Department of Health and Human Services, Report on Carcinogens, 11th ed., U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, December 2004.

Vahey, J.W. et al., Carcinogenicity and metal implants, Am. J. Orthop., 24(4), 319, 1995.

Visuri, T. and Koskenvuo, M., Cancer risk after Mckee-Farrar total hip replacement, Orthopedics, 14(2), 137, 1991.

Weisburger, J.H. and Williams, G.M., Metabolism of chemical carcinogens, in Cancer: A Comprehensive Treatise, Vol. 1, Becker, F.F. (Ed.), Plenum Press, New York, 1975, 185.

Ambrose, E.J. and Roe, F.J.C., The Biology of Cancer, D. Van Nostrand, New York, 1966.

Berenblum, I., Carcinogenesis as a Biological Problem, North-Holland Pub. Co., Amsterdam, 1974.

Becker, F.F., Cancer: A Comprehensive Treatise, Vol. 1: Etiology: Chemical and Physical Carcinogenesis, Vol. 4: Biology of Tumors: Surfaces, Immunology, and Comparative Pathology, Plenum Press, New York, 1975

Haag, M. and Adler, C.P., Malignant fibrous histiocytoma in association with hip replacement, J. Bone Joint Surg., 71B, 701, 1989.

Kolstad, K. and Högstorp, H., Gastric carcinoma metastasis to a knee with a newly inserted prosthesis, Acta Scand. Orthop., 61, 369, 1990.

Roe, F.J.C., Introduction, in The Biology of Cancer, Ambrose, E.J. and Roe, F.J.C. (Eds.), D. Van Nostrand, New York, 1966, 28.

Tait, N.P. et al., Malignant fibrous histiocytoma occurring

at the site of a previous total hip replacement, Br. J. Radiol., 61, 73, 1988.

Troop, J.K. et al., Malignant fibrous histiocytoma after total hip arthroplasty, Clin. Orthop. Rel. Res., 253, 297, 1990.

U.S. Department of Health and Human Services, Proceedings of a workshop/conference on the role of metals in carcinogenesis, Atlanta, GA, March 24-28, 1980, Environmental Health Perspectives, Vol. 40, 1981.

van der List, J.J.J. et al., Malignant epithelioid hemangioendothelioma at the site of a hip prosthesis, Acta Orthop. Scand., 59, 328, 1988. 273

14

Mineral Metabolism

14.1 Introduction

The next chapter will deal with the distribution of metallic ions and some

simple models for their dispersion. This chapter will consider one well

known metal — iron — in detail and a lesser known metal — chromium.

This consideration is important in its own right, as well as being an indicator

of the complexity of the metabolism of metals. As in the case of most other

metals, the details of metabolic pathways and kinetics of these two metals

are not fully known. However, the attempt will be to contrast iron meta

bolism with chromium metabolism.

As discussed in Section 2.2 and Section 2.4, the human body is primarily

composed of four nonmetallic elements (in declining order of abundance):

oxygen, carbon, hydrogen, and nitrogen, which make up 96.9% of body

tissues by weight. Six additional elements, of which only two are metals

(calcium and sodium), play major physiological roles and contribute a fur

ther ~3.2% of body weight. All other constituents contribute together no

more than 30 g and are termed trace elements. These include at least 13

metals, of which 10 are used routinely as nontrace constituents in human

implants: iron, copper,* aluminum, vanadium, manganese, nickel, molybde

num, titanium, chromium, and cobalt.

Most of these trace elements (with the possible exception of titanium) play

vital physiological roles and thus are termed essential trace elements. The

role of each is characterized by three important attributes (Mertz 1981):

• Amplification: all known essential trace elements exert their biological actions through a succession of regulatory and/or synthetic steps that produce a many-fold amplification function and lead to effects on the whole body.

• Specificity: each essential trace element has a specific role as a moiety in a molecule or as an enzyme cofactor. This specificity depends on

* Copper is not routinely used in human implants, due to its cytotoxicity, but is a component of

some designs of semipermanent intrauterine contraceptive devices (IUDs). ionic size and valence. Other ions may interfere with the specific role of a trace element but may not replace its function.

• Homeostatic regulation: without exception, for each essential trace element, a panoply of absorption, transport, storage, and excretion mechanisms regulates concentration at the site of action within an optimum range.

Our interest in trace elements is related to this third attribute — to the

possibility that the introduction of an endogenous source, i.e., release of

material from an implant, may interfere with homeostatic regulation and

produce adverse effects at the site of normal action or at other sites, directly

or by interference with other trace element-mediated processes.

In discussing the toxic effects of mercury and its organometallic com

pounds, Schwarz (1977) makes the following point: Below a certain threshold [of concentration], the organism can maintain an equilibrium. However, once the threshold level is reached, small increases in doses lead to great increases of toxic effects…. Indeed, this relationship pertains not only to all metals but anything. It is universal, with the possible exception of mutagenicity and carcinogenicity, but even there repair mechanisms are at work which may give a small area of tolerance (p. 3).

The general relationship between metal concentration level and functional

effect is shown in Figure 14.1. It should be emphasized that this is only

schematic in nature; the details and relative extent of each range depend

upon the nature of the metal involved and, probably, upon individual dif

ferences between patients. Thus, although calculations may be performed

that predict various levels of metallic ions in blood, tissues, etc. (Section

15.4), the real need is to know the details of the metabolic, storage, and

excretory pathways. The next two major sections outline iron metabolism,

whose details are well known, and chromium metabolism, which is less well

known and understood. Until the comparable systems are as well known

for the other major metallic components of common implant alloys such as

aluminum, chromium, cobalt, nickel, titanium, etc. as they are for iron, great

care must be taken in the interpretation of animal and clinical determinations

of metallic content in vivo.

14.2 Iron Metabolism

14.2.1 Introduction

Iron is a biologically ubiquitous metal that is essential to all higher forms of

life owing to its central role in the heme molecule facilitating oxygen and

electron transport. The capacity of porphyrin-Fe-protein complexes to bind

large quantities of oxygen reversibly makes hemoglobin and myoglobin well

suited to the transport and storage of oxygen in higher organisms. Iron

containing enzymes include the cytochromes, catalase, cytochrome c reduc

tase, succinic dehydrogenase, and fumaric dehydrogenase. Total body iron

in an average adult ranges from 2 to 6 g, depending on body weight, hemo

globin concentration, age, sex, and size of the storage compartment. As a

trace element, iron’s presence in the body is exceeded only by magnesium

(see Table 2.3).

On the basis of function, two iron metabolic compartments are recognized:

• An essential compartment containing 70% of the total body iron is composed of hemoglobin, myoglobin, heme enzymes, cofactor, and transport iron.

• A nonessential storage compartment accounts for 30% of the total body iron in a normal individual and consists of iron storage in the form of ferritin and hemosiderin, primarily in the liver, spleen, and bone marrow.

The essential compartment can be further subdivided into the following

distribution: 85% in hemoglobin, 5% in myoglobin, 10% in intracellular heme

enzymes and iron cofactors in other enzyme systems, and 0.1% as transport

iron bound to transferrin.

FIGURE 14.1

Relation between metal concentration and its functional consequence. Lethal Toxic Normal or tolerable F U N C T I O N Normal Tolerable Toxic CONCENTRATION

14.2.2 Absorption

Absorption of iron (see Figure 14.2) represents the single most important

factor maintaining the normal balance of iron in the body. It is influenced

by age, state of health, current body iron status, and

conditions within the

gastrointestinal tract, as well as by the amount and chemical form of iron

ingested and by the relative iron-chelating nature of other dietary constitu

ents (e.g., phosphates, phytates, ascorbic acid, and amino acids). Dietary

intake varies between 10 and 30 mg/day, with a common range of 12 to 5

mg/day. Normally, 0.6 to 1.5 mg/day are absorbed through the gastrointes

tinal mucosa, representing only 5 to 10% of total dietary iron intake.

FIGURE 14.2

Iron metabolism in adults. (From Fairbanks, V.F. and Beutler, E., in Modern Nutrition in Health

and Disease, 7th ed., Shils, M.E. and Young, V.R. (Eds.), Lea & Febiger, Philadelphia, 1988, 193.)

EXCRETION Death of Cells

~ Fe 2+ DUODENUM JEJUNUM ILEUM COLON IMPLANT Plasma Iron ~ 3mg (Fe 2+ - transferrin) All Body Cells Fe 3+ 12-15 mg Food Fe Hemorrhage RBC lost in trauma, urine (0.1 - 0.5 mg/day) Menstruation (<1.2 mg/day) Bone Marrow 20-25 mg/day Hemoglobin Hemoglobin Catabolism Urine, Sweat, Bile, Feces (0.5 - 1 mg/day) Fe Storage RE system, Liver, Spleen, Bone marrow

(0.9 - 2.5 mg/day)

STORAGE

(1000 mg

capacity)

UTILIZATION and

CONSERVATION

TRANSPORTATION

(30 - 40 mg/day)

ABSORPTION

(0.6 - 1.5 mg/day) Desquamation of Cells (0.2 mg/day)

The actual mechanisms of absorption and transport of iron or iron chelates

at the mucosal cell level remain unclear; however, it appears that iron enters

the mucosal brush border by a passive diffusion process and exits on the

serosal surface to the plasma transferrin by an energy-requiring step. Intra

cellular absorbed iron in excess of immediate physiological needs is com

bined with a protein, apoferritin, to form ferritin, a water-soluble iron

storage complex. As the mucosal cells become laden with ferritin, further

absorption is impeded consistent with diffusion kinetics until ferritin iron is

released to the plasma in response to body needs. Most absorbed iron, in

the form of intracellular ferritin, is lost into the intestinal lumen when the

crypt cells complete their 2- to 3-day maturation and migration to the tips

of the villi and are sloughed. Intraluminal factors that decrease iron absorp

tion include rapid gastrointestinal transit time; achylia; malabsorption syn

drome; precipitation by alkalinization by phosphates and phytates; and

ingested alkaline clays and antacid preparations. Despite intensive research,

the systemic factors regulating iron absorption have not been identified. In

general, iron absorption increases whenever erythropoiesis (red blood cell

production) is stimulated, during pregnancy, and in patients with hemochro

matosis; decreased absorption is associated with depressed erythropoiesis

and iron overload.

14.2.3 Transportation

After an iron atom enters the physiological system, it is virtually trapped,

cycling almost endlessly from plasma to developing erythroblasts. Iron is

then released into the circulation for 100 to 160 days, moved to phagocytic

cells where it is cleaved from hemoglobin, and finally released into the

plasma to repeat the cycle. From the standpoint of distribution of total body

iron, the transport compartment is the smallest (~0.008%). However, kinet

ically, it is by far the most active, turning over as often as 10 times every 24

hours.

The vehicle of this rapid transport and turnover of iron is transferrin, a

β 1 -globulin of approximately 8.6 × 10 4 molecular weight, with a half-life of

8 to 10.5 days. Transferrin is synthesized in the liver, and the total body

transferrin content of 7 to 15 g is nearly equally distributed between the

intra- and extravascular spaces. It functions to accept iron from gut absorp

tion, storage sites, and phagocytic cells and to deliver iron to erythroid

marrow for hemoglobin synthesis, to cellular reticuloendothelium for stor

age, to the developing fetus, and to all cells for incorporation into iron

metalloenzymes. Normally, approximately one-third of the total body trans

ferrin (termed total iron-binding capacity; TIBC = 300 to 360 µg/100 ml) is

saturated with iron. The remaining transferrin represents a latent or unbound

reserve (unbound iron-binding capacity [UIBC]). The degree of saturation

(%) and the TIBC are important parameters in the study of iron metabolism

and related disease syndromes.

For example, increased TIBC is characteristically found in iron deficiency,

in the third trimester of pregnancy, and in response to hypoxic states,

whereas decreased TIBC is evident in infection, protein malnutrition, iron

overload conditions, malignancy, cirrhosis of the liver, nephrosis, and pro

tein-losing exteropathies. Figure 14.3 illustrates the relationships between

plasma iron and transferrin in a variety of clinical conditions. In general, the

level of plasma iron and saturation of TIBC are determined by the sum of

factors extracting iron from the blood for storage and utilization balanced

against those factors releasing iron into the blood, e.g., absorption, hemolysis,

and storage site release.

14.2.4 Utilization

It can be estimated from adult blood volume (typically ~5 l) and erythrocyte

lifetime (t 1/2 ≈ 60 days) that, although more than 2.5 g of iron exists in

hemoglobin within red blood cells, only 20 to 25 mg/day is used in hemo

globin synthesis in bone marrow. This is supplied through the transferrin

transport pathway from absorption or release from storage. Defects in

absorption, release, and/or transport may produce suppression of hemoglo

bin synthesis and, over time, lead to an erythrocyte deficiency or anemia.

FIGURE 14.3

Serum iron concentration and the specific size of the transport compartment in a variety of

clinical conditions. (Adapted from Fairbanks, V.F. and Beutler, E., in Modern Nutrition in Health

and Disease, 7th ed., Shils, M.E. and Young, V.R. (Eds.), Lea & Febiger, Philadelphia, 1988, 193.) I r o n (m g / 1 0 0 m l) 100 200 300 400 500 N O R M A L I R O N D E F I C I E N C Y L A T E P R E G N A N C Y I N F E C T I O N I N F L A M M A T I O N M A L I G N A N C Y H E M O C H R O M A T O S I S H E M O S I D E R O S I S N E P H R O S I S T H A L A S S E M I A M A J O R L I V E R C E L L N E C R O S I S P

R O P H Y R I A TIBC UIBC Serum Iron

14.2.5 Storage and Excretion

Iron in excess of metabolic needs is stored intracellularly as ferritin or hemo

siderin in various tissues of the body. Ferritin is normally found in many

tissues of the body; however, the reticuloendothelial system of the liver and

cells in the intestinal mucosa are the most significant metabolic storage sites.

Hemosiderin, a granular water-soluble compound, is thought to be an

aggregation of ferritin molecules. It can be seen microscopically in unstained

tissue sections of bone marrow as clumps or granules of golden refractile

pigment. Similar material is occasionally found in vivo in association with

iron-bearing implants such as stainless steel device components (Winter

1976) and is thought by some investigators to be locally produced hemosid

erin.* Although macrophages adjacent to implants can accumulate hemosid

erin from endogenous sources, the source of this particular material is

thought to be a combination of iron released from the original hematoma

(formed during surgery) and iron oxides and hydroxides formed during

corrosion. Primary storage sites are the hepatic parenchymal cells and retic

uloendothelial cells of the bone marrow, liver, and spleen.

The relationship governing deposition of iron as ferritin or as hemosiderin

is unclear. However, it is postulated that the relative content of iron in either

storage form is a function of the total storage iron concentration. By chem

ically binding or shielding iron from the surrounding intracellular environ

ment, ferritin and hemosiderin serve to reduce its inherent toxicity. Iron in

its ionic form in excess of the TIBC of the blood is extremely and instanta

neously toxic, as demonstrated by Gitlow and Beyers (1952). Slow intrave

nous injection of only 10 mg ferric ammonium citrate totally saturated the

blood’s iron-binding capacity of all patients tested, and the excess randomly

diffused into all body tissues. The toxic response was manifested by cough

ing, sneezing, nausea, and, occasionally, vomiting.

However, the human body tenaciously conserves its content of iron, losing

less than 0.01% of the total amount daily through excretory and other mech

anisms (see Figure 14.2). Iron loss from the body consists of routine excretion

(in urine, bile, feces, sweat), periodic loss (desquammation of cells and men

strual flow [in women]), and occasional loss (hemorrhage secondary to

trauma or disease). Iron excretion is essentially passive and increases only

very slowly with increases in body stores of iron.

14.2.6 Iron Overload

Considering the precisely regulated intestinal absorption of iron coupled

with limited physiological excretory capabilities, one can easily envision the

development of an iron overload state if iron, by pathological or iatrogenic

route, gained access to the endogenous system. For example, excessive

* Titanium-containing hemosiderin-like complexes are seen adjacent to titanium alloy implants,

further suggesting that hemosiderin is a nonspecific precipitate.

absorption of iron occurs in idiopathic hemochromatosis, a situation in which

iron is continually deposited in the parenchymal cells of various organs,

often resulting in arthritis, liver disease, cardiac failure, and diabetes. Exces

sive intake of iron may lead to hepatic and reticuloendothelial involvement

manifesting as portal cirrhosis. This is demonstrated by the Bantu tribesmen

of Africa, who have traditionally consumed large quantities of food cooked

and stored in iron pots. Additionally, a few reported instances of parenteral

iron administration to treat misdiagnosed anemias have resulted in iatro

genic iron overload states with consequent toxic signs indistinguishable from

those of hemochromatosis.

Therefore, evidence indicates that excessive amounts of intracellular iron

stemming from an iron overload condition may predispose to a variety of

liver disorders (Bacon 1998), primarily by causing progressive destruction

of parenchymal cells and subsequent fibrotic replacement. The positive rela

tionship of cardiomyopathies and diabetes mellitus in iron overload to the

deposition of hemosiderin in the myocardium and the pancreas further

substantiates the toxicity of iron even in its bound storage form (Sullivan

2004). In an iron overload state, the serum iron and transferrin saturation

are usually increased and the TIBC is somewhat depressed (Figure 14.3).

14.2.7 Iron and Susceptibility to Infectious Disease

For nearly half a century, it has been recognized that an element of host

response to bacterial invasion is a reduction in the iron content of the blood

serum (reduction in SI; see Figure 14.2) (Weinberg 1974; Ward et al. 1996).

The mechanism of this reduction has been identified as a suppression of

intestinal absorption of iron concurrent with an increase in storage of iron

in the liver and a concomitant reduction in transferrin saturation. The net

effect is that growth-essential iron is made less available

to microbial invad

ers, thus producing a so-called “nutritional immunity” (Kochan 1973) for

the host.

To illustrate the strength of this argument, patients with infection and

inflammation are unable to mobilize iron from reticuloendothelial cell depots

irrespective of a normal total body iron content (Shils et al. 1993) and thus

experience a transient anemia. This suggests that the physiological system

would rather endure a short period of iron deficiency than risk a microbial

invasion. In a survey of pathogen-host metal interrelationships, Weinberg

(1971) concluded that “…in the contest between the establishment of a bac

terial or mycotic disease and the successful suppression of the disease by

animal hosts, iron is the metal whose concentration in host fluids appears

to be most important.”

To acquire iron, microbial cells must often synthesize siderophores, phe

nolates, or hydroxamates, whose function is to solubilize ferric iron at neutral

pH and assimilate the metal. In the presence of small iron-containing metallic

particles, such as wear debris from stainless-steel implants up to 10 to 15

μm in major dimension, macrophages may assist this process by attempts

to digest or dissolve iron and iron hydroxide. In addition, many microorgan

isms have the potential to produce powerful iron-binding ligands that com

pete with the host compounds, e.g., transferrin, for the available iron.

Organisms that have the ability to solubilize, assimilate, and bind iron inde

pendently are termed autosequesteric.

Because most bacteria and fungi require only 0.3 to 4.0 μM concentrations

of iron for growth, human blood plasma with a concentration of 10 to 65

μM would appear suitable to support bacterial growth and multiplication,

leading to bacteremia. That bacteremias are the exception rather than the

rule illustrates the profound role plasma transferrin plays in resistance to

disease by production of “nutritional immunity.” Transferrin has an associ

ation constant for iron of approximately 10 30 . This indicates that, in the

normal physiological situation in which transferrin is 25% saturated with

iron, the equilibrium free, ionic iron concentration is approximately 6 × 10 −9

μM or 10 8 -fold less than that required for microbial growth. Thus, for micro

bial invaders to have any chance of survival in a foreign host, they must

have evolved the capability to synthesize siderophores with association con

stants for iron of 10 30 or greater in order to compete for the available iron.

Indeed, many bacterial invaders have iron-binding ligands capable of

extracting iron from host transferrin that is saturated 30% or more. Kochan

(1973) has demonstrated the microbiostatic action of various mammalian

serums in culture media with respect to bacterial growth of tubercle bacilli

(Table 14.1). For example, human serum containing 30% saturated transferrin

inhibited bacterial multiplication of the BGG strain of Mycobacterium tuber

culosis. Addition of 36 μM iron neutralized this bacteriostatic activity.

Similar results were observed for bovine, mouse, and rabbit sera. However,

owing to their normally high transferrin saturation, guinea pigs had sera

equally susceptible to tuberculosis before and after iron addition. Other

microorganisms demonstrating similar behavior include species of Candida,

TABLE 14.1

Correlation of Transferrin Saturation (TR) with Bacterial Growth a in Mammalian

Sera in Vitro

Source of Sera No. Samples Fe Concentration in Serum (μm) Saturation TR (%) Bacterial Growth a No Added Fe 36 μm Added Fe

Human 10 17 30.0 0–1 10–14

Cow 4 34 39.0 0–1 10–14

Mouse 10 41 60.2 1–5 9–15

Rabbit 8 36 64.3 1–5 10–15

Guinea pig 20 49 84.2 9–14 9–14

a Bacterial growth expressed as the number of generations of M. tuberculosis in 14 days.

Source: Adapted from Kochan, I., Curr. Top. Microbiol. Immunol., 60, 1, 1973.

Clostridium, Escherichia, Pasteurella, Shigella, and Staphylococcus. In vivo

studies using strains of Pseudomonas aeruginosa, Staphylococcus typhimurium,

Listeria monocytogenes, and E. coli have corroborated the in vitro results.

Weinberg (1974) summarized the role that iron plays in nutritional immunity: A very consistent finding is that the intricate checks and balances between the iron chelators of the microbes and of hosts are readily and markedly upset by changes in the environmental concentration of iron. If the metal is added, microbial growth is enhanced; if the metal is deleted, host defense is strengthened. This situation obtains not only in experimental systems in vitro and in vivo, but also in clinical disease situations.

Weinberg (1974) asks, “Might cryptic disturbances in iron metabolism

during the lifetime of individual hosts permit resurgence of latent infections

such as tubercular lesions?” In light of a report concerning tuberculosis in

dialysis patients (Pradhan et al. 1974), perhaps this question has been

unknowingly addressed. Pradhan and colleagues have attributed the 15

times higher incidence of tuberculosis in dialysis patients to an increased

susceptibility stemming from the uremic state and a consequently decreased

immunological responsiveness. These conditions notwithstanding, it may be

possible that sufficient iron (owing to the inherent iron concentration of the

dialysate) enters the blood stream during repeated dialysis and constitutes

a “cryptic disturbance,” thus rendering the patient more susceptible to tuber

cular infection and/or relapse. Weinberg (1996) and Walter et al. (1997)

provide modern reviews of this topic.

14.2.8 Role of Implants in TIBC Saturation

As mentioned previously, Gitlow and Beyers (1952) have shown that 10 mg

of intravenous ferric-ammonium citrate was sufficient to saturate the TIBC

of the blood and produce immediate signs of toxicity. Weinberg (1974) has

expressed the belief that even small additions of iron may increase the

transferrin saturation of the blood, rendering an individual more susceptible

to infection. The use of stainless steel in joint replacement and fracture

fixation applications, coupled with the evidence of Lux and Zeisler (1974)

demonstrating the nature and relative proportions of corrosion products in

metallotic tissue, would seem at this junction to warrant investigation of the

possibility that the well recognized (and accepted) local corrosion may even

tually elicit subtle long-term systemic consequences.

A single calculation can illustrate the minute quantities of iron involved

in these considerations and, similarly, the amount of corrosion that these

quantities represent. For a standard 316L stainless steel orthopaedic total hip

replacement prosthesis with a total surface area of approximately 200 cm 2 ,

corrosion equivalent to 10 mg of iron release would constitute a general

surface dissolution to a depth of 625 Å — an amount beyond light

microscopic resolution. In terms of local corrosion, a pit of 1 mm depth

would release 10 mg of iron. Naturally, for bilateral hip implantation or for

devices with a porous sintered stainless-steel surface, the increased surface

area would mean that proportionately less iron would need to corrode per

unit area for equivalent effects. As suggested in Figure 14.2, the most likely

mode of release is into the transferrin transport system.

It is clear, however, that such corrosion would not be equivalent to the

clinical experiment of Gitlow and Beyers (1952). Corrosion would release

iron over a period of time rather than in a single “dose.” Furthermore, other

implant-derived metals such as chromium and aluminum can

also bind to

transferrin, further reducing the UIBC and contributing to a higher apparent

transferrin saturation (TR).

14.3 Chromium Metabolism*

14.3.1 Introduction

Chromium differs from iron by only two atomic numbers (24 vs. 26) and by

less than 7% in average atomic weight. Both elements can form divalent and

trivalent ions, although chromium can additionally form a hexavalent ion.

However, there are profound differences in their biological roles. Iron is well

known for its primary role in hemoglobin, the primary oxygen transport

molecule in mammals; chromium plays a no less vital role in regulating

metabolism. These differences in biological roles and metabolic pathways

are an excellent example of the principle of specificity in essential trace

element function. Figure 14.4 compares and contrasts these roles and also

illustrates the principle of amplification of function: extremely small daily

intakes of each element have led to vital physiological roles in the whole

organism.

It would be desirable to be able to depict a complete and systemic overview

of chromium uptake, transportation, utilization and

conservation, storage,

and excretion, as shown in Figure 14.2 for iron; however, this is not possible.

Based in part on estimates, Table 14.2 summarizes the overall picture of the

situation.

14.3.2 Absorption

Absorption of Cr +3 takes place in the gastrointestinal tract. Although the diet

may contain Cr +2 and Cr +6 as well as Cr +3 , the latter valence is the predom

inant form in the acidic conditions of the stomach and upper digestive tract

(Mertz 1983). Because Cr +3 is essentially excluded from cellular contents due

* This section draws strongly on the work of Langård and Norseth (1986).

to an inability to cross cellular membranes (Sanderson 1976), it is very poorly

absorbed. However, chromium can be found within cells in nonimplanted

individuals, suggesting that mechanisms exist in vivo to oxidize dietary Cr +3

to Cr +6 (Rogers 1984). Detection of chromium in nonparticulate form, espe

cially in nonphagocytic cells such as erythrocytes, must be considered as

strong evidence of the presence of Cr +6 .

FIGURE 14.4

Comparison of iron and chromium amplification. (Adapted from Mertz, W., Science, 213, 1332,

1981.)

TABLE 14.2

Chromium Metabolism

Daily intake

Dietary supply a 200 µg

Absorbed (@1.5% absorbance) b 3 µg

Transport

Serum content (3.2 L @ 0.16 ppb c) 0.5 mg

Daily utilization Unknown, leads to 2 mg insulin synthesis/day d

Storage

Daily addition 1 µg

Total body burden (70-kg individual) 7 mg

Daily excretion

Urinary (1.5 l @ 0.2 ppb e) 0.3 µg

Fecal, desquammation, etc. (balance) ~ 1.7 µg

a Source: Table 14.3, maximum recommended.

b Source: Table 14.3, mean value.

c Source: Versieck, J. and Cornelis, R., Anal. Chim. Acta, 116, 217, 1980.

d Source: Mertz, W., Science, 213, 1332, 1981.

e Source: Cornelis, R. and Wallaeys, B., in Trace Element — Analytical Chemistry in Medicine

and Biology, Vol. 3., Walter de Gruyter & Co., Berlin, 1984, 219. IRON CHROMIUM Dietary: Fe 3+ Absorbed: Fe 2+ Dietary: Cr 3+,6+ Absorbed: Cr 3+ Turnover: 2 x 10 -3 g/day Turnover: 10 -9 g/day Hemoglobin Glucose tolerance factor Potentiation of insulin Turnover: 2 x 10 -3 g/day Regulation of energy metabolism (1500 - 4000 kcal/day) Oxidative phosphorylation Oxygen transport Turnover: 3 x 10 -2 g/day

Although daily absorption of chromium is very small compared to that of

iron (3 µg vs. 1 to 2 mg), the serum concentration is even lower (5 µg [0.16

ppb] vs. 3 mg [0.94 ppm]). As in the case of iron, serum chromium is

primarily bound to transferrin (Hertel 1986), although it can also be nonspe

cifically bound to albumin. The turnover of biosynthetic chromium as an

element in a glucose tolerance factor (GTF) leads to the synthesis of insulin

and to the ability to metabolize carbohydrates (Schroeder 1966).

14.3.3 Storage and Excretion

About one third of the daily absorption (perhaps that portion reduced to

Cr +6) is stored in the reticuloendothelial structures in cells and nonspecifically

in other cells, such as erythrocytes. The balance is excreted, primarily fecally

and through desquammation of cells. In comparing chromium metabolism

to iron metabolism, the overall picture is one of radical differences, despite

the similarity of the elements, even in the absence of implants. This should

highlight the difficulties in understanding release, storage, and excretion of

metals from implants in which less knowledge of the metabolic pathways

is involved.

14.3.4 Biological Consequences of Excess Chromium

As indicated elsewhere in this work, chromium has historically been viewed

benignly, due to its essential role in sugar metabolism and the widely held

belief that the dietary form, Cr +3 , was the only or predominant form encoun

tered in vivo, no matter what the route of release. More recent views suggest

roles for chromium and chromium-bearing molecules in a wide variety of

toxic, carcinogenic, and allergenic effects. The latter two phenomena are

discussed in Chapter 13 and Chapter 12, respectively; see Dayan and Paine

(2001) for a comprehensive historical review of all three effects.

14.4 Human Dietary Metal Intake

The only significant source of essential trace elements, including metals, for

human metabolic processes is through the gastrointestinal tract. Transdermal

absorption and inhalation, although capable of causing local host responses,

rarely can be shown to contribute to internal metal concentrations or remote

storage. Primarily, humans depend upon dietary sources for essential trace

elements. Table 14.3 lists the recommended dietary allowances (RDAs) and

suggested safe and adequate intakes (SAIs) for two physiological and ten

essential trace elements, as determined by the U.S.

National Research

Council.* Note that, because of its strong action in preventing tooth decay,

fluorine is included, although its natural concentration in the body is very

low and despite the absence of a known normal biological role in mammals.

This table also lists ranges of percent absorption and resulting internal avail

ability. It is against this latter amount that release by an implant should be

judged.

Three final points deserve to be made to complete this discussion of normal

mineral metabolism. In the first place, even in the absence of the routine

common consumption of the “one-a-day” type of vitamin and mineral sup

plements (which usually contain 50 to 150% of the RDA or SAI of all essential

trace elements), modern diets in the developed nations generally provide all

essential minerals required for normal physiological functions in healthy

individuals. The widespread “enrichment” of foodstuffs such as milk, bread,

and breakfast cereals; the increasing amounts of fresh foods consumed; and TABLE 14.3 Daily Recommended and Safe Mineral Intake Mineral Dietary Content Absorbed (%) Internal c Recommended dietary allowances (RDA) a,b Phosphorus 800 mg 50–70 400–560 mg Calcium 800 mg 20–40 160–320 mg Magnesium 315 mg 40–60 125–190 mg Zinc 14.5 mg 2–38 0.3–5.1 mg Iron 10 mg Heme: 20 d Nonheme: 6–18 0.5–1.0 mg Iodine 150 µg 30–50 45–75 µg Selenium 62.5 µg 80 50 µg Safe and adequate intake (SAI) a Fluorine 1.5–4.0 mg 35–100 0.5–4.0 mg Manganese 2.0–5.0 mg ? <5.0 mg Copper 1.5–3.0 mg

36 0.5–1.1 mg Molybdenum 75–250 µg ? <250 µg Chromium 50–200 µg 0.5–2 e 0.25–1.0 µg a Source: National Research Council, Recommended Dietary Allowances, 11th ed., National Academy Press, Washington, D.C., 1992. b Adjusted for average of male (79 kg) and female (63 kg), 25 to 50 years old. c Calculated; presumably equal to loss by all routes. d Decreases with increasing nonheme iron in meal. e Decreases with increasing daily chromium intake.

* The roles of trace metallic elements in human nutrition are coming under much more scrutiny

than in previous years. Perhaps this is a partial explanation for a more recent replacement of

RDAs and SAIs with the concept of daily adequate intake (DAI) (Vincent 2004).

modern food-preservation and -preparation techniques virtually guarantee

this result.* Furthermore, the homeostatic systems that control metal absorp

tion, transport, storage, and excretion render the occasional practice of con

suming “megadoses” of essential trace elements meaningless: in the general

case, the excess will not be absorbed and will simply be excreted directly.

For some easily absorbed minerals, excess consumption may lead to transient

toxicity. If defects in regulation exist, excessive intakes may lead to one or

another of various metal storage diseases (Underwood 1977; Mertz 1988).

Fortunately, these are rare and, in many cases, have familial, presumably

genetic, predispositions.

In the second place, it must be emphasized that concern about in vivo metal

released from implants centers primarily on two situations:

- The possibility of very elevated (10- to 100-fold normal) concentrations occurring near implants or in remote storage sites

- The possibility of release of metal in a different valence state than normally occurs in the body with subsequent formation of biologically active organometallic species

As will be discussed at further length in Chapter 15, measurements of

serum concentrations and urinary excretion of metals, although useful, do

not provide a true picture of either of these effects. Unfortunately, with the

advent of modern, highly sensitive techniques for determining metal content

of biological materials (atomic absorption spectroscopy, neutron activation

analysis, inductively coupled plasma-mass spectroscopy, etc.), a number of

commercial concerns have become involved in diagnostic studies of trace

element profiles in patients and in normal individuals. Homeostasis permits

a broad range of concentrations about the optimal concentration for any

essential trace element (see Figure 14.1); thus, in the absence of a metallic

implant, which could produce elevated concentrations and/or different

valence states, small changes in serum metal concentrations within a normal

range may only reflect daily variations in intake, utilization, etc.

It is highly unlikely that such studies can lead to primary diagnosis of

actual metal deficiencies or overloads, with a concomitant need for corrective

therapy, that have not already been detected by clinical indications

(Kruse-Jarres 1987). Thus, the validity of such studies in healthy individuals

or in nonimplant patients for other than verification of prior diagnoses must

be viewed with great skepticism. In current practice, the appropriate use of

such studies is for large-scale, prospective epidemiology to determine

whether relationships exist between group mean values and incidence or

severity of metal induction or storage diseases.

* One exception to this assertion may be chromium; increasing dietary use of refined (white)

sugar, which contains less chromium than raw sugars but requires insulin for metabolic conver

sion (Mertz 1983), may lead to progressive chromium deficiency. See Baran (2004) for a more

complete discussion.

Finally, because implants can release metal in various forms, including

inorganic ions, organometallic soluble complexes, and fine particles, prima

rily or secondarily by precipitation (Jacobs et al. 1995), the mere presence of

metal in a biological fluid or tissue cannot be placed in context without an

understanding of the bioavailability of that metal. That

is, the discussion of

the role of bacterial access to iron (Section 14.2.8) can and should be gener

alized to address the question of which cells encounter metals in their peri

cellular environment and whether the form permits chemical and

biochemical interaction with extra- or intracellular process. Unfortunately,

traditional approaches to the issue of bioavailabilty (see Caussy et al. 2003)

neglect release from implants. Thus, the question raised by MacDonald

(2003) as to whether a safe level of metal ions is released from a particular

class of orthopaedic implants simply cannot be answered at this time.

Notwithstanding these caveats, the next chapter will take up in detail more

general issues of release, distribution, and excretion of ions from implants

for which some data and models exist.

Bacon, B.R., Metabolic liver disease. Iron overload states, Clin. Liver Dis., 2(1), 63, 1998.

Baran, E.J., Trace elements supplementation: recent advances and perspectives, Mini Rev. Med. Chem., 4(1), 1, 2004.

Caussy, D. et al., Lessons from case studies of metals: investigating exposure, bioavailability, and risk, Ecotox. Environ. Safety, 56, 45, 2003.

Dayan, A.D. and Paine, A.J., Mechanisms of chromium toxicity, carcinogenicity, and allergenicity: review of the literature from 1985 to 2000, Hum. Exp. Toxic., 20, 439, 2001.

Fairbanks, V.F. and Beutler, E., Iron, in Modern Nutrition in Health and Disease, 7th ed., Shils, M.E. and Young, V.R. (Eds.), Lea & Febiger, Philadelphia, 1988, 193.

Gitlow, S.E. and Beyers, M.R., Metabolism of iron, J. Lab. Clin. Med., 39, 337, 1952.

Hertel, R.F., Sources of exposure and biological effects of chromium, in Environmental Carcinogens: Selected Methods of Analysis, Vol. 8, O'Neill, I.K., Schuller, P. and Fishbein, L. (Eds.), IARC Scientific Publication 71. International Agency for Research on Cancer, Lyon, 1986, 63.

Jacobs, J.J. et al., Local and distant products of modularity, Clin. Orthop. Rel. Res., 319, 94, 1995.

Kochan, I., The role of iron in bacterial infections with special consideration of hosttubercle bacillis interaction, Curr. Top. Microbiol. Immunol., 60, 1, 1973.

Kruse-Jarres, J.D., Clinical indications for trace element analysis, J. Trace Elem. Electrolytes Health Dis., 1, 5, 1987.

Langård, S. and Norseth, T., Chromium, in Handbook on the Toxicology of Metals, 2nd ed. Vol. II: Specific Metals, Friberg, L., Nordberg, G.F. and Vouk, V.B. (Eds.), Elsevier, Amsterdam, 1986, 185.

Lux, F. and Zeisler, R., Investigations of the corrosive deposition of components of metal implants and the behavior of biological trace elements in metallosis tissue by means of instrumental multielement activation analysis, J. Radioanal. Chem., 19, 289, 1974.

MacDonald, S.J., Can a safe level for metal ions in patients with metal-on-metal total hip arthroplasties be determined? J. Arthropol., Suppl. 3, 19(8), 71, 2004.

Mertz, W., The essential trace elements, Science, 213, 1332, 1981.

Mertz, W., Chromium: an ultra-trace element, Chemica Scripta, 21, 145, 1983.

Mertz, W. (Ed.), Trace Elements in Human and Animal Nutrition, 5th ed. Academic Press, New York, 1988.

National Research Council, Recommended Dietary Allowances, 11th ed., National Academy Press, Washington, D.C., 1992.

Pradhan, R.P. et al., Tuberculosis in dialyzed patients, JAMA, 229, 798, 1974.

Rogers, G.T., In vivo production of hexavalent chromium, Biomaterials, 5, 244, 1984.

Sanderson, C.J., The uptake and retention of chromium by cells, Transplantation, 21, 526, 1976.

Schroeder, H.A., Chromium deficiency in rats: a syndrome simulating diabetes mellitus and retarding growth, J. Nutrition, 88, 439, 1966.

Schwarz, K., Essentiality vs. toxicity of metals, in Clinical Chemistry and Chemical Toxicology of Metals, Brown, S.S. (Ed.), Elsevier/North-Holland, Amsterdam, 1977, 3.

Shils, M.E., Olson, J.A. and Moshe, S. (Eds.), Modern Nutrition in Health and Disease, 8th ed., Lea & Febiger, Philadelphia, 1993.

Sullivan, J.L., Is stored iron safe? J. Lab. Clin. Med., 144(6), 280, 2004.

Underwood, E.J., Trace Elements in Human and Animal Nutrition, 4th ed., Academic Press, New York, 1977.

Vincent, J.B., Recent developments in the biochemistry of chromium (III), Biolog. Trace Elem. Res., 99, 1, 2004.

Walter, T. et al., Iron, anemia, and infection, Nutr. Rev., 55(4), 111, 1997.

Ward, C.G., Bullen, J.J. and Rogers, H.J., Iron and infection: new developments and their implications, J. Trauma, 41(2), 356, 1996.

Weinberg, E.D., Roles of iron in host-parasite interactions, J. Infect. Dis., 124, 401, 1971.

Weinberg, E.D., Iron and susceptibility to infectious disease, Science, 184, 952, 1974.

Weinberg, E.D. Iron withholding: a defense against viral infections, Biometals, 9(4), 393, 1996.

Winter, G.D., Wear and corrosion products in tissues and the reactions they provoke, in Biocompatibility of Implant

Materials, Williams, D. (Ed.), Sector Publications, London, 1976, 28.

Brown, S.S. and Savory, J. (Eds.), Clinical Chemistry and Chemical Toxicology of Metals, Academic Press, Amsterdam, 1984.

Burrows, D., Chromium: Metabolism and Toxicity, CRC Press, Boca Raton, FL, 1983.

Cohen, M.D. et al., Mechanisms of chromium carcinogenicity and toxicity, Crit. Rev. Toxicol., 23(3), 255, 1993.

Cornelis, R. and Wallaeys, B., Chromium revisited, in Trace Element — Analytical Chemistry in Medicine and Biology, Vol. 3., Walter de Gruyter & Co., Berlin, 1984, 219.

Crichton, R.R. and Ward, R.J., Iron homeostasis, Met. Ions Biol. Syst., 35, 633, 1998.

Davies, I.J.T., The Clinical Significance of the Essential Biological Metals, Charles C Thomas, London, 1972.

Ducros, V., Chromium metabolism. A literature review, Biol. Trace Elem. Res., 32, 65, 1992.

Friberg, L., Nordberg, G.F. and Vouk, V.B. (Eds.), Handbook on the Toxicology of Metals, 2nd ed. Vol. I: General Aspects. Vol. II: Specific Metals. Elsevier, Amsterdam, 1986.

Gibson, R.S., Essential trace elements and their nutritional importance in the 1990s, J. Can. Diet. Assoc., 51, 292, 1990.

Goldenberg, H.A., Regulation of mammalian iron metabolism: current state and need for further knowledge, Crit. Rev. Clin. Lab. Sci., 34(6), 529, 1997.

Mertz, W., Chromium in human nutrition: a review, J. Nutr., 123(4), 626, 1993.

Mu, Y. et al., Causes of titanium release from plate and screws implanted in rabbits, J. Mater. Sci.: Mater. Med., 13, 583, 2002.

Okazaki, Y. et al., Comparison of metal concentrations in rat tibia tissues with various metallic implants, Biomaterials, 25, 5913, 2004.

Schroeder, H.A., The Trace Elements and Man: Some Positive and Negative Aspects, Devin-Adair, Old Greenwich, CT, 1973.

da Silva, J.R.R.F. and Williams, R.J.P., The Biological Chemistry of the Elements, 2nd ed., Oxford University Press, Oxford, 2001.

Theil, E.C., Iron, ferritin, and nutrition, Annu. Rev. Nutr., 24, 327, 2004.

Versieck, J. and Cornelis, R., Normal levels of trace elements in human blood plasma or serum, Anal. Chim. Acta, 116, 217, 1980.

Von Schroeder, H.P. et al., Titanemia from total knee arthroplasty, J. Arthropol., 11, 620, 1996.

Wang, Y.T. and Shen, H., Bacterial reduction of hexavalent chromium, J. Ind. Microbiol., 14(2), 159, 1995.

Williams, D.R., The Metals of Life: The Solution Chemistry of Metal Ions in Biological Systems, Van Nostrand Reinhold, London, 1971.

Xiu, Y.M., Trace elements in health and diseases, Biomed. Environ. Sci., 9(2-3), 130, 1996.

Zaffe, D. et al., Accumulation of aluminium in lamellar bone after implantation of titanium plates, Ti-6Al-4V screws, hydroxyapatite granules, Biomaterials, 25, 3837, 2004. 291

15

Systemic Distribution and Excretion

15.1 Introduction

The traditional approach to consideration of biological performance has been

to focus on the implant-host interface. Thus, material response studies have

dealt with degradation of implant properties and host response studies have

focused on formation of a capsule and other events within the adjacent tissue.

More modern considerations recognize that a mammal, such as a test animal

or a human patient, is an interconnected structure with various mechanisms

permitting exchange between all of its tissues and organs. The systemic and

remote site results of such exchanges involving implants and implant deg

radation products will be dealt with in Chapter 16.

Chapter 3 through Chapter 5 and Chapter 7 have considered mechanisms

that can modify native proteins or release materials from implants. This

chapter examines some aspects of the distribution and excretion of these

implant-related products. Their distribution through the various systems of

the body can take place in a number of different ways:

- Movement of solid bodies
- Movement of particulate materials, passively or actively (cell mediated)
- Movement of dissolution or corrosion products by passive diffusion or by active circulatory transport
- Movement of modified cells or native proteins

15.2 Movement of Solid Bodies

15.2.1 Large Particles

Large particles or portions of implants can move through soft tissue if they

possess a certain degree of structural asymmetry. A sphere, such as a

shotgun* pellet, will stay in its initial position for an indefinite time. An

asymmetric “needle,” such as a sewing needle or a porcupine quill, will

move point first and may travel for long distances due to the action of muscle

forces on it.

It is also possible for large material particles to become involved in blood

circulation. Wear particles from vascular prostheses will move “down

stream” until they are trapped in reduced vessel diameters on the arterial

side of capillary beds or in the lungs on the venous side of the circulatory

path. Much larger particles can also be transported. A report of four cases

of shell fragments transported into the cerebral circulation is a dramatic

illustration of this possibility (Kapp et al. 1973).

More common is the finding of extracellular particles too large to be

phagocytosed, such as some wear debris, precipitated corrosion products,

or fibrillar fragments from tendon prostheses, in the lymphatic drainage, in

regional lymph nodes, or in remote medullary locations or organs. Such

observations have been made in animals (Margevicius et al. 1996) as well as

in patients (Case et al. 1994; Jacobs et al. 1995; Urban et al. 2004) with

functioning implants of various types. Note that all “foreign” particles found

in remote sites in patients with implants may not have been released from

implants (Gatti and Rivasi 2002), so care should be taken in their iden

tification and analysis.

Pins, wires, and other implants used for internal fixation of fractures and

for adjunctive tissue immobilization during placement of permanent

implants can also become dislodged and migrate. Lyons and Rockwood

(1990) reviewed reports of 47 such occurrences after surgery in the vicinity

of the shoulder. Smooth pins and wires were more likely to be reported as

migrating than threaded ones; screws and staples were not reported as

migrating. Eight of the patients died (six of them suddenly) due to damage

to heart and blood vessels near the heart by the migrating implants. In a

majority of the reports (35 of 39) in which a postoperative time course could

be determined, migration apparently occurred within 8 months of implan

tation, although the mean time to diagnosis was 22 months.

Migrating device fragments are no respecter of organs; they have been

reported to enter the lungs (Aalders et al. 1985) and the heart (Lyons and

Rockwood, 1990) and to move as far as from the shoulder to the spleen

(Potter et al. 1988). Therefore, thoughtful design of

materials and the

implants using them should minimize or eliminate the possibility of release

of macroscopic fragments.

* It was once a reasonable assumption that such pellets were composed primarily of lead; how

ever, since 1981 lead shot has been illegal for use by hunters over wetlands in the U.S. Thus, pel

lets that have been in situ for less than 25 years may be copper- or nickel-coated lead or made of

copper-coated steel, tungsten, or bismuth. This should be taken into account when host response

is considered.

15.2.2 Phagocytic Transport

As Section 8.2.3 discussed, particles that are sufficiently small are phagocy

tosed by a variety of cells. Cellular phagocytosis has four possible results:

- The phagocytic cell (PC)* can successfully digest the particle. Partial digestion and externalization (exocytosis) of the particle may also occur, but rarely so.

- The PC attempts to digest the particle but the degradation products prove to be cytotoxic. Then the PC dies, its phagosomes and cell membrane lyse, and another PC may attempt to phagocytose the particle and digest it. If this progression continues through many repetitions, dead PCs accumulate, resulting in caseation; the resulting mass of dead cells resembles cheese.

- The PC may transport the particle by passing into the blood or lymphatic circulation, but most usually to regional lymph nodes where particle-loaded cells accumulate and may produce granulomas, such as the “teflonomas” reported by Charnley (1961) after the use of a poly(tetrafluoro)ethylene as a bearing surface in total hip replacement. In some cases, this may lead to a secondary histiocytic response in the vessels or lymph nodes (Albores-Saavedra et al. 1994).

• The PC may be able to transport the particle to the lungs. There it is possible for the particle to be extruded through the lung wall and exhaled through the airway (Styles and Wilson 1976).

It should additionally be noted that all of these outcomes may result in

activation of the PC (Schnyder and Baggiolini 1978), with concomitant

release of biologically active agents, which may alter local host response to

the implant (see Section 8.2.3)

In the context of this chapter, it would be very desirable to make some

statements about the rates of transport of particles by phagocytes in the third

and fourth situations listed previously. It is probably not possible to gener

alize, but some extension of the comments in Section 8.2.3 is desirable.

The transport of particles by phagocytic cells (primarily macrophages

because neutrophils are short lived and FBGCs tend to remain near the

implant site) consists of at least two major steps: uptake and transport. Very

little is known about transport rates in the lymphatic system, primarily

because most uptake studies have been done in vitro or by systemic injection

of a colloid of particles in vivo followed by sequential sampling of the PC

population in the arteriovenous circulatory system.

* The term phagocytic cell (PC) is used here for

generality, rather than the more common term

phagocyte, because it now appears that a number of different cell types may display phagocytic

behavior.

Some details are known about the first step, uptake. Two general

approaches have been taken to describe the uptake process. The first is

to fit the kinetics of phagocytic removal of particles to the Michae

lis-Menten model used in studies of enzyme activity (Normann 1974). In

this approach, uptake is considered to have two phases: attachment to the

PC and engulfment.

Attachment is modeled as consisting of a reversible attachment step and

an irreversible engulfment step: (15.1)

where P is an extracellular particle, and p is an intracellular one. Previous

studies have shown that, for a wide variety of animal species, V, the velocity

of clearance of circulating particles (uptake), follows a first-order propor

tional absorption law dependent upon particle concentration, C (Normann

1974): (15.2)

The following equation is typical of the results of this approach: (15.3)

where

V = clearance velocity (uptake rate of particles by PCs)

C = concentration of extracellular particles

E o = total available attachment sites

K c = overall kinetic constant = (k 2 + k 3 /k 1)

A saturation effect (presence of a fixed maximum rate) is attributed to the

fact that the number of sites on the phagocyte membrane that can initiate

invagination and engulfment (E o) is limited.

This result faces two major criticisms. The first is that the uptake velocity

is not a first-order process for all particle concentrations, and the second is

that it seems unlikely that specific limited numbers of membrane loci exist.

The second approach (Stiffel et al. 1970) is to describe the observed kinetics

as exponential in the general form given by Equation 15.4: C = C o 10 -Kt (15.4) P P k k + ← →——— - ⎡ ⎣ ⎤ ⎦ PC PC 1 attachment engulfmen k 2 3 t PC— →—— p V dC dt kC= = - 1 1 1 3 3 V k E K k E C o c o = + ⎡ ⎣ ⎦ ⎤ ⎥ ⎡ ⎣ ⎤ ⎦

where

K = total body phagocytic index (essentially, the particle clearance velocity)

C o = initial particle concentration

t = time

The major difficulty with this result is that, once again, it is not a good

description of the kinetics of phagocytic behavior. What is actually observed

is a complex uptake velocity behavior with three domains, provided that the

particles are within a defined size range and that the

initial concentration is

high enough so that the kinetics are not dictated by flow processes (Ver

non-Roberts 1972). The initial phase seems to be first order and dictated by

the adsorption of serum opsonins to the particles or the adsorption of the

coated particles to the phagocyte. The second phase is exponential, dictated

by the dose (concentration of particles) as in any other dose-response situ

ation. The third phase is a slowly disappearing component seen when a

heterogeneous distribution of particles is injected. What this “tail” actually

represents is the removal of smaller particles.

The possible explanation for this strange kinetic pattern is that there are

two opposing effects. One is a saturation effect attributed to a limited number

of binding sites by some and, more appropriately, to a limited concentration

of serum opsonins by others (Jenkin and Rowley 1961). The second, coun

tervailing effect is the increased efficacy of clearance as the blood (or pre

sumably tissue) concentration of particles goes down. The limit on the

particle size range mentioned in Chapter 8 restricts these investigations to

particles on the order of the size of leukocytes, approximately 4 to 7 μm.

A somewhat more pragmatic approach (Korn and Weisman 1967;

Weisman

and Korn 1967) has led to the conclusion that the kinetics of uptake are

determined by a constant (absorption) vesicle volume. Careful studies with

well controlled particle size ranges led to the conclusion that, in an amoeba

model, although larger particles are taken up singly, small particles are

accumulated external to the cell until a critical volume is reached, whereupon

the “cemented” mass is absorbed simultaneously. Typical results obtained

by earlier investigators in a mammalian model that also lead to this conclu

sion are given in Table 15.1. In this table, it is also useful to note that oxygen

consumption is required during phagocytosis by PMNs (because the process

requires energy and PMNs are aerobic cells) and that it increases with particle

size.

There are however, additional difficulties. All particles are not equal: com

position, morphology, and surface charge may play a role in uptake velocity.

As discussed in Section 8.4.1, a variety of dissolved metal ions, such as Ni +2

and Cr +3 , suppress phagocytic efficiency (Graham et al. 1975). Therefore, one

might expect a slower uptake of nickel- or chromium-bearing particles, due

to high local metal concentrations, than of polymeric

particles of the same

size, tissue concentration, etc. Kawaguchi et al. (1986) have shown addition

ally that phagocytosis of polystyrene (as measured by cellular oxygen

consumption) depends strongly upon surface potential and thus upon fixed

surface charge. Kapur et al. (1996) have also shown that surface charge

heterogeneity can greatly affect phagocytic ability.

Although these models, calculations, and experiments tell something

about the relatively likelihood of uptake (clearance velocity) as a function

of particle size and properties, they shed little light upon the question of net

removal rates from implant sites. This remains an area for further investiga

tion. Far more is known about active and passive removal of dissolved

species.

15.3 Transport of Dissolved Species

15.3.1 Leaching of Monomers

Leaching or dissolution of polymers into circulatory system fluids results in

rapid dispersion throughout the body. This is a result of an arteriovenous

circulatory rate of approximately 1 min −1 . That is, the normal blood volume

(about 6 to 8% of body weight or about 5 l) passes through the lungs once

a minute. An illustration of the rapidity of this

circulation is the study of

Homsy et al. (1972) concerning release of monomer from poly(methyl)meth

acrylate bone cement upon its insertion into the body. In a canine model,

insertion of a dose of freshly mixed cement as a femoral transcortical plug

in a dose of less than 2 g/kg body weight produced monomer levels of up

to 1 mg/100 ml in the inferior vena cava within 2 min of implantation. The

peak concentration was reached in 3 to 4 min, followed by a decline ascribed

to monomer clearance by evaporation through the lungs as well as progres

sion of polymerization of the cement that reduced the source concentration.

Similar results were obtained in patients receiving PMMA-cemented femoral

endoprostheses: peak monomer concentrations occurred in the vena cava by TABLE 15.1 Effect of Particle Size on Phagocytosis by Guinea Pig PMNs Diameter of Particles (μm) Polystyrene Uptake (μg/mg wet wt. PMNs) O 2 Consumption (μl/mg PMN/min) No. Particles/PMN 0.088 7.4 0.0144 24,000 0.264 30.1 0.0372 3,600 0.557 28.1 0.0412 360 0.871 36.9 0.0396 102 1.305 34.3 0.0427 34 3.04 35.9 0.0422 3 >7 0 <0.012 0 No polystyrene 0 0.0124 0 Source: Adapted from Roberts, J. and Quastel, J.H., Biochem. J., 89, 150, 1963.

2 minutes postimplantation and 99%+ of (integrated) exhaled monomer was

detected in the airway within 6 min.

15.3.2 Corrosion of Metals

15.3.2.1 Local Effects

The corrosion of metals has been discussed in Chapter 4. It is appropriate

to inquire how metallic corrosion and dissolution products are distributed

in the body.

It is clear that, usually, an accumulation of corrosion products is found

around a metal implant. These products include membrane-bound ions,

particles released by intergranular and fatigue processes, locally precipitated

products resembling hemosiderin, and insoluble reaction products such as

metal hydroxides. The combination of these leads to the familiar tissue

discoloration termed metallosis, particularly in older reports. In addition to

tissue discoloration, consequences of passive diffusion and distribution adja

cent to an implant may also be seen histologically as a varying degree of cell

reaction. Figure 15.1 shows the variation of effect with material “reactivity”

— that is, corrosion and/or dissolution rate combined with tissue response

— for needles inserted in the cerebral cortex of rabbits for periods of up to

1 to 1.5 years. Typical materials used were aluminum; platinum (nonreac

tive); molybdenum; tantalum (reactive); and silver, iron, and cobalt (highly

reactive and toxic).

The picture presented by Figure 15.1 reflects corrosion and diffusion of

metal; however, it is complex and difficult to analyze because the breadth

and type of response about each implant depend upon the rate of corrosion,

the valence (speciation) of released metal, its diffusion constant, and its

toxicity. Furthermore, the release may be affected by anatomical location

FIGURE 15.1

Histological changes around implants of increasing reactivity (left to right) in the rabbit cerebral

cortex. (Adapted from Stensaas, S.S. and Stensaas, L.J., Acta. Neuropath. (Berl.), 41, 145, 1978.) Leptomeningeal Connective Tissue Implant Glia Limitans Normal Central Nervous System Tissue Macrophages Zone of Astrocytosis Necrosis Giant Cells

because local physicochemical conditions vary (see Section 2.2), resulting in

different rates of corrosion (Oron and Alter 1984). Implant site infection may

also affect the corrosion rate (Hierholzer et al. 1984) as well as tissue response

to the corrosion products.

A more accurate view of passive diffusion may be obtained by direct

analysis of the tissues in and near the implant site. Energy-dispersive

microanalysis has been widely used to study situations such as metal diffu

sion into bone from implanted dental devices (Arvidson and Wroblewski

1978). One of the more graphic studies is that of Lux and Zeisler (1974), who

used neutron activation analysis to examine the spatial

distribution of cor

rosion products in soft tissues adjacent to a steel fracture fixation device.

Their results, obtained by analysis of tissues obtained at device retrieval, are

shown in Figure 15.2.

FIGURE 15.2

Tissue metal content surrounding an implant. (Adapted from Lux, F. and Zeisler, R., J. Radioanal.

Chem., 19, 289, 1974.) Fe Fe minus background Cr 1 1 2 3 4 Distance from implant (cm) M e t a l c o n c e n t r a t i o n (m g / k g = p p m) 0.1 10 100 AFFECTED TISSUE UNAFFECTED TISSUE Fe Mo not detectable Cr Mo: < 0.1 ppm

In a study of 38 patients with histologically diagnosed metallosis at

retrieval of fracture fixation hardware, Lux and Zeisler found mean concen

trations of iron, chromium, and molybdenum near a stainless-steel–tissue

interface to be two orders of magnitude above background values previously

determined in tissues from patients without metallic implants. These con

centrations declined logarithmically with distance from the implant, reach

ing background (“normal”) levels at distances of greater than 4 cm from the

implant. The ratio of Fe:Cr:Mo in the alloy (V4A) was 66:17.5:2.3 (≅ 29:7.5:1)

and typical tissue concentration ratios were 56.5:8:1 (at the tissue–implant

interface) and 117:9:1 (1 cm away from the interface). Nickel, which formed

12% of the implant alloy, was detected at the interface but not in the sur

rounding tissue.

A number of conclusions may be drawn from these results:

• Ion concentrations (and persuadably leachate concentrations from polymeric materials) may be very high in the vicinity of implants when compared to systemic and remote site concentrations.

• The local accumulation of released products depends upon the nature of their reactions with surrounding tissues and their diffusion concentrations. In this example, nickel diffuses away rapidly and is seen only at the interface, chromium and molybdenum diffuse less rapidly, and iron is accumulated locally, presumably due to the formation of precipitates that contribute to the discoloration of metallosis.

• Tissue concentrations do not necessarily reflect alloy proportions. Finding metals near implants in their alloy constituent proportions is more evidence of wear debris accumulation than of burdening of tissues with soluble or precipitated corrosion products (Michel 1987).*

• Finally, it should be pointed out that the mere detection of metal in tissues does not reflect its biological availability. Metal may be present as free ions (unlikely), bound to specific carrier molecules (e.g., Fe-transferrin), nonspecifically bound (e.g., to albumin), in the form of a wear particle, or as a precipitate. Any of these forms may be extracellular or intracellular.

This pattern observed by Lux and Zeisler (1974) reflects the end stage of

an equilibrium between the implant and the tissue. In a later study utilizing

a rabbit implant model, Lux et al. (1976) reported a nonspecific decrease in

* One of the difficulties in understanding such results arises in distinguishing among corrosion

products in solution, local precipitates, and insoluble particles, whether intra- or extracellular. If

the local composition matches the composition of the implant, then the evidence is fairly reliable

that the material is present in particulate form (as Michel, 1987, suggests), even if not resolvable

by light microscopy. However, the reverse is not true because selective corrosion may change the

apparent composition of small particles.

transport rate with time for all detectable corrosion products; this was

ascribed to maturation of the fibrous capsule about the implant. Further

more, they showed an inverse correlation between tissue iron and zinc

content, even though zinc was not released by the implant. These findings

underline the great complexity of consideration of release and distribution

of implant degradation products, even in the near vicinity of the implant.

In a traditional sense, as would be observed in an in vitro corrosion study,

equilibrium would nevertheless be reached when an equilibrium concentra

tion of ions was reached in the surrounding fluid. However, in vivo, the

bathing medium is dynamic, and a fractional excretion process is always in

competition with corrosion processes as they approach equilibrium.

15.3.2.2 Distribution of Body Water

If maximum implant corrosion rates (as determined by formation of soluble

species) can be measured, then equilibrium times should depend only upon

the volume of the medium and the fractional excretion rates. The medium

under discussion, water, has the relative volumes and distribution in the

human body as shown in Figure 15.3.

If no input/output of fluid occurs, a volume of 42 l would be under con

sideration. Similarly, if no compartmental exchange took place, smaller vol

umes of fluid might be considered — as small as 3.2 l in the case of an implant

bathed in blood. However, the situation is dynamic, as shown in Figure 15.4.

In this figure, note that some water entering the gastrointestinal tract never

exchanges directly with the internal water compartments but passes straight

through as a portion of fecal excretion (dashed line to right of plasma pool).

The 1.3 l/day excretion identified as “other” includes this volume as well as

sweat (lost from the fast interstitial pool) and the water content of sloughed

or desquammated cells (lost from the intracellular pool).

FIGURE 15.3

Water content of the human body (70 kg). TOTAL BODY WATER: 42 LITERS 60% OF BODY WEIGHT
BY COMPARTMENT BY TISSUE EXTRACELLULAR PLASMA INTRACELLULAR MUSCLE SKIN BLOOD OTHER NON-WATER COMPONENTS
15.7 (37.3%) 3.2 (7.6%) 23.1 (55.1%) 22.1 (52.6%) 9.1 (21.6%) 4.7 (11.1%) 6.1 (14.7%)

One can now see that volumes vary considerably depending

upon the

details of consideration. An implant placed in soft or hard tissue is directly

in contact with a fast interstitial pool of 8.4 l, as shown. This contacts slower

exchange pools of 7.3 l (interstitial) and 23.1 l (intracellular). It also contacts

a fast exchange pool of 3.2 l (plasma water). This pool passes through the

kidneys at a rate of 180 l/24 h and experiences a net throughput (intake =

output) of 2.5 to 2.8 l/24 h. Thus, on an annual basis, an implant is in contact

with a pool size exceeding 1000 l. The point of equilibrium of corrosion or

leached products depends on the overall kinetics of release from the implant,

exchange, and excretion. These kinetics are difficult to analyze. The previous

chapter considered the details of one system, the iron system, in some depth.

15.4 Distribution and Excretion of Dissolved Species

15.4.1 Metallic Ion Distribution

However, some of the elements of these distribution systems can be studied

in more detail. One factor to examine is urinary excretion, which is probably

the major route for clearance from the body of metals released from implants,

although biliary excretion may also play a role for some metals (Brauer 1959).

Of the metals of interest as components of implants, only iron is known to

be excreted (incorporated in porphyrins, which are degradation products

of hemoglobin) predominantly through a biliary route (Ishihara and

FIGURE 15.4

Daily water input/output/exchange for the human body (70 kg). SLOW INTERSTITIAL 7.3 liters FAST INTERSTITIAL 8.4 liters INTRACELLULAR 23.1 liters PLASMA 3.2 liters 2.5 liters/24 hr 0.3 liters/24 hr (metabolism) Implant 2.8 liters/24 hr (1.5 urine, 1.3 other)

Matsushiro 1986). Biliary excretion is mediated by concentration in and/or

excretion by the liver of low molecular weight (<10,000) organometallic

species known collectively as metallothioneins (Cherian and Goyer 1978;

Klaassen 1976). These are released through the bile duct, stored in the gall

bladder, and released as bile at a rate of 0.4 to 1.2 l/day into the jejunum. A

significant proportion of the ionic content of bile, perhaps as much as 95%,

is reabsorbed in the ileum, with only 200 mg/day excreted. Biliary excretion

serves primarily to aid in digestion of fats and metal excretion appears to

be a secondary role (Ganong 1989).

Urine, on the other hand, is formed primarily to regulate plasma compo

sition and pH. It is formed in the mammalian kidney by a combination of

three processes: glomerular filtration, tubular reabsorption, and tubular

secretion. In the glomeruli, all formed cellular elements of blood and any

molecules with a molecular weight above approximately 5000 are retained

while all small molecules and a considerable amount of water are filtered

into the proximal renal tubules. In a 70-kg person, between 115 and 125 ml/

min of plasma are filtered. Normally nearly all of the water is also filtered

out. If this were excreted, it would result in a 24-h urine volume of as much

as 180 l.

This does not happen because over 99% of the water is reabsorbed in the

proximal renal tubules, resulting in a nominal rate of urine production near

1 ml/min. In addition, other materials such as the physiological metal ions

(Na + , K + , etc.), essential anions (Cl − , OH − , etc.) and organic molecules (glu

cose, urea, etc.) are reabsorbed. Some reabsorption processes are passive but

others are active (energy requiring). As shown in the left portion of Figure

15.5, each active reabsorption process — for example, for glucose — has an

asymptotic limit (different for each reabsorbed species) termed the tubular

reabsorption limit (T m). This has the effect of limiting and controlling the

maximum concentration of that particular species in plasma.

FIGURE 15.5

Renal reabsorption and secretion. (Adapted from Pitts, R.F., in Physiology of the Kidney and Body

Fluids, An Introductory Text, Year Book Medical Pub. Inc., Chicago, 1963, 69, 116.) Tm E x c r e t e d Plasma Concentration Secreted Tm Plasma Concentration Reabsorbed F i l t e r e d C l e a r a n c e R a t e REABSORPTION SECRETION C l e a r a n c e R a t e F i l t e r e d E x c r e t e d

Finally, materials may be removed from plasma by secretion through the

walls of the distal renal tubules. This process may be passive or active; in

the latter case (right portion of Figure 15.5), the effect is also to demonstrate

a limit. Metals in plasma are bound specifically to transferrin or other carrier

proteins (nickeloplasm, etc.) or nonspecifically to albumin, all of which have

too high a molecular weight to be filtered in the glomeri. Therefore, urinary

excretion of essential and trace metals must be primarily through a tubular

secretion pathway.* Because this represents an interaction between post

glomerular plasma and distal tubule urine, it is instructive to look at the

relative concentrations of metal in these fluids (Table 15.2).

The permeability ratio, K x, is the ratio of concentration in urine to that in

plasma. Values greater than 1 suggest positive secretion, values near 1 indi

cate simple equilibrium between urine and plasma, and values less than 1

suggest a barrier to secretion. The permeability ratio times the relative vol

umes of urine and plasma (= 0.78) is the proportion of normal plasma content

secreted in 24 h. The excretion ratio,** E x , based upon a 24-h urine volume of

2.5 l and a renal filtration of 180 l/24 h, reflects the efficiency of secretion or

the proportion of the renal filtrate secreted in 24 h. The higher the value of

E x is, the greater is the probability of secretion of an ion in any one pass

through the kidneys. The clearance rate, C x , of a substance, x, is given by:

TABLE 15.2

Urinary Secretion of Implant Alloy Components a Element Plasma Conc. (μg/l) Urine Conc. (μg/l) Permeability Ratio (K x) Excretion Ratio (E x)

Al 2.2 6.4 2.9 0.040

Co 0.05 0.33 6.6 0.092

Cr 0.06 0.13 2.2 0.030

Ni 0.2 1.0 5.0 0.069

Ti 3.3 0.41 0.12 0.006

V 0.16 0.61 3.8 0.053

Reference: creatinine 10 mg/l 1.5 g/l 150 2.08

a These data differ considerably from those in the first edition due to significant improvements in collection and analysis techniques. However, it is widely believed that urine collection, especially from female subjects, is subject to contamination. Therefore, K x and E x may be too high; values should be considered in relative rather than absolute terms.

b Reconstructed, assuming 1.5 g creatinine/liter.

Sources: Al, Ti, V: Jacobs, J.J. et al., J. Bone Joint Surg., 73A, 1475, 1991; Co, Cr, Ni b :

Sunderman, F.W., Jr. et al., J. Orthop. Res., 7, 307, 1989; creatinine: Ganong, W.F., in

Review of Medical Physiology, 14th ed., Appleton & Lange, Norwalk, CT, 1989, 593.

* However, some metal-protein dissociation may occur, leading to direct excretion; tubular reab

sorption is also possible (Araki et al. 1986a).

** The term “excretion ratio” is used irrespective of renal mechanism involved. C x = K x V (ml/min) (15.5)

where V = rate of urinary output.

Creatinine is a degradation product released by cell death and is widely

used as a concentration marker for studying ionic concentration in urine.

Urine may be more or less concentrated, depending on fluid intake, perspi

ration loss, etc., but the serum concentration and amount of urinary creati

nine excretion in 24 h remains remarkably constant in normal individuals

(Ganong 1989; Araki et al. 1986b).

15.4.2 Distribution Models: One Compartment

Projections of the equilibrium accumulations of metals in the body have been

made using this type of data (Taylor 1973). Taylor proposed that, for a given

rate of continuous release of corrosion products, R, per day, the increase in

an organ or the total body content of a metal can be given as (15.6)

where

Q o = the normal metal content

Q t = the content after “t” days

k = the fractional rate of excretion of the metal

That is, in a given day, R metal is released and kQ t is excreted. Letting t go

to infinity (when equilibrium is presumably achieved), one then finds that (15.7)

where Q e is the equilibrium metal content. Note that this is a first-order analysis

that treats the body as a single homogeneous compartment. For a hypothetical

cobalt-chromium implant (60% Co, 30% Cr, 8% Mo, 1% Ni, 1% Fe) with a

surface area of 200 cm 2 and a corrosion rate of 30 mg/cm 2 /day, Taylor obtains

the results given in Table 15.3. Taylor concluded that modest elevations of

cobalt and nickel and large elevations of chromium content should occur in

this case. Similar calculations for implantation of stainless steel predict a mod

est elevation of nickel and a large increase in chromium content.

Taylor’s calculations are probably in error on two fundamental grounds.

Although admittedly using high corrosion rates, he does not point out that

these rates are high by at least an order of magnitude. Second, the fractional

excretion rates used are based upon urine/plasma concentration ratios and

do not take into account exchange with slower compartments, particularly

situations in which precipitated storage is possible, as in the liver. Reducing Q Q R k e t o kt = + − ( ) − 1 Q Q R k e o = +

the corrosion rate by an order of magnitude and, continuing to use his

assumption, calculating fractional excretion rates based upon whole-body

content (Q o) and urine concentrations (Sunderman et al. 1989) for Co, Cr,

and Ni yields the results given in Table 15.4. The very large Q e /Q o ratios for

Co and Cr suggest that concentrations of these elements would never come

to equilibrium but should be observed to increase steadily with time postim

plantation. Such effects have been reported in animals (Woodman et al. 1983)

and humans (Michel et al. 1991) for long periods of time.

The fundamental error in all of these considerations is the idea that the

metals distribute freely and do not concentrate or bind preferentially in any

site. In perhaps the first attempt to study systemic distribution of metals

released from implants in animals, Ferguson and his coworkers (1962a, b)

observed the following patterns:

• A large regional variation of metal ion concentration can be found in normal rabbit and human tissue. Furthermore, different metals have different patterns. Thus, the nickel concentration is higher in the liver than in other tissues, and the molybdenum concentration is higher in liver and

kidney than in lung or spleen.

• After implantation of metals, organ concentrations of ions rise. The spleen has a broad ability to retain metals; nickel and cobalt are preferentially retained by the kidney. TABLE 15.3 Secretion and Accumulation Rates of Alloy Components of a Cobalt-Chromium Alloy Element Q o (mg) k (day −1) R (mg/day) Q e (mg) Q e /Q o Co 3 0.07 3.6 54 18 Cr 6 0.0011 1.8 1636 273 Mo 5 0.139 0.48 8 1.7 Fe 4000 0.0010 0.06 4060 1.02 Ni 10 0.0010 0.06 70 7 TABLE 15.4 Recalculation of Secretion and Accumulation Rates of Alloy Components of Cobalt-Chromium Alloy of Table 15.3 Element Q o (mg) Secretion (24 h, μg) k (day −1) R (mg/day) Q e (mg) Q e /Q o Co 3 0.82 0.00027 0.36 1336 445 Cr 6 0.32 0.00005 0.18 3606 601 Ni 10 2.5 0.00025 0.006 34 3.4

Continuing studies of accumulation and distribution of corrosion products

released by implants up to and including autopsy studies on patients with

long-term implants (Michel et al. 1991) support these observations.

15.4.3 Distribution Models: Multicompartment

For technical and ethical reasons, it is extremely difficult to perform whole

body studies of metal metabolism in humans. However, a methodology has

been developed that involves study of the distribution and excretion of a single

dose of radioactive metal ions administered intravenously in animals. It is

possible that this method may be applied selectively to humans in the future.

Although the technique was originally developed by Sunderman at the

University of Connecticut, Greene et al. (1975) provide the best early report.

An experimental animal, such as the rat or rabbit, is used

as a model. A

single intravenous injection of nickel as 63 NiCl 2 is given at a dose of 0.24

mg/Ni/kg body weight. The animals are housed in metabolic cages so that

urine and feces can be collected, and serum specimens are obtained period

ically over a period of time.

For nickel in the rabbit, an expression for the concentration of nickel in

serum takes the form of: (15.8)

The first term is large, corresponding to an early rapid disappearance rate,

and the second term is small, corresponding to a reduced disappearance rate

from 3 to 7 days after injection. This can be interpreted in terms of a large,

fast exchange compartment (the intercellular space) exchanging with a

smaller, slower compartment of undetermined identity. The four constants

assume different values for rats and rabbits.

Greene et al. (1975) made the following extrapolations: From what is known about nickel corrosion, one can estimate that in humans who have implants made of a nickel-containing alloy, the rate of nickel release from the device can range between 5 and 500 mg/year per individual. This corresponds to a range of 0.81 to 0.0081 µg/h per kg body weight on the basis of 70 kg for humans. The following table gives the estimated steady state values of nickel concentration in plasma resulting from three different input rates within that range. Infusion Rate (µg/h per kg of Body Weight) Steady State Ni Concentration (µg/l) Rabbit Rat 0.81 45 19.9 0.081 4.5 1.99 0.0081 0.45 0.20 S A e A e a t a t µg liter/ ( ) = + − − 1 2 1 2 These figures have to be compared with the normal range of nickel concentration in human plasma…2.6* ± 0.08 µg/l.

Taylor’s calculations (Taylor 1973) for an alloy that released 22 mg per year

predict a 7× increase (3.4× corrected calculation based upon his secretion

data) in total body burden of nickel. Because Greene made no assumption

on the partitioning of metallic ions between various compartments, the

elevation that he predicts for plasma must be taken as the total body eleva

tion. For a 2 mg per year release rate, Greene would predict a 1.76× increase

(by rabbit data) or a 1.34× increase (by rat data). These are somewhat smaller

than Taylor’s original calculations (but near to the corrected calculations of

Table 15.3); however, they lend credence to the idea that net concentrations

of metal ions will rise in the presence of an endogenous source of ions, such

as a corroding implant.

Sunderman’s approach has a number of difficulties, including the partition

question and the inability to identify internal compartments except by infer

ence from calculations. This work has been extended and is reported by

Onkelinx (1977). He has developed a more general multicompartment

model, as shown in Figure 15.6. Here, V 1 represents the intracellular com

partment, and V 2 and V 3 represent other compartments with net (reversible)

interchange flow rates f 2 and f 3 , respectively. Again, the assumption of a

partition coefficient of 1 is made so that ion fluxes can be represented as

fluid flow rates at constant concentration. Excretion is represented by a flow

* Note that this is significantly higher than typical modern values; see, for instance, Table 15.2.

The probably lower true value makes the predicted increases even more striking.

FIGURE 15.6

General multicompartment model for metal metabolism. (Adapted from Onkelinx, C., in Clinical

Chemistry and Chemical Toxicology of Metals, Brown, S.S. (Ed.), Elsevier North-Holland, Amster

dam, 1977, 37.) f s S F t f d f u INJECTION V 3 f 3 f 2 V 1 V 2

rate, F t , composed of collection in irreversible sinks (f s), urinary excretion

(f u), and fecal excretion (f d). Loss of tissue, desquammation, etc. are lumped

with f s .

Table 15.5 reports some results obtained by injection of nickel, cobalt, and

chromium into rats between 2 and 3 months old. Onkelinx (1977) reported

results for other ages, suggesting age dependence, especially for chromium.

Examination of this table graphically shows the differences in metal meta

bolism for these ions. Although it is difficult to apply physical identities to

compartment volumes, the differences are obvious. Nickel does not penetrate

V 3 , as previously pointed out, and the relative penetration of each ion is

quite different. Of particular interest is the ratio f s /F t . Here, modest amounts

of nickel and cobalt are trapped in a tissue sink, but over 30% of chromium

is retained. Again, with reference to Taylor (1973), if this material is bound

irreversibly, the effect would be to lower transient tissue concentrations and

lengthen the time until steady state is reached, but raise the final body burden

above that originally predicted.

It is inviting to equate secondary compartments (in this case, V 1 , V 2 , and

S), as derived from Onkelinx' analysis with specific tissue types or organs,

on the basis of apparent volumes. This is simplistic; metabolic pools and TABLE 15.5 Comparison among Compartment Volumes, Interchange, and Excretion for Ni, Co, and Cr in Rats 63 Ni 2+ 57 Co 2+ 51 Cr 3+ Age (days) 85 60 60 Compartment volumes (ml/100 g body wt.) V 1 36.1 46.4 30.8 V 2 4.0 78.2 16.7 V 3 — 65.6 7.7 Apparent excretory flow rates (ml/h) F t 3.91 7.29 1.42 f u 3.07 5.97 0.91 f d 0.62 0.72 0.07 f s 0.22 0.60 0.44 Ratios of excretory flow rates f u /F t 0.79 0.82 0.64 f d /F t 0.16 0.10 0.05 f s /F t 0.06 0.08 0.31 Compartment net interchange flow rates (ml/h) f 2 0.06 13.11 2.47 f 3 — 0.56 0.13 Source: Adapted from Onkelinx, C., in Clinical Chemistry and Chemical Toxicology of Metals, Brown, S.S. (Ed.), Elsevier North-Holland, Amsterdam, 1977, 37.

storage depots can only be identified by following the course of metal, in

the form of a suitable radioactive isotope, from the implant site to its eventual

destination. Unfortunately, such studies may not ethically be performed in

humans, so compartment identities may remain unclear for a long time

to come.

15.4.4 Equilibrium Models

Another experimental approach to this problem (Smith and Black 1977;

Smith 1982) is to implant metallic devices with varying surface areas and

track the plasma levels as a function of time. In these reports, an experiment

was performed in a short-term rabbit model to investigate whether implan

tation of 316L stainless steel is accompanied by elevated plasma levels of

iron and chromium.

For a given alloy system with a uniform processing history, the parameter

that would appear to govern the rate of corrosion product delivery to the

body in any particular implant site is the ratio of implant surface area to

body weight (SA/BW). For a 70-kg patient receiving a typical total hip joint

replacement (surface area = 200 cm 2), this ratio is approximately 2.86 cm 2 /

kg. This value is termed “1×” and multiples of it reflect higher relative

exposures. Note that the use of such a ratio probably underestimates the

exposure in small-animal models. Renal clearance is roughly proportional

to basal metabolic rate (per kilogram of body weight). Because individual

metabolic rate in adult mammals, including humans, is proportional to

(BW) 0.734 (Brody 1945), a 1.5-kg rabbit has a basal metabolic rate/kg 2.78

times that of a 70-kg patient. Thus, 100× for the patient is approximately 36×

for the rabbit, if adjusted to reflect basal metabolic rates, or, conversely, 100×

for the rabbit is 278× for the patient. The concept of SA/BW ratio can be

extended to in vitro studies by recognizing that a 70-kg patient has a water

content of 42 l (Figure 15.4), forming the ratio of surface area to body fluid

volume (SA/BFV) and assigning a value of 4.76 cm 2 /l.

In Smith and Black’s (1977) studies, New Zealand white rabbits received

implants of passivated surgical grade 316L stainless steel (ASTM F 55, type

B) in two forms (Steinmann pin segments and 40-μm spherical powders) at

two anatomic sites (paraspinal musculature and femoral medullary canal)

as shown in Table 15.6. Blood specimens were obtained at intervals of up to

7 months, and tissue specimens were obtained at sacrifice. The serum was

analyzed for chromium, free (nonheme) iron (PI), total iron-binding capacity

(TIBC), and percent of TIBC saturation (% sat.). The tissues were analyzed

for iron and chromium.

No significant differences (experimental vs. control) were detected in PI,

TIBC, or % sat. until 20 weeks postoperative. Group V plasma iron concen

tration was 14% elevated ($p < 0.05$) by 20 weeks postoperative. None of the

groups exhibited significant changes in TIBC or % sat.; however, the latter

showed a “tendency” toward elevation, particularly in Group V. The kidney

showed an ability to accumulate iron; however, Group V liver iron concen

trations were elevated 30% on dry weight and total protein basis.

The results for chromium are shown in Table 15.7. Plasma iron elevations

in Group V at 20 and 28 weeks indicated that iron release (corrosion into

the blood circulation) exceeded the inherent iron turnover rate of the

Fe-transferring-binding system. The consequent trend toward elevation in

% sat., if observed in humans, might occasion a reduction in a patient’s

disease resistance (see Section 14.2.8). Plasma iron and, especially, plasma

chromium concentrations appear to reflect the duration of implantation and

the SA/BW ratio. Sporadic elevations in plasma chromium in Groups I

through IV toward the last 2 months of the study may suggest periods of TABLE 15.6 Animal Groups for Evaluation

of SA/BW Effects Group N = Implant Site SA/BW (Unadjusted) I 10 Pin Muscle 1 II 10 Pin Bone 1 III 15 Microspheres Bone 1 IV 10 Microspheres Bone 10 V 15 Microspheres Bone 100 VI 14 None — 0

TABLE 15.7

Serum and Tissue Chromium Content after Stainless Steel Implantation as a

Function of Implantation Time and SA/BW Ratio in Rabbit

Sample

(ng/ml) Control (Group VI) % Change from Control (Significance) a Group I Group II Group III Group IV Group V

Serum

Pre-op 13.1 ± 0.9 −11.4 ($p < 0.05$)

4 wk PO 11.4 ± 0.4 +16.7 ($p < 0.001$)

8 wk PO 12.9 ± 0.1 Lost group +12.8 ($p < 0.08$)

20 wk PO 11.2 ± 0.4 +6.2 ($p < 0.05$) +21.4 ($p < 0.01$)

24 wk PO 10.3 ± 0.7 +15.5 ($p < 0.01$) +17.5 ($p < 0.01$) +24.3 ($p < 0.01$) +23.3 ($p < 0.01$)

28 wk PO 15.3 ± 0.7 +17 ($p < 0.01$) +10.4 ($p < 0.01$)

Tissue (ng/mg dry wt.)

Kidney 1.97 ± 0.5

Liver 1.07 ± 0.7 +64.2 ($p < 0.02$) +85 ($p < 0.01$)

a Only significant changes are shown.

Source: Adapted from Smith, G.K., Ph.D. thesis, University of Pennsylvania, Philadelphia, 1982.

accelerated corrosion or release into the circulation. Because plasma chro

mium concentrations are probably not in equilibrium with storage compart

ments, these chromium elevations are not likely to be an indicator of body

stores but rather a dynamic measure of serum transport at the moment of

sampling. The kidney demonstrated no capacity to accumulate iron

or chromium.

On the other hand, the liver exhibited elevated iron and chromium accu

mulations, which were apparently a function of SA/BW ratio, in contrast to

Ferguson's study (Ferguson et al. 1962a, b), which reported no elevations in

iron or chromium in the liver or kidney. From persistently elevated plasma

iron and chromium concentrations, it can be expected that liver accumula

tions would have continued beyond the experimental period and that, with

time, groups I through III may have exhibited elevations.

One of the weaknesses of this approach is that it is impossible to distin

guish the metal released from the implant from that available from dietary

sources or storage depots. The presence of the implant may alter the binding

and storage mechanisms that normally handle metal (Woodman et al. 1983).

An alternate approach would be to use radioactive isotopes as injected

materials (Bergman et al. 1980) or, preferably, as components of implant

alloys, followed by periodic sacrifice and autoradiography.

However, the

rarity of appropriate isotopes, difficulties in fabricating suitable implants,

and safety concerns about handling the animals and their waste products

severely handicaps this approach.

It is clear from these equilibrium studies that trace metal metabolism is

highly complex and that detailed studies of each metal of implant impor

tance should be carried out in the future.

15.5 Final Comment

Systemic distribution, storage, and excretion of corrosion and degradation

products from implants has not attracted great attention as a subfield of study

within biomaterials science and engineering. Initially, this was due to an inabil

ity to detect normal or elevated levels of such materials, especially metal

bearing ions, and a parallel failure to recognize their biological importance.

More recently, studies of host response have continued largely to focus on

circumimplant effects and have continued to equate low corrosion/elution

rates and small plasma concentration elevations with absence of accumulation

of degradation products and, thus, absence of biological effects. The weakness

of this assumption may be illustrated by the following argument.

A proposal may be to establish how many cars are in a particular turnpike

rest area by only examining the flow of traffic on the roadway. First consid

erations suggest a possible positive correlation between the number of cars

passing a marker nearby on the main roadway and the number to be found

in the rest area. However, the rest area might be closed for repairs (large

number on roadway, none in rest area) or the driving conditions may have

recently become treacherous, perhaps due to icing, causing drivers to decide

to delay their further travel (small number on roadway, large number in rest

area). Thus, on second consideration, the conclusion is that the only way

reliably to determine the number of cars in a turnpike rest area at any one

time is to count them. The situation for detection of debris and corrosion

products in remote tissues and organs is parallel by analogy.

What is required is the recognition that any implant, whether designed

specifically for that purpose or not, acts as a slow-release system in vivo.

Thus, the appropriate approach to understanding the total host response to

implants must parallel that of biological fate studies in pharmacology and

environmental fate studies in ecology.

From this viewpoint, three important questions should be answered when

a new implantable biomaterial is evaluated:

• What is the nature of the degradation products released from the implant in vivo?

• Where do they go within the body?

• What is the host response to release, distribution, remote concentration, and excretion of these degradation products?

These are extremely difficult questions to answer. Although there are the

oretical bases for the answers to the first and second questions, the third

remains conjectural until actual human clinical data can be obtained. This

can only be done within the context of carefully controlled prospective

studies in well identified cohorts of patients with implants and suitable

controls. Jacobs et al. (1991) offer an example of this approach in a study

that has now extended some 15 years and is gradually being correlated with

studies of retrieved tissues and fluids as patients reach the end of life.

Previously, some aspects of local host response have been considered. The

next chapter will take up the more global issue of systemic and remote site

host response produced by the transport phenomena discussed in this chapter.

Aalders, G.J. et al., An exceptional case of pneumothorax — “a new adventure of the K wire,” Injury, 16, 564, 1985.

Albores-Saavedra, J. et al., Sinus histiocytosis of pelvic lymph nodes after hip replacement. A histiocytic proliferation induced by cobalt-chromium and titanium, Am. J. Surg. Pathol., 18, 83, 1994.

Araki, S. et al., Filterable plasma concentration, glomerular filtration, tubular balance, and renal clearance of heavy metals and organic substances in metal workers, Arch. Environ. Health, 41, 216, 1986a.

Araki, S. et al., Comparison of the effects of urinary flow on adjusted and nonadjusted excretion of heavy metals and organic substances in "healthy" men, J. Appl. Toxicol., 6, 245, 1986b.

Arvidson, K. and Wróblewski, R., Migration of metallic ions from screwposts into dentin and surrounding tissues, Scand. J. Dent. Res., 83, 200, 1978.

Bergman, B. et al., The distribution of nickel in mice, an autoradiographic study, J. Oral Rehabil., 7, 319, 1980.

Brauer, R.W., Mechanisms of bile secretion, JAMA, 169, 1462, 1959.

Brody, S., Bioenergetics and Growth, with Special Reference to the Efficiency Complex in Domestic Animals, Reinhold, New York, 1945, 352.

Case, C.P. et al., Widespread dissemination of metal debris from implants, J. Bone Joint Surg., 76B, 701, 1994.

Charnley, J., Arthroplasty of the hip. A new operation, Lancet, 1, 1129, 1961.

Cherian, M.G. and Goyer, R.A., Minireview, metallothioneins and their role in the metabolism and toxicity of metals, Life Sci., 23, 1, 1978.

Ferguson, A.B. et al., Trace metal ion concentration in the liver, kidney, spleen, and lung of normal rabbits, J. Bone Joint Surg., 44A, 317, 1962a.

Ferguson, A.B. et al., Characteristics of trace ions released from embedded metal implants in the rabbit, J. Bone Joint Surg., 44A, 323, 1962b.

Ganong, W.F., Renal function and micturation, in Review of Medical Physiology, 14th ed., Appleton & Lange, Norwalk, CT, 1989, 593.

Gatti, A.M. and Rivasi, F., Biocompatibility of micro- and nanoparticles. Part I: in liver and kidney, Biomaterials 23(11), 2381, 2002.

Graham, J.A. et al., Effect of trace metals on phagocytosis by alveolar macrophages, Infect. Immunol., 11, 1278, 1975.

Greene, N.D. et al., Engineering and biological studies of metallic implant materials, in Biomaterials, Horowitz, E. and Torgesen, J.L. (Eds.), NBS Special Publication 415, U.S. Government Printing Office, Washington, D.C., 1975, 45.

Hierholzer, S. et al., Increased corrosion of stainless steel implants in infected plated fractures, Arch. Orthop. Trauma Surg., 102, 198, 1984.

Homsy, C.A. et al., Some physiological aspects of prosthesis stabilization with acrylic polymer, Clin. Orthop. Rel. Res., 83, 317, 1972.

Ishihara, N. and Matsushiro, T., Biliary and urinary excretion of metals in humans, Arch. Environ. Health, 41, 324, 1986.

Jacobs, J.J. et al., Local and distant products from modularity, Clin. Orthop. Rel. Res., 319, 94, 1995.

Jacobs, J.J. et al., Release and excretion of metal in patients with titanium-base alloy total hip replacement components, J. Bone Joint Surg., 73A, 1475, 1991.

Jenkin, C.R. and Rowley, D., The role of opsonins in the clearance of living and inert particles by cells of the reticuloendothelial system, J. Exp. Med., 114, 363, 1961.

Kapp, J.P. et al., Metallic fragment embolization to the cerebral circulation, J. Trauma, 13, 256, 1973.

Kapur R. et al., Human monocyte morphology is affected by local substrate charge heterogeneity, J. Biomed. Mater. Res., 32, 133, 1996.

Kawaguchi, H. et al., Phagocytosis of latex particles by leukocytes, I, Dependence of phagocytosis on the size and surface potential of particles, Biomaertials, 7, 61, 1986.

Klaassen, C.D., Biliary excretion of metals, Drug Metab. Rev., 5, 165, 1976.

Korn, E.D. and Weisman, R.A., Phagocytosis of latex beads by acanthamoeba. II. Electron microscopic study of the initial events, J. Cell. Biol., 34, 219, 1967.

Lux, F. and Zeisler, R., Investigations of the corrosive deposition of components of metal implants and of the behavior of biological trace elements in metallosis tissue by means of instrumental multi-element activation analysis, J. Radioanal. Chem., 19, 289, 1974.

Lux, F. et al., A mechanistic model for the metabolism of corrosion products and of biological trace elements in metallosis tissue based on results obtained by activation analysis, J. Radioanal. Chem., 32, 229, 1976.

Lyons, F.A. and Rockwood, C.A., Current concepts review. Migration of pins used in operations on the shoulder, J. Bone Joint Surg., 72A, 1262, 1990.

Margevicius, K.J. et al., Identification and distribution of synthetic ligament wear particles in sheep, J. Biomed. Mater. Res., 31, 319, 1996.

Michel, R., Trace metal analysis in biocompatibility testing, CRC Crit. Rev. Biocompat., 3, 235, 1987.

Michel, R. et al., Systemic effects of implanted prostheses made of cobalt-chromium alloys, Arch. Orthop. Trauma Surg., 110, 61, 1991.

Normann, S.J., Kinetics of phagocytosis. II. Analysis of in vivo clearance with demonstration of competitive inhibition between similar and dissimilar foreign particles, Lab. Invest., 31, 161, 1974.

Onkelinx, C., Whole-body kinetics of metal salts in rats, in Clinical Chemistry and Chemical Toxicology of Metals, Brown, S.S. (Ed.), Elsevier North-Holland, Amsterdam, 1977, 37.

Oron, U. and Alter, A., Corrosion in metal implants embedded in various locations of the body in rats, Clin. Orthop. Rel. Res., 185, 295, 1984.

Pitts, R.F., Tubular reabsorption; tubular secretion, in Physiology of the Kidney and Body Fluids, An Introductory Text, Year Book Medical Pub. Inc., Chicago, 1963, 69, 116.

Potter, F.A. et al., The migration of a Kirschner wire from

shoulder to spleen: a brief report, J. Bone Joint Surg., 70B, 326, 1988.

Schnyder, J. and Baggiolini, M., Role of phagocytosis in the aviation of macrophages, J. Exp. Med., 148(6), 1449, 1978.

Smith, G.K., Systemic transport and distribution of iron and chromium from 316l stainless steel implants, Ph.D. thesis, University of Pennsylvania, Philadelphia, 1982.

Smith, G.K. and Black, J., Elevation of Fe and Cr concentrations in blood plasma after stainless steel implantation, Trans. ORS, 2, 281, 1977.

Stensaas, S.S. and Stensaas, L.J., Histopathological evaluation of materials implanted in the cerebral cortex, Acta. Neuropath. (Berl.), 41, 145, 1978.

Stiffel, C. et al., Kinetics of the phagocytic function of reticuloendothelial macrophages in vivo, in Mononuclear Macrophages, van Furth, R. (Ed.), Academic Press, New York, 1970, 335.

Styles, J.A. and Wilson, J., Comparison between in vitro toxicity of two novel fibrous mineral dusts and their tissue reactions in vivo, Ann. Occup. Hyg., 19, 63, 1976.

Sunderman, F.W., Jr. et al., Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses, J. Orthop. Res., 7, 307, 1989.

Taylor, D.M., Trace metal patterns and disease, J. Bone Joint Surg., 55B, 422, 1973.

Urban, R.M. et al., Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty, J. Arthroplasty, 19 (8 Suppl. 3), 94, 2004.

Vernon-Roberts, B., The kinetics of phagocytosis stimulation and depression of the phagocytic activity of macrophages, in Vernon-Roberts, B., The Macrophage, Cambridge University Press, Cambridge, 1972, 92.

Weisman, R.A. and Korn, E.D., Phagocytosis of latex beads by acanthamoeba I. Biochemical properties, Biochemistry, 6, 485, 1967.

Woodman, J.L. et al., Release of cobalt and nickel from a

new total finger joint prosthesis made of vitallium, J. Biomed. Mater. Res., 17, 655, 1983.

Anderson, J.M. and Miller, K.M., Biomaterial biocompatibility and the macrophage, Biomaterials, 5, 5, 1984.

Friedman, M.H., Principles and Models of Biological Transport, Springer-Verlag, Berlin, 1986.

Guyton, A.C., The kidneys and body fluids, in Textbook of Medical Physiology, 8th ed., Guyton, A.C. (Ed.), W.B. Saunders, Philadelphia, 1991, 273.

Harrison, P.M. and Treffry, A., Storage and transport of transition-metal ions, in Inorganic Biochemistry, A Review of the Recent Literature Published up to Late 1977, Vol. 1, H.A.O. Hill (Ed.), The Chemical Society, London, 1979, 120.

Ingham, E. and Fisher, J., The role of macrophages in osteolysis of total joint replacement, Biomaterials, 26, 1271, 2005.

Iyengar, G.V., Review: reference values for the concentrations of As, Cd, Co, Cr, Cu, Fe, I, Hg, Mn, MO, Ni, Pb, Se, and Zn on selected human tissues and body fluids, Biol. Trace Elem. Res., 12, 263, 1978.

Koushanpour, E. and Kriz, W., Renal Physiology, Principles, Structure, and Functions, 2nd ed., Springer-Verlag, New York, 1986.

Langkamer, V.G. et al., Systemic distribution of wear debris after hip replacement. A cause for concern? J. Bone Joint Surg., 74B, 831, 1992.

Lote, C.J., Principles of Renal Physiology, 4th ed., Chapman & Hall, London, 2000.

Pitts, R.F., Physiology of the Kidney and Body Fluids, An Introductory Text, 3rd ed., Year Book Medical Pub. Inc., Chicago, 1974.

Roberts, J. and Quastel, J.H., Particle uptake by polymorphonuclear leucocytes and Erlich ascites-carcinoma cells, Biochem. J., 89, 150, 1963.

da Silva, J.J.R.F. and Williams, R.J.P., The Biological Chemistry of the Elements, 2nd ed., Clarendon Press, Oxford, 2001.

Solomon, A.K., Compartmental methods of kinetic analysis, in Mineral Metabolism, Vol. 1A, Comar, C.L. and Bronner, F. (Eds.), Academic Press, New York, 1960, 119.

Valtin, H. and Schafer, J.A., Renal Function, 3rd ed., Little, Brown and Co., Boston, 1994. 317

16

Effects of Degradation Products on Remote Organ Function

16.1 Introduction

This chapter will complete the discussion of the effects of materials on biological systems (host response). With the exception of a number of recognized systemic effects, this chapter will simply recapitulate and emphasize areas already discussed in Chapter 8 through Chapter 15.

Systemic effects of foreign materials, such as implants, are now well recognized. It is more correct to distinguish between remote effects (involving actions, perhaps secondary to deposition and concentration of degradation products) on a target tissue or organ and systemic effects (those affecting large-scale systems such as the cardiovascular or neurological systems) However, for the sake of brevity, they will be grouped together here under the common title of systemic effects.

The effects of drugs, collectively pharmacological effects, are by and large

necessarily systemic or remote effects. Drugs are given or injected in one

portion of the body and directly or indirectly affect cellular and systemic

physiology in other areas, even if a purely local or topical effect is intended.

Discussion of such effects is beyond the scope of this book; however, many

of the effects that have been discussed are essentially pharmacological effects

secondary to the primary or intended effect. Nonetheless, drug release mate

rials provide a hypothetical example that illustrates the complexity of pos

sible host response to an implant:

- The drug and/or carrier material is designed to evoke a local (implant site) response, such as alleviation of pain or reduction of fibrosis.

- The drug and/or degradation products from the carrier may evoke desirable or undesirable systemic effects, such as alteration of arterial pressure.

- The drug may have a specific remote organ target, such as the heart.

- The degradation products of the carrier might produce adverse effects in other remote organs, such as the kidney.

16.2 Examples of Systemic Effects

16.2.1 Polymers

An example of these types of effects is that associated with release of methyl

methacrylate monomer during the polymerization of PMMA-type cements

in vivo. Homsy et al. (1972) (see Section 15.3.1) were attracted to this problem

not by the observation of the rapid transport of the monomer to the lungs,

but by the observed systemic effects. Early in the use of these cements, it

was observed that systemic hypotension developed immediately after the

insertion of the cement into the prepared bone cavity. Arterial pressure drops

of more than 15 mmHg were observed associated with transient cyanosis,

and a number of cardiac arrests drew medical attention to the effect (Keret

and Reis 1980). Further studies in dogs showed that this problem is accen

tuated by marked fluid and/or blood loss (McMaster et al. 1974).

The corrective therapy now used to prevent the development of centrally

mediated hypotension after PMMA insertion is maintenance of the patient

in a state of positive hydration. In addition, it has been shown that venting

the bony (medullary) cavity with a drain line during device insertion reduces

the driving pressure differential that aids in monomer take-up by blood and

may reduce the embolization of fat to the lungs as encountered in intramed

ullary fixation of fractures (Giannoudis et al. 2002). Polymers released from

implants have few if any known systemic effects beyond this hypotensive

effect. The rates of release and the normal routes of molecular catabolism

apparently combine to keep concentrations of products from common poly

meric implants below levels required for direct pharmacological activity.

This is not to suggest that elevated blood levels of polymer degradation

products do not exist or that they may be harmless in the long term. In the

short term, host responses may be indistinguishable from disturbances of

homeostasis associated with surgery (Dahl 1997). However, in cases of high

surface area and/or repetitive exposure, as in hemodialysis (as a treatment

for renal insufficiency or failure), significant deviations from normal condi

tions may be encountered. Lewis et al. (1977) examined the blood of indi

viduals undergoing chronic hemodialysis, looking explicitly for breakdown

products or plasticizers that might be released from the polyvinyl chloride

(PVC) polymer used as a blood conduit material. Significant levels, up to a

mean level of 751 ng/ml serum of bis (2-ethylhexyl) phthalate, a common

PVC plasticizer, were found in these patients after dialysis. Although the

catabolism of this material was rapid and thus led to its being undetectable

in blood 5 to 6 hours after completion of dialysis, the yearly dose for the

chronic dialysis patient was estimated to be 150 to 250 mg.

The long-term

effects of this are unknown, as is the case for the majority of long-term, low

level exposures to foreign materials and their degradation products.

A final interesting example is provided by the early (now abandoned)

practice of using injected fluid silicone materials for cosmetic tissue augmen

tation. In addition to producing local fibrosis, these fluids can migrate

through tissue and produce a variety of remote effects, including tissue mass

formation, adenopathy, and, possibly, pulmonary failure (Kossovsky and

Heggers 1987). However, broader claims of connective tissue and immune

disorders associated with silicone gel-filled breast augmentation devices

appear to have no firm basis (Gabriel 1998; Noone 1997).

16.2.2 Metals

The situation with metals is somewhat different. In addition to the “physi

ological” metals (Ca, Na, K, and Fe) and despite very low normal plasma

and tissue concentrations, a large number of metals, including Co, Cr, Mg,

Zn, and Cu, have normal roles in metabolism and are thus classified as

essential trace elements. Therefore, it should come as no surprise that natu

rally occurring diseases of inherited as well as acquired etiology involve

imbalances in the metabolism of these metals.

In addition to anemia (iron deficiency), iron overload diseases also exist.

One such disease, hemochromatosis (Elinder 1986), results in the accumula

tion and deposit of iron in the form of the compound hemosiderin in tissues

with rough endoplasmic reticulae. This accumulation has a number of phys

iological effects. One example is the development of diffuse arthritis in

widely separated joints. This also occurs secondarily to the internal bleeding

associated with hemophilia. Hemochromatosis involves skin pigmentation,

liver failure, and diabetes. Elinder (1986) points out that although iron is a

physiological element, it is potentially toxic in all doses and forms and is

capable of producing a variety of local and systemic toxic effects in animals

and humans.

A less well-known disease is Wilson’s disease (Aaseth and Norseth 1986),

or the so-called copper man syndrome. This is an accumulation disease,

primarily hereditary, in which copper accumulates in a variety of tissues,

including liver, cornea, and skin, instead of being maintained in balance. A

green skin color develops and a high incidence of mortality due to intravas

cular hemolysis and liver failure results from the cytotoxicity of copper and

its compounds.

Metals that are normally foreign to the body, such as Pb, Be, and As, can

combine competitively with enzymes that normally use other trace metals

as cofactors. Even normally present metals, such as Al and Cr, may do so,

if present in sufficiently high concentrations. The abnormal cofactor–enzyme

combinations may have higher stability than the normal cofactor bonds.

Thus, the effect is to inactivate a portion of the enzyme pool without

stimulating additional enzyme production. In low concentrations, the net

effect will be to inhibit enzyme activity. This can be seen in a reduction of

the efficiency or effectiveness of an enzyme process. Examples of this are the

peripheral neuropathy observed in the case of long-term, low-level ingestion

of lead and the suppression of hemoglobin synthesis by chromium. At higher

concentration levels, metals can be highly toxic poisons through enzyme

inactivation as in the familiar case of arsenic.

Beyond these specific mechanisms, a wide variety of systemic medical

problems has been suggested as associated with imbalances in trace metal

levels. As noted in Section 14.4, care must be taken in

dealing with this

literature because a less than totally scientific nutritional school of thought

ascribes virtually all unexplained physical and mental disabilities to such

effects. The mere detection of a foreign metal with adverse biological effects,

such as mercury, is insufficient to reach conclusions concerning possible

clinical problems; for example, recent studies associate autoimmunity in

patients with dental amalgam more with the silver content of the restoration

than with mercury or its compounds (Enestrom et al. 1995). There are, how

ever, legitimately recognized associations, such as the increased incidence

of cardiomyopathy associated with elevated cobalt intake (Alexander 1972)

and the recognized association of arteriosclerosis with hardness (primarily

Ca content) of ground water (Perry 1973).*

Consideration of the effects of metals must address all aspects of physiol

ogy. Perhaps one should be more observant of systemically detectable devi

ations from mean values of clinical parameters, such as liver transaminase

serum concentrations in patients with chronic implants (Chopra 1988), even

when they remain within “normal” limits. Concentrations of metals well

below those needed to produce externally measurable changes

in such phys

iological variables can produce profound behavioral abnormalities and men

tal disorders (Weiss 1978).

16.2.3 Ceramics

As noted in Section 4.11, ceramics used in implants may be insoluble or

soluble. Insoluble ceramic biomaterials, such as alumina, titania, zirconia,

etc., pose no systemic challenge, at least in nonparticulate form. To avoid

unwanted local site responses, resorbable ceramics, such as tricalcium phos

phate, etc., are chosen so that their elemental cations and anions (including

Cl^-, SO_4^{-2}, CO_3^{-2}, and PO_4^{-3}) lie primarily within the range of physiological

compositions. However, the possibility of soluble mineral components such

as Sr** in the latter generally argues for the use of fully defined (synthetic)

* As well as, presumably, the general levels of trace element intake.

** 90 Sr, a radioactive element with a half-life of 29 years, was present as a natural impurity in zir

conium and zirconia in their early use as biomaterials (Burger et al. 1997). Although they are now

fully removed from such materials, its presence presented an early example of an unwanted

source of systemic effects.

materials rather than those obtained from natural sources to avoid possible

systemic effects caused by their dissolution products.

16.3 A Review of Systemic Aspects of Host Response

Host responses will now be reviewed briefly in terms of systemic or remote

site effects.

16.3.1 Interaction of Molecules with Surfaces

Proteins and enzymes released from surfaces in an irreversibly denatured

state will possibly elicit remote effects directly or indirectly through the

action of the immune system. Depletion of pools of unactivated coagulation

or complement factors, as frequently occurs during hemodialysis or blood

oxygenation, may suppress coagulation effects at remote sites of injury.

Conversely, the increased circulating concentration of surface-activated fac

tors may also have systemic or remote sequelae. It is also possible that

denatured molecules bound to wear debris subject to passive or active trans

port can elicit systemic or remote effects.

16.3.2 Inflammation

Inflammation would be expected to be a local effect restricted to the

vicinity of the implant. It is possible that an implant can release pyrogenic

agents directly or produce them indirectly through denaturation pro

cesses. Some evidence indicates that denatured molecules or released

products of unknown identity may produce long-term systemic hallmarks

of inflammation, as in the chronic erythrocyte sedimentation rate elevation

observed by Shih et al. (1987) in patients after PMMA-cemented total hip

replacement. In addition, friction, wear, and some dissolution processes

that release particulate material may result in an inflammatory response

at a site of remote accumulation. An example of this is the abdominal

“teflonoma” frequently seen after use of poly(tetrafluoro) ethylene as the

material for fabrication of acetabular cups in Charnley’s early efforts at

hip replacement (Charnley 1979). More subtle may be the effects associ

ated with particulate transport and accumulation through venous or lym

phatic return pathways (Langkamer et al. 1992). Precipitation/

redissolution of corrosion products in remote sites may also be expected

to produce inflammation due to response to the resulting particulate

material or to increased local concentrations of ions.

16.3.3 Coagulation and Hemolysis

Similarly, one can expect that primary coagulation problems would be local

ized to the vicinity of a cardiovascular system implant or external blood

conduit or treatment device. The ability of implants to surface activate factors

in the coagulation cascade (as noted earlier), as well as to shed thrombi,

renders this a systemic effect with remote site manifestations. Similarly,

whether through blood-surface interactions, turbulent shear, or by direct

mechanical damage in valves, pumps, etc., hemolysis is a systemic problem

due to the reduction in viable erythrocytes and the rapid dispersion of

hemoglobin and cell fragments. It is clear that the current factors limiting

successful long-term left ventricular assist and total (artificial) heart replace

ment are remote effects (primarily cerebral and pulmonary infarcts) second

ary to systemic distribution of shed thrombi.

16.3.4 Adaptation

The discussion of adaptation emphasized the effects at the biomaterial-tis

sue interface. This is certainly the most important adaptive remodeling

site, and it is expected that systemic or remote effects would be secondary

to this and thus not directly related (if they occur at all). However, one

should not rule out, a priori, the possibility of cytokines, growth factors,

etc. released from sites of adaptive remodeling having effects on remote

tissues or organs.

16.3.5 Chemical Carcinogenesis

Of necessity, chemical carcinogenesis must be considered a systemic problem

because of the variable sensitivity of cells to chemically induced neoplastic

transformation and the possibility of metastases. If chemically mediated

carcinogenesis occurs in humans due to the use of implant materials, it can

thus be expected to have a significant systemic manifestation. It is worth

pointing out again that possibilities of systemic and remote-site tumorgen

esis associated with implants tend to be overlooked in patient populations

for two reasons:

- The tumor types expected are no different from those that would already exist in a comparable patient population without implants.

- The specialization of medicine makes the connection of a tumor in a remote tissue or organ system to the presence of an implant in another tissue or organ system unlikely (Black 1984).

16.3.6 Foreign-Body Carcinogenesis

One would expect foreign-body carcinogenesis that occurs in patients to be

a local problem. However, the ability of particulate materials to move in the

body and the inherent ability of many neoplasms to metastasize render it a

potential systemic problem. It must be emphasized that this is a putative

consideration because the presence of primary foreign body

neoplasias (at the implant site) has not been reliably detected in humans (see Section 13.3).

16.3.7 Infection

Acceptance of Weinberg's (1974) arguments concerning nutritional immunity (see Chapter 14) means that it is necessary to recognize the possibility of problems associated with elevated iron concentrations in the vicinity of implants and with elevated concentrations in remote storage sites. Furthermore, suppression of the immune system may also predispose to infection at distant sites as well as at the implant–tissue interface.

The possibility of the inverse — that is, of hematogenous "seeding" of an implant site infection from a distant site such as a dental abscess or urinary tract infection — must not be discounted, although clinical data remain equivocal at this time (Thyne and Ferguson 1991). In most surgical specialties, pre- and perioperative precautions are now employed for implantation procedures when there is foreknowledge of infection present at a remote site, particularly in the oral cavity (Carmona et al. 2002).

16.3.8 Allergic Foreign-Body Response

The discussion of this subject (Chapter 12) emphasized the systemic nature of the response. Therefore, in addition to possible

problems in the vicinity

of the implant such as pain, loosening, etc., a wide variety of allergic

responses at remote sites can potentially be associated with the presence of

metallic, and possibly polymeric, implants as sensitizing or challenge agents.

Sensitization is a matter of particular concern because it may evoke a later

local or systemic response apparently spatially unrelated to the original site

of implantation.

16.4 A Final Comment

It is important to re-emphasize that studies of host response have focused

primarily on the implant site and adjacent tissues. In the future, a much

broader view must be taken and the response of the entire host, whether

experimental animal or human patient, must be studied in detail.

However, a major pitfall in such considerations must be avoided. Much is

made in the lay press about individuals who develop an apparent “environ

mental allergy”: an elevated sensitivity, with immune response symptoms,

to a very broad variety of agents that have in common only that they are

man-made. An analogous situation exists in the field of clinical application

of biomaterials with lay concern over the relationship between release of

mercury from mercury-based dental amalgams and a broad variety of patient

symptoms. Without passing judgment on either of these situations,* I would

like to suggest, somewhat in the spirit of Furst's requirements for accepting

the carcinogenicity of a metal in animal models (see Section 13.2.4), that the

following criteria should be met before the existence of a remote or systemic

effect in humans is taken as proven:

- The basic mechanism of the biological response must be demonstrated in at least one in vitro situation or in an animal biological model.

- After the causative implant-related species has been identified, its release by a functional implant and systemic distribution in an animal model or in patients (preferably both) must be shown.

- The putative biological response must be identified in an animal model or in patients (preferably both) with functional implants.

- If it is demonstrated in patients, the biological response must be recognized on the basis of a statistically sound epidemiological study, with suitable nonexposed controls and, unless the response is of a threshold type, must demonstrate a dose–response or exposure–incidence relationship.

In my mind, these are the necessary and sufficient conditions to conclude

that an implant-related systemic (and/or remote site) effect exists in patients.

Their presence does not settle the issue of the clinical importance of the effect;

this depends upon other considerations such as treatment alternatives

(including no treatment) and the benefit of the use of the device in which

the biomaterial is incorporated.

However, I would suggest that if the first criterion is met — that is, a

biological mechanism leading to a putative systemic or remote site effect is

identified — then an index of suspicion should be attached to the biomaterial

in question. Similarly, isolated case reports of local or distant adverse

implant-related responses should also arouse a degree of suspicion; what

they lack in numbers they make up for to a degree in specificity. A lack of

sound knowledge in any of the latter three areas should not lead to an

inference of safety; this would be morally equivalent to the statement that

“What I don’t know can’t hurt me.”

* See Section 12.4 for a more complete discussion of immune responses to implants and Section

14.4 for a critique of environmental allergy and related issues.

For this reason, I have suggested that a biomaterial can never be considered

safe or unsafe, but merely biocompatible (or not) in a specific application

(Black 1995). Rather, satisfaction of the first criterion should lead to changes

in behavior in consideration of that biomaterial for specific current device

designs (Black 1988) and in planning future basic and

applied studies of the

biomaterial's safety and efficacy in present as well as proposed applications.

Aaseth, J. and Norseth, T., Copper, in Handbook on the Toxicology of Metals, Vol. II., Friberg, L., Nordberg, G.F. and Vouk, V.B. (Eds.), Elsevier, Amsterdam, 1986, 233.

Alexander, C.S., Cobalt-beer cardiomyopathy, Am. J. Med., 53, 395, 1972.

Black, J., Systemic effects of biomaterials, Biomaterials, 5, 11, 1984.

Black, J., Does corrosion matter? J. Bone Joint. Surg., 70B, 517, 1988.

Black J., "Safe" biomaterials, J. Biomed. Mater. Res., 29, 791, 1995.

Burger, W. et al., New Y-TZP powders for medical grade zirconia, J. Mater. Sci. Mater. Med., 8, 113, 1997.

Carmona, I.T. et al., An update on the controversies in bacterial endocarditis of oral origin, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod., 93, 660, 2002.

Charnley, J., Low Friction Arthroplasty of the Hip, Springer-Verlag, Berlin, 1979, 6.

Chopra, S., Disorders of the Liver, Lea & Febiger, Philadelphia, 1988.

Dahl, O.E., Cardiorespiratory and vascular dysfunction related to major reconstructive orthopedic surgery, Acta Orthop. Scand., 68, 607, 1997.

Elinder, C.-G., Iron, in Handbook on the Toxicology of Metals, Vol. II., Friberg, L., Nordberg, G.F. and Vouk, V.B. (Eds.), Elsevier, Amsterdam, 1986, 276.

Enestrom, S. and Hultman, P., Does amalgam affect the immune system? A controversial issue, Int. Arch. Allergy Immunol., 106(3), 180, 1995.

Gabriel, S.E., Soft tissue response to silicones, in Handbook of Biomaterial Properties, Black, J. and Hastings, G. (Eds.), Chapman & Hall, London, 1998, 556.

Giannoudis, P.V. et al., Review: systemic effects of femoral nailing: from Kuntscher to the immune reactivity era, Clin. Orthop. Rel. Res., 404, 378, 2002.

Homsy, C.A. et al., Some physiological aspects of prosthesis stabilization with acrylic polymer, Clin. Orthop. Rel. Res., 83, 317, 1972.

Keret, D. and Reis, D.R., Intraoperative cardiac arrest and mortality in hip surgery. Possible relationship to acrylic bone cement, Orthop. Rev., IX(7), 51, 1980.

Kossovsky, N. and Heggers, J.P., The bioreactivity of silicone, CRC Crit. Rev. Biocompat., 3, 53, 1987.

Langkamer, V.G. et al., Changes in the proportions of peripheral blood lymphocytes in patients with worn implants, J. Bone Joint Surg., 74B, 831, 1992.

Lewis, L.M. et al., Determination of plasticizer levels in serum of hemodialysis patients, Trans. Am. Soc. Artif. Intern. Organs, XXIII, 566, 1977.

McMaster, W.C. et al., Blood pressure lowering effect of methylmethacrylate monomer, Clin. Orthop. Rel. Res., 98, 254, 1974.

Noone, R.B., A review of the possible health implications of silicone breast implants, Cancer, 79(9), 47, 1997.

Perry, H.M., Jr., Minerals in cardiovascular disease, J. Am. Diet. Assoc., 62, 631, 1973.

Shih, L.-Y. et al., Erythrocyte sedimentation rate and C-reactive protein values in patients with total hip arthroplasty, Clin. Orthop. Rel. Res., 225, 238, 1987.

Thyne, G.M. and Ferguson, J.W., Antibiotic prophylaxis during dental treatment in patients with prosthetic joints, J. Bone Joint Surg., 73B, 191, 1991.

Weinberg, E.D., Iron and susceptibility to infectious disease, Science, 184, 952, 1974.

Weiss, B., The behavioral toxicology of metals, Fed. Proc., 37(1), 22, 1978.

Davies, I.J.T., The Clinical Significance of the Essential Biological Metals, Charles C Thomas, Springfield, IL, 1972.

Debelian, G.J. et al., Systemic diseases caused by oral microorganisms, Endod. Dent. Traumatol., 10, 57, 1994.

DiCarlo, E.F. and Bullough, P.G., The biological responses to orthopedic implants and their wear debris, Clin. Mater., 9(3-4), 235, 1992.

Friberg, L., Nordberg, G.F. and Vouk, V.B. (Eds.), Handbook on the Toxicology of Metals, Vols. I and II. Elsevier, Amsterdam, 1986.

Ling, R.S.M., Systemic and miscellaneous complications, in Complications of Total Hip Replacement, Ling, R.S.M. (Ed.), Churchill-Livingstone, London, 1984, 201.

McCall, J.T. et al., Implications of trace metals in human diseases, Fed. Proc., 30(3), 1011, 1971.

Pier, S.M., The role of heavy metals in human disease, Tex. Rep. Biol. Med., 33(1), 85, 1975.

Rothman, R.H. and Hozack, W.J., Complications of Total Hip Arthroplasty, W.B. Saunders, Philadelphia, 1988.

Schroeder, H.A., Trace metals and chronic diseases, Adv. Intern. Med., 8, 259, 1956.

Schierholz, J.M. and Beuth, J., Implant infections: a haven for opportunistic bacteria, J. Hosp. Infect., 49(2), 87, 2001.

Webb, M., Metabolic targets of metal toxicity, in Clinical Chemistry and Chemical Toxicology of Metals, Brown, S.S. (Ed.), Elsevier North-Holland, Amsterdam, 1977, 51.

Williams, D.F. (Ed.), Systemic Aspects of Biocompatibility, Vols. I and II, CRC Press, Boca Raton, FL, 1981. 327

Interpart 2

Implant Materials: Clinical Performance*

I2.1 Introduction

Elaine Duncan (1990) once posed the question of whether biomaterials are

at risk of becoming endangered species. Her query was motivated, in part,

by a letter distributed by Dow Corning, Inc. (Midland, MI) warning of the

company's intention of withdrawing an old standby polyurethane biomate

rial, Pellethane™, from the market — at least for applications intended to

last longer than 30 days in vivo. Citing published reports of cracking of the

material after longer times in vivo (Stokes and Chem 1988), a company

representative, J.R. Stoppert (1989), asserted that no data support long-term

use of the material.

My immediate reaction to this statement was incredulity. The use of mate

rials similar to Pellethane had been reported by Boretos and Pierce (1968)

more than 20 years earlier. Discussing such materials, Boretos (1973) said

that "[they] possess a combination of properties not available in other mate

rials, outstanding of which [is]...excellent stability over long implant period."

So, how can there be no data to support long-term human implantation of

Pellethane?

I believe that what Stoppert (1989) meant is that there were, literally, no

data. That is, there was evidence neither to support nor to contradict bio

medical device designers' decisions to use Pellethane ™ in long-term appli

cations. Boretos' (1973) comments are not data and neither

are the majority

of papers published about this material or, for that matter, about virtually

any other biomaterial in use in long-term clinical applications.** Most of

these papers, especially those dealing with clinical observations, are not

studies in the strict scientific sense, and the failure to conduct studies results

in the absence of data, whether positive or negative.

* An earlier version of this interpart was published in Black (1990). Table I2.1 is adapted from

Table 14.2 in Black (1988).

** The first competent study that I am aware of documenting in vivo stress-related degradation

of such materials, albeit in an animal model, did not appear until 1990 (Zhao et al. 1990).

What has happened is that workers in the field of biomaterials have been

blinded by success. The techniques used in the 1960s to qualify materials

(limited in vitro studies, 12- to 104-week animal studies, 2-year human clin

ical studies; see Chapter 18 and Chapter 19) are still current practice in the

early 2000s. This is despite the widespread use of biomaterials in long-term

clinical applications that, in at least one device type (total hip replacement;

Malchau et al. 2002), exceed 25 years in individual and group patient expe

rience. It appears that two critical aspects of the study of biomaterials have

been neglected: the epidemiology and human physiology of biomaterials.

I2.1.1 Epidemiology of Biomaterials

Continuing to study the success and failure of implanted materials in exper

iments with animals numbering in the tens and twenties, biomaterials

researchers have largely overlooked the vast clinical “experiments” under

way in which thousands, in many cases tens or hundreds of thousands, of

human patients receive virtually identical biomaterials as chronic implants.

A Center for Disease Control survey performed in 1988 (Moss et al. 1991)*

suggests that as many as 14.5 million people, or nearly 1 in 20 in the U.S.,

had permanent implants. With the exception of occasional reports of clinical

failures and studies of the materials aspects of retrieved devices, almost

nothing is known about biomaterials' performance in these implants in the

human clinical environment. Dependable incidence and prevalence data on

the devices are hard to obtain; such data on the materials from which they

are made, including their exact (not merely specified) composition and pro

cessing, are still essentially nonexistent.

Today, making the same mistake as certain penologists who, wishing to

know about crime, study only failed criminals (that very small nonrandom

proportion of the criminal population actually apprehended, convicted, and

incarcerated), one persists in studying only random device failures. Even

these limited studies, based upon clinical or postmortem retrievals, are fre

quently incomplete, focusing on the clinical features of the failure or upon

the physical attributes of the failed device, depending upon the background

and interests of the principal investigator, but rarely dealing with both

aspects in a balanced way.

Recent increased interest in studying outcomes of surgical procedures

(change in patient lifestyle, satisfaction level, relative cost, etc.) rather than

merely the success of the procedure (rated as excellent, good, etc. on largely

subjective bases) may improve matters, but only if accurate information on

the implant and its materials of construction is made part of the permanent

* As this is written in 2005, it is odd, bordering on the bizarre, that Moss et al. 1991, which is

based upon data that is now 17 years old (!), remains the most reliable source of such data for the

U.S. experience with permanent implants. This stands in stark contrast to many other countries

in which device registries and resultant up-to-date statistics are now available for periods

exceeding two decades of clinical use.

clinical record. Suggestions have been repeatedly made concerning the need

for registration systems for implants in the U.S. so that this information may

follow patients as they move from place to place. Countries with national

health services, such as the U.K., have had some success in developing such

national registries. National systems exist for registration of certain classes

of implants such as hip replacements — for example, in Sweden (from 1979)

and Norway (from 1987).

However, countries with predominantly private health care systems, such

as the U.S., have encountered difficulties in establishing such systems.

Numerous proposals have been made for a national system for all permanent

implants in the U.S. (Black 1996; see also Chapter 22). An important contem

porary effort is one sponsored by the American Academy of Orthopedic

Surgeons (Maloney 2001), but it has been very slow to get under way, even

on a pilot basis, due to concerns about protection of patient confidentiality

(Maloney 2004). Some medical device manufacturers maintain registries of

their products, but access to these is severely restricted. Efforts by profit and

nonprofit private concerns have floundered after a few

years due to their

voluntary and incomplete nature.

I2.1.2 Human Physiology of Biomaterials

One would be quick to discount the knowledge of a nephrologist who based

his or her entire understanding of human renal function on the study of

healthy rats, rabbits, dogs, and an occasional human autopsy specimen.

Fortunately, professional nephrologists have a vast armamentarium of in vivo

tests that permit them to study the physiology of the functioning human

kidney in health and in disease. The biomaterials scientist, when addressing

functioning human implants, lacks all but the most rudimentary of these

capabilities: clinical imagining, using primarily single-plane x-rays. The pH,

pO 2 , interfacial stresses, etc. in the vicinity of a functioning implant and the

ranges of values that assure long-term success or predict imminent failure

cannot be stated with any certainty.

However, it is possible to obtain such data, at least in animal models.

Baranowski and Black (1987) reported repetitive in vivo measurement of pH

and pO 2 , associated with successful and unsuccessful stimulation of bone

growth, near active and inactive implanted stainless steel electrodes in the

tibial medullary canal of rabbits. With care and well-designed protocols, such

techniques could be extended to studies in human subjects, especially with

the increasing development of microcatheters and arthroscopes. Already, as

discussed in Chapter 15, studies are being performed to detect and quantify

metal-bearing species associated with implants in human patients. Early

studies even suggest a correlation between elevations in serum concentra

tions and loosening of implants (Jacobs et al. 1991), although the relation

ships between cause and effect remain unclear.

I2.2 An Example: Total Hip Replacement

Even in the absence of clinical epidemiology and the development of clinical

tests of biomaterials' performance, it is still possible to gain some knowledge

from current clinical experience. A clinical internship and, if possible, con

tinuing contact with a clinical population can be extremely valuable for a

biomaterials scientist or engineer, especially if he or she is prepared to be

observant and analytical in approach. It is probably possible in any clinical

implant application to produce a list of symptoms (radiographic, clinical, or

histological findings) and associated putative mechanisms leading to impli

cations or conclusions concerning the clinical performance

of the implanted

materials. Table I2.1 presents such a triple listing for a frequent orthopaedic

procedure: total replacement of the hip. Note that other device-related clin

ical findings are possible; those listed are believed to be directly referable to

the biomaterials used in or in conjunction with the device rather than to

device design, surgical technique, or patient use factors.

TABLE I2.1

Materials-Associated Findings in Total Hip Replacement
Finding Mechanism Implication

Radiographic

PMMA fragments (early) Operative debris Third-body wear; single-cycle fracture

PMMA fragments (late) Fatigue Third-body wear; cup loosening

PMMA mantle fracture

(early) Inadequate bony support; single-cycle fracture
Stem subsidence; loosening

PMMA mantle fracture

(late) Inadequate bony support; fatigue Stem subsidence; loosening

Broken cerclage wire Fatigue (early) Trochanteric dislodgement, nonunion, wire migration; (late) wire migration

Stem deformation Plastic deformation Change in bony support; inadequate stem size or yield point; impending failure

Stem, cup, or cup screw

fracture Fatigue Manufacturing defect; chronic mechanical overload; (early) inadequate bony support; (late) change

in bony support

Eccentric cup-head

centers Plastic deformation; wear UHMWPE creep; uniform wear; spalling?

Loose metallic debris Wear Third-body wear; fretting (loose component) Fatigue ± corrosion Inadequate processing of porous coating (continued)

TABLE I2.1 (CONTINUED)

Materials-Associated Findings in Total Hip Replacement
Finding Mechanism Implication

Loose ceramic debris Cracking Component impingement, subluxation, recurrent dislocation

Focal lytic lesion a Particle phagocytosis Excessive wear debris; endotoxin? Immune response? Metal sensitivity? (both) Progressive failure?

Progressive dissecting

lesion a Osteoclasis Excessive wear debris; metal sensitivity? Neoplasm?

Clinical

Intraoperative

hypotension Central control Methyl methacrylate (monomer) sensitivity? Fat embolism?

Hip pain a Immune response Venous blockade Metal sensitivity? Excessive wear

Bursa formation Local inflammation Metal sensitivity?

Ectopic calcification Wear debris nucleation? Excessive wear

Dermatitis Delayed hypersensitivity? Metal sensitivity?

Eczema Delayed hypersensitivity? Metal sensitivity?

Bronchospasm Delayed hypersensitivity? Metal sensitivity?

Histologic

Fibrous capsule Local host response Normal response

Histiocytosis with

multinuclear cells Chronic inflammation Manufacturing defect; inappropriate material; excessive wear

Lymphocytic infiltration

with plasma cells Delayed hypersensitivity? Metal sensitivity? Polymer sensitivity?

Fibrosarcoma Neoplastic transformation Chemical neoplasia?

Lymphoma Neoplastic transformation Chemical neoplasia?

Rhabdomyosarcoma Neoplastic transformation Chemical neoplasia?

Malignant fibrous

histiocytoma Neoplastic transformation Chemical neoplasia?

Osteosarcoma Neoplastic transformation Chemical neoplasia?

a In absence of infection.

Note: ? = possible mechanism or implication.

Source: Adapted from Black, J., Orthopedic Biomaterials in Research and Practice, Churchill-

Livingstone, New York, 1988, 319.

I2.3 A Final Word

Many of the basic sciences underlying the field of biomaterials science and

engineering have been neglected. When issues of long-term survival of bio

materials in vivo are considered, the lack of attention to epidemiology and

physiology still remains a key issue. Unless researchers become more careful

and observant of clinical performance, biomaterials may, indeed, as Elaine

Duncan suggested, become endangered species and one will hear more

often, "'And there are no data,' he said."

Baranowski, T.J., Jr. and Black, J., The mechanism of faradic stimulation of osteogenesis, in Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems, Blank, M. and Findl, E. (Eds.), Plenum Press, New York, 1987, 399.

Black, J., Orthopedic Biomaterials in Research and Practice, Churchill-Livingstone, New York, 1988, 319.

Black, J., "And there are no data, he said," Biomater. Forum, 12(4), 9, 1990.

Black, J., Overview of PMS in an international perspective: global developments and global cooperation, Int. J. Risk Safety Med., 8, 3, 1996.

Boretos, J.W., Concise Guide to Biomedical Polymers: Their Design, Fabrication, and Molding, Charles C Thomas, Springfield, IL, 10, 1973.

Boretos, J.W. and Pierce, W.S., Segmented polyurethane: a polyether polymer, J. Biomed. Mater. Res., 2, 121, 1968.

Duncan, E., Editorial: endangered species? Biomater. Forum, 12(3), 4, 1990.

Jacobs, J.J. et al., Release and excretion of metal in patients who have a total hipreplacement component made of titanium-base alloy, J. Bone Joint Surg., 73A, 1475, 1991.

Malchau, H. et al., The Swedish Total Hip Replacement Register, J. Bone Joint Surg., 84A Suppl 2, 2, 2002 (Erratum: J. Bone Joint Surg., 86A, 363, 2004).

Maloney, W.J., National Joint Replacement Registries: has the time come? J. Bone Joint Surg., 83A, 1582, 2001.

Maloney, W.J., Personal communication, 2004.

Moss, A.J. et al., Advance Data No. 191, (PHS) 91-1250. U.S. Government Printing Office, Washington, D.C., 1991.

Stokes, K.B. and Chem, B., Polyether polyurethanes, biostable or not? J. Biomater. Appl., 3, 228, 1988.

Stoppert, J.R. (1989), Letter cited in Duncan, E., Biomater. Forum, 12(3), 4, 1990.

Zhao, Q. et al., Cellular interactions with biomaterials: in vivo cracking of prestressed Pellethane 2363-80A, J. Biomed. Mater. Res., 24, 621, 1990.

Finerman, G.A.M. et al. (Eds.), Total Hip Arthroplasty Outcomes, Churchill-Livingstone, New York, 1998.

Fraker, A.C. and Griffin, C.D. (Eds.), Corrosion and Degradation of Implant Materials: Second Symposium, ASTM Special Technical Publication 859, American Society for Testing and Materials, Philadelphia, 1985.

Hench, L.L. and Wilson, J. (Eds.), Clinical Success of Skeletal Prostheses, Chapman & Hall, London, 1995.

Improving medical implant performance through retrieval information, Current Bibliographies in Medicine, 99-5, National Library of Medicine, Washington, D.C., 2000.

Improving medical implant performance through retrieval information: challenges and opportunities, National Institutes of Health Technology Assessment Conference Summary, Technology Assessment Statement 19, 2000.

Leir, H.K., Casebook: Alien Implants, Dell, New York, 2000.

Syrett, B.C. and Acharya, A. (Eds.), Corrosion and Degradation of Implant Materials, ASTM Special Technical Publication 684 American Society for Testing and Materials, Philadelphia, 1979.

Weinstein, A., Horowitz, E. and Ruff, A.W. (Eds.), Retrieval and Analysis of Orthopedic Implants, NBS Special Publication 472, U.S. Government Printing Office, Washington, D.C., 1977.

Weinstein, A. et al. (Eds.), Implant Retrieval: Material and Biological Analysis, NBS Special Publication 601, U.S. Government Printing Office, Washington, D.C., 1981.

Methods of Testing for Biological Performance

Abbracchio, M.P., Heck, J.D. and Costa, M., The phagocytosis and transforming activity of crystalline metal sulfide particles are related to their negative surface charge, Carcinogenesis, 3, 175, 1982.

ASTM International, Standard practice for assessment of hemolytic properties of materials, F756-00, in 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, PA, 2004.

ASTM International, Standard practice for testing for whole complement activation in serum by solid materials, F1984-99, in 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, PA, 2004.

ASTM International, Standard practice for testing for alternate pathway complement activation in serum by solid materials, F2065-00, in 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, PA 2004.

ASTM International, Standard practice for assessment of white blood cell morphology after contact with materials, F2151-01, in 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, PA, 2004.

Ames, B.N., Identifying environmental chemicals causing mutations and cancer, Science, 204, 587, 1979.

Ames, B.N., McCann, J. and Yamasaki, E., Methods for detecting carcinogens and mutagens with the salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347, 1975.

Ashby, J. and Styles, J.A., Does carcinogenicity potency correlate with mutagenic potency in the Ames assay? Nature, 271, 452, 1978.

Autian, J., Toxicological evaluation of biomaterials: primary acute toxicity screening program, Artif. Organs, 1(1), 53, 1977.

Bélanger, M.-C. et al., Hemocompatibility, biocompatibility, inflammatory, and in vivo studies of

primary reference materials low-density polyethylene and polydimethylsiloxane: a review, J. Biomed. Mater. Res. (Appl. Biomater.), 58, 467, 2001.

Boyden, S., The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leukocytes, J. Exp. Med., 115, 453, 1962.

Charissoux, J.L. et al., Development of in vitro biocompatibility assays for surgical material, Clin. Orthop. Rel. Res., 326, 259, 1996.

Courtney, J.M. et al., Biomaterials for blood-contacting applications, Biomaterials, 15, 737, 1994.

DeSerres, F.J. and Shelby, M.D., The Salmonela mutagenicity assay: recommendations, Science, 203, 563, 1979.

Dillingham, E.O., Primary acute toxicity screen for biomaterials, in Cell-Culture Test Methods, ASTM STP 810, Brown, S.A. (Ed.), American Society for Testing and Materials, Philadelphia, 1983, 51.

Epstein, S.S. and Swartz, J.B., Carcinogenic risk estimation, Science, 240, 1043, 1988.

Forster, R., Mutagenicity testing and biomaterials, in Techniques of Biocompatibility Testing, Vol. II, Williams, D.F. (Ed.), CRC Press, Boca Raton, FL, 1986, 137.

Galin, M.A., Chowchuvech, E. and Galin, A., Tissue culture methods for testing the toxicity of ocular plastic materials, Am. J. Opthalmol., 79, 665, 1975.

Grabowski, E.F. et al., Platelet adhesion to foreign surfaces under controlled conditions of whole blood flow, Trans. Am. Soc. Artif. Intern. Organs XXIII, 141, 1977.

Hallab, N. et al., Hypersensitivity to metallic biomaterials: a review of leukocyte migration inhibition assays, Biomaterials, 21, 1301, 2000.

Hanks, C.T. et al., In vitro models for biocompatibility, Dent. Mater., 12(3), 186, 1996.

Harker, L.A., Ratner, B.D. and Didisheim, P. (Eds.), Cardiovascular Materials and Biocompatibility, Cardiovas. Pathol. 2(3) (Suppl.), 1993.

Hay, R.J., Availability and standardization of cell lines

at the American Type Culture Collection, in Cell-Culture Test Methods, ASTM STP 810, Brown, S.A. (Ed.), American Society for Testing and Materials, Philadelphia, 1983,114.

Homsy, C.A. et al., Rapid in vitro screening of polymers for biocompatibility, J. Macromol. Sci.-Chem., A4(3), 615, 1970.

Johnson, H.J. and Northup, S.J., Tissue-culture biocompatibility testing program, in Cell-Culture Test Methods, ASTM STP 810, Brown, S.A. (Ed.), American Society for Testing and Materials, Philadelphia, 1983, 25.

Kirkpatrick, C.J. et al., Current trends in biocompatibility testing, Proc. Inst. Mech. Eng., 212(H), 75, 1998.

Lindholm, D.D., Klein, E. and Smith, J.K., Relative thrombogenicity of blood interface materials: methods and results, Proc. Dialysis Transplant Forum, 3, 39, 1973.

Mason, R.G., Blood compatibility of biomaterials: evaluation of a simple screening test, Biomater. Med. Dev. Artif. Organs, 1(1), 131, 1973.

Mason, R.G. et al., Blood compatibility of biomaterials: further evaluation of the Lindholm test, Biomater. Med. Dev. Artif. Organs, 2(1), 21, 1974.

McCann, J. et al., Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals, Proc. Nat. Acad. Sci., 72(12), 5135, 1975.

Merritt, K., Immunological testing of biomaterials, in Techniques of Biocompatibility Testing, Vol. II, Williams, D.F. (Ed.), CRC Press, Boca Raton, FL, 1986, 123.

Merritt, K. and Brown, S.A., Tissue reaction and metal sensitivity, Acta Orthop. Scand., 51, 403, 1980.

Mital, M. and Cohen, J., Toxicity of metal particles in tissue culture. Part II: a new assay method using cell counts in the lag phase, J. Bone Joint Surg., 50A, 547, 1968.

Northup, S.J., Mammalian cell culture methods, in Handbook of Biomaterials Evaluation., von Recum, A.F. (Ed.), Macmillan, New York, 1986, 209.

Pappas, A.M. and Cohen, J., Toxicity of metal particles in

tissue culture. Part I: a new assay method using cell counts in the phase of replication, J. Bone Joint Surg., 50A, 535, 1968.

Purchase, I.F.H. et al., An evaluation of six short-term tests for detecting organic chemical carcinogens, Br. J. Cancer, 37, 873, 1978.

Rae, T., A review of tissue culture techniques suitable for testing biocompatibility of implant materials, in Advances in Biomaterials, Vol. 1: Evaluation of Biomaterials, Winter, G.D., Leray, J.L. and de Groot, K. (Eds.), John Wiley & Sons, Chichester, U.K., 1980, 289.

Schmalz, G., Concepts in biocompatibility testing of dental restorative materials, Clin. Oral Invest., 1(4), 154, 1997.

Shanbhag, A.H. et al., Macrophage/particle interactions: effect of size, composition, and surface area, J. Biomed. Mater. Res., 28, 81, 1994.

Skarja, G.A. et al., A cone-and-plate device for the investigation of platelet biomaterial interactions, J. Biomed. Mater. Res., 34, 427, 1997.

Wieslander, A., Magnusson, Å. and Kjellstrand, P., Use of cell culture to predict toxicity of solid materials in blood contact, Biomater. Artif. Cells Artif. Org., 18(3), 367, 1990.

Wilsnack, R.E., Quantitative cell culture biocompatibility testing of medical devices and correlation to animal tests, Biomater. Med. Dev. Artif. Org., 4(3-4), 235, 1976.

Anderson, D., An appraisal of the current state of mutagenicity testing, J. Soc. Cosmet. Chem., 29, 207, 1978.

Autian, J., The new field of plastics toxicology — methods and results, CRC Crit. Rev. Toxicol., 2, 1, 1973.

Brown, S.A. (Ed.), Cell-Culture Test Methods, ASTM STP 810, American Society for Testing and Materials, Philadelphia, 1983.

Douglas, J.F., Carcinogenesis and Mutagenesis Testing, Humana Press, Totowa, NJ, 1984.

Grandjean-Laquerriere, A. et al., Importance of surface area ratio on cytokines production by human monocytes in vitro induced by various hydroxyapatite particles,

Biomaterials, 26, 2361, 2005.

Hanson, S.R., Blood-material interactions, in Handbook of Biomaterial Properties, Black, J. and Hastings, G. (Eds.), Chapman & Hall, London, 1998, 545.

Helgason, C.D. and Miller, C.L., Basic Cell Culture Protocols, 3rd ed., Humana Press, Totowa, NJ, 2004.

Kitchin, K.T., Carcinogenicity: Testing, Predicting, and Interpreting Chemical Effects, Marcel Dekker, New York, 1999.

Kleinschmidt, J.C. and Hollinger, J.O., in Bone Grafts & Bone Substitutes, Habal, M.B. and Reddi, A.H. (Eds.), W.B. Saunders, Philadelphia, 1992, 133.

Moroff, G., Methods for evaluating alterations in platelet and red cell properties, in von Recum, A.F. (Ed.), Handbook of Biomaterials Evaluation, 1st ed., Macmillan, New York, 1986, 233.

Rice, R.M. et al., Biocompatibility testing of polymers: in vitro studies with in vivo correlations, J. Biomed. Mater. Res., 12, 43, 1978.

Venitt, S., Crofton-Sleigh, C. and Forster, R., Bacterial mutation assays using reverse mutation, in Venitt, S. and Perry, J.M. (Eds.), Mutagenicity Testing: A Practical Approach, IRL Press, Oxford, 1984, 45.

Venitt, S. and Perry, J.M. (Eds.), Mutagenicity Testing: A Practical Approach, IRL Press, Oxford, 1984.

von Recum, A.F. (Ed.), Handbook of Biomaterials Evaluation, 1st ed., Macmillan, New York, 1986; 2nd ed., Taylor & Francis, Boca Raton, FL, 2004.

Waters, R., DNA repair tests in cultured mammalian cells, in Venitt, S. and Perry, J.M. (Eds.), Mutagenicity Testing: A Practical Approach, IRL Press, Oxford, 1984, 99.

Wennberg, A. et al., A method for toxicity screening of biomaterials using cells cultured on millipore filters, J. Biomed. Mater. Res., 13, 109, 1979.

Wilson, R.S. et al., Blood-material interactions: assessment of in vitro and in vivo test methods, in Techniques of Biocompatibility Testing, Vol. II, Williams, D.F. (Ed.), CRC Press, Boca Raton, FL, 1986, 151.

Yuspa, S.H., Tumor promotion in epidermal cells in culture, in Mechanisms of Tumor Promotion, Vol. III: Tumor Promotion and Carcinogenesis in Vitro, Slaga, T.J. (Ed.), CRC Press, Boca Raton, FL, 1984, 1. 355

18

In Vivo Implant Models

18.1 Introduction

18.1.1 Approaches to In Vivo Tests

After acute screening by physical or biological in vitro techniques, it is the

practice to test new implant materials, or old materials in significantly dif

ferent applications, in extended-time, whole-animal tests. Although the use

of nonhuman species involves many limitations and compromises, it is the

common judgment that such tests involving the exposure of materials to

systemic physiological processes are a necessary practical and ethical prece

dent to human clinical testing.

With the exception of materials for application in the cardiovascular sys

tem, the site chosen for initial nonfunctional (see Section 18.2.1) testing is

usually in soft tissue. This decision is based on the assumption that cytotoxic

effects have a generality of action and because soft tissue sites can be

approached in animals with relatively minor surgery. For these reasons, the

peritoneal cavity (Wortman et al. 1983) and subcutaneous

“air pouch” (Wil

loughby et al. 1986) have been widely used as sites for acute in vivo screening

studies. For joint replacement or fracture fixation applications, initial implan

tation is in cortical and, occasionally, cortico-cancellous bone. Specialized

sites such as the cornea and the cerebral cortex are used for materials

intended for specific, limited applications.

Chick embryo and fetal rodent models have been used; however, most

testing now uses mature, higher animals. Although still used in multispecies

tests, rodents are rarely used alone since the experience of the Oppenheimers

(see Chapter 13). A variety of sites have been used for chronic testing; the

most popular ones are:

- Subcutaneous
- Intramuscular (e.g., supraspinatus)
- Intraperitoneal
- Transcortical (e.g., femur, tibia, and cranium)
- Intramedullary (e.g., femur and tibia)

Functional testing (see Section 18.2.2) requires a wider range of species

due to the specific requirements of the material or device configuration

selected. No single species presents an ideal general model for the human

species, and some human structural functions, such as

patellar motion, are

not attainable in animal models. Anderson and Hughes (1986) provide a

still relevant overview to the problems of selection of appropriate animal

models.

18.1.2 Animal Welfare

In recent years, the use of animals in medical research has come under strong

criticism from a number of organizations, particularly People for the Ethical

Use of Animals (PETA).* This criticism, strident at times, tends to ignore two

key features of animal use:

- Investigators are generally sensitive individuals concerned about the well-being of their test subjects.

- Sound research applicable to problems of human disability and disease requires that the test subjects, of whatever species, generally be healthy and not subject to avoidable stress (unrelated to the experimental design).

Nevertheless, there is now a well-developed system for monitoring and

controlling animal research in the U.S. The enabling legislation is the Ani

mal Welfare Act (7 USC 2131, December 23, 1985) and a final regulation

issued by the U.S. Department of Agriculture regarding inspection and

compliance (Dept. of Agriculture 1991). The requirements of the Animal

Welfare Act are summarized in an NRC publication (National Research

Council, 1996) that should be on the desk** of any

investigator involved

in research using animals. The central points of this system of regulation

and inspection are:

• Research involving animals may be performed only under a prospective protocol that describes the purpose and significance of the experiment; the species, source, and number of animals to be studied; the procedures to be performed; and the general care and housing conditions of the experimental animals and identifies the personnel involved in animal experimentation and animal care and the qualifications of these personnel.

* http://www.peta.org.

** Also available online: http://oacu.od.nih.gov/regs/guide/guidex.htm.

• The protocol must be reviewed and approved before initiation by an institutional animal care committee, although this review applies only to the animal welfare aspects of the protocol and not the scientific content or objectives of the study.

• The facilities in which surgical and experimental procedures are performed and animals are housed must meet specific minimum requirements.

• The personnel, including students, who conduct the procedures, must be adequately trained and prepared.

• The animal housing facilities and all procedures involving animals must be under the supervision of a veterinarian.

Additionally, standards are set forth concerning specific housing require

ments (cage type, size, etc.) for each species and for the provision of veter

inary care to minimize pain and treat conditions unrelated to the experiment.

The vast majority of U.S. fund-granting agencies and organizations now

require that research proposals be reviewed before submission to determine

that they meet the requirements of the Animal Welfare Act. This is a worth

while and humane system that may at times seem burdensome to the inves

tigator, particularly because some institutional review committees have

experienced confusion when trying (in many cases mistakenly) to balance

concerns about animal welfare against the scientific and technological require

ments of the proposed studies. This occasionally produces the unusual result

of withholding permission to perform procedures on animals that are routine

in human clinical practice, such as multiple procedures on the same individual.

However, such reviews are necessary because of societal requirements and

ethical considerations, and their conduct emphasizes the investigator’s pro

fessional and ethical responsibilities for experimental animals.

If the in vivo testing is intended to support future claims of safety in the

clinical use of the material used in fabricating the animal implants, additional

requirements are imposed by the Good Laboratory Practices (GLPs) regula

tion of the U.S. Food and Drug Administration.* Although these practices

generally describe good procedures for conducting research, three sections

explicitly relate to animal care facilities and the provisions made for care

within them. Although these generally duplicate the provisions of the Ani

mal Welfare Act, the overall requirements imposed by the GLPs make safety

studies difficult to perform in university or other educational settings. Such

studies are often more easily carried out by one of the commercial enterprises

that have sprung up in recent years.

Three additional ethical responsibilities must be emphasized at this point:

• The general obligation is to avoid unnecessary use of animals as experimental subjects. Part of the decision to use an animal model

*

Part 58. should involve careful a priori investigation (and rejection) of alternative approaches (cell culture; mechanical, electronic, or computational simulations; etc.).

• A determination should be made that the experiment has not been done before or that reliable data are not available from other sources.

• Once a determination has been made to use animals and a surgical model has been selected, the experiment should be designed to use the minimum but sufficient number to provide a reasonable assurance of a statistically valid result. Failure to provide adequate prospective statistical design in an animal experiment can lead to the need to replicate the experiment and, in some cases, to use a significantly larger total number of animals than would have been required by a better thought out approach. In this regard, sequential designs that use a few animals to work out experimental design and procedure uncertainties before larger statistically valid main experiments are done are strongly recommended.

The National Institutes of Health (U.S.) now provide an extramural com

petitive grant program for development of alternatives to the use of animals

in drug and biomaterials evaluation. In some areas, this has resulted in

significant progress, as in the development of a number of cell and tissue

culture screening techniques as candidates to replace the Draize rabbit ocular

irritation test (Curren and Harbell 1998). However, more complex clinical

applications, especially those involving blood contact and/or chronic

implantation, will probably always require the use of animal testing before

there is sufficient confidence in safety to conduct initial human studies.

18.2 Test Types

18.2.1 Nonfunctional Tests

Tests divide globally into two types: functional and nonfunctional. In the

nonfunctional type, the implant is of an arbitrary shape, perhaps in a form

required for later mechanical tests of material response, and “floats” pas

sively in the tissue site. Ferguson et al. (1960) popularized the prototype for

such tests. This is a supraspinatus implantation in the rabbit in a cavity

produced by blunt dissection, followed by a 16-week observation period.

This test series formed the basis for a peer-reviewed,

national-consensus

protocol now in use, the F 981 method of the American Society for Testing

and Materials (ASTM, 2004b) (see Chapter 18, Appendix 1).

Nonfunctional tests focus on the direct interactions between the substance

of the material and the chemical and biological species of the implant envi

ronment. The absence of mechanical loads and other elements of function

limits the usefulness of such tests. Thus, they tend to be of short to interme

diate duration, usually a few weeks to 24 months in length. For these results

and those of later functional tests to be useful predictors of biological per

formance in patients, the implants must be in a condition as close as possible

to the physical and chemical condition proposed to be used in the final

clinical application. Care must be taken, especially in cleaning and steriliza

tion, because surface contaminants may affect the host response (Greenfield

et al. 2005).

A typical short-term study of this type is described in the British Standards

Institute Method BS 5736, part 2 (1981). This test protocol utilizes 1- × 10

mm strips of material, with positive and negative controls, implanted by

blunt stylet in the paravertebral (supraspinatus) muscle of the rabbit and

recovered by sacrifice after 7 days. Thus, although it is an in vivo method, it

evaluates only acute soft-tissue response. Turner et al. (1973) have shown

that such a 7-day model, although capable of producing false negatives,

produces no false positives (when compared with local host response to 12

weeks), thus justifying the use of this model for acute in vivo screening. A

similar updated procedure for 7-, 30-, and 90-day studies is F 763 (ASTM,

2004a). To examine more fully the effects of systemic physiology on material

and host response, a longer term study of materials that pass such a short

term in vivo screen is needed.

F 981 (Chapter 18, Appendix 1) illustrates the typical course of such a

longer term study. Standard-sized implants fabricated from the material in

question, as well as one or more well-characterized comparative control

materials, are used. They are selected so as to come close to SA/BW ratios

for major implantation in humans (see Section 15.4.4), at least for soft-tissue

sites. The method uses muscle sites in the rat, rabbits, and larger animals,

as well as femoral transcortical sites, if indicated by the proposed application.

Rats are maintained and sacrificed at 12, 26, and 52 weeks postimplantation.*

Evaluation consists primarily of inspection of the test and control implants

and the sites of implantation.

At present, no control materials for the F 981 protocol are universally

available. The method specifies the use of a number of metals and one

ceramic and one polymer that have a long history of experimental evaluation

and human clinical use as reference or control materials. However, individ

ual variations in composition, surface properties, etc. in these materials make

intertest comparisons difficult. There is considerable continuing interest in

developing positive and negative metallic and polymeric controls that might

be made available through a national program such as the Standard Refer

ence Material program administered by the National Institute of Standards

and Testing (NIST). No reference standards for studies of porous implants

are currently recognized.

* Previous practice had been to use dogs when larger species were needed and to utilize a 2-year

implantation period in addition. Improved understanding of host response has permitted the

routine use of alternative large animal species such as sheep and goats and eliminated the 104

week sacrifice period as redundant in most cases. See SectionX1.9, Appendix 1 (Chapter 18).

Major defects in the design and practice of F 981 have been recognized.

Notwithstanding its strong position as a consensus test method providing

standardized results that can be compared with others (Escalas et al. 1975)*

even when variants from the method are used, these shortcomings must be

recognized. In its concentration on study of the implant site, F 981 overlooks

systemic or remote site effects unless they are extreme enough to produce

visible morbidity or mortality. Thus, remote site neoplastic transformation

will not be seen in this test even if adequate implantation time has elapsed.

Additionally, implantation times are probably too short in the rabbit or dog,

or even the rat, to overcome latency effects (see Section 13.2.5). Furthermore,

for practical reasons, the numbers of test animals used are so small that even

observation of a tumor at the implant site or at a remote site cannot be

evaluated statistically with any acceptable level of certainty. Thus, the

method is unsuited for yielding information beyond the magnitude of the

acute and chronic inflammatory processes and subsequent fibrotic responses.

A question can be raised about the quantitative significance of the fibrotic

response. Measurement of capsule thickness in muscle-site implant studies

tends to show large variances. In most studies, differences must exceed 25

μm to be statistically significant. This result is usually ascribed to “biological”

variation. A study (Kupp et al. 1982) suggests a different explanation. In this

study, sites were identified in the rat hind quarter that produced considerable

motion between implant and muscle (intermuscular) when the leg was

moved passively from full extension to full flexion and that produced neg

ligible relative motion (intramuscular). The relative degrees of motion in the

two sites were verified radiologically. Spherical capped cylindrical implants

of a polyester (PE) and a polyacetal (PA) were placed in each of these two

sites, and capsule mean thicknesses were studied at 21 days. The results are

given in Table 18.1.

A one-way analysis of variance (ANOVA) was performed, using the

method of contrasts. A near significant effect of motion may be seen in the

response to PA (25.1 vs. 14.1 μm) (H 2). However, the greater intrinsic reac

tivity of PE masks this effect (H 1). This greater reactivity may be seen by

comparison of the minimal motion sites, a more usual place for implant

evaluation (24.3 vs. 14.1 μm) (H 3). An apparent additive effect of motion in

the maximal motion implant site masks this difference (H 4). Thus, capsule

thickness seems to reflect the additive response to two factors: an intrinsic

(chemical) activity and an extrinsic (mechanical) activity.

It is clear from this study that relative tissue-implant motion may have a

large influence on the observed capsule thickness. It may be that specimen

geometries should be changed in this type of test or the specimen secured

to the surrounding tissue to minimize such motion variables. Experiments

of this sort are called two-factor experiments because they examine effects

related to chemical and mechanical factors. For more complete evaluations,

* Escalas et al. (1975) used a precursor method, ASTM F 361. See Rationale (X1), Appendix 1

(Chapter 18) for a more complete discussion.

one must move to three-factor experiments that include (or control for)

electrical effects. Thus, in this study, it may have been the case that differing

electrical charge densities at the polymer–tissue interfaces could account in

part for the observed effects.

The findings of Kupp and colleagues (1982) are particularly important

when one is considering host response to the implant’s degradation prod

ucts, such as wear debris or precipitated corrosion

products, rather than to

the implant. Several models utilizing deliberate imposed motion at the

implant–tissue interface demonstrate effects on materials response (Over

gaard et al. 1996) and host response (Howie et al. 1988).

In any case, implant shape must be carefully selected and standardized

for each test protocol to avoid effects on capsule thickness associated with

surface features of the biomaterial. It has long been recognized that sharp

edges on an implant produce a locally increased capsule thickness. Thus,

when a flat-ended cylinder is used (Wood et al. 1970), the familiar dog-bone

shaped capsule results from a local thickening over the circular edges of the

rod ends. This effect has been more generally studied by Matlaga et al. (1976),

and it has been shown that tissue response is inversely related to the included

angle at the edge of the implant. Finally, all soft-tissue sites, in any given

species, are probably not equivalent in terms of the fibrous response evoked

by an implant (Bakker et al. 1988).

One might further point out that observation of capsule thickness is an

indirect measure of cellular response. Dillingham (1983) has shown a good

correlation between capsular response and in vitro cytotoxicity; however, a

useful addition to this type of test might be to evaluate the concentration TABLE 18.1 Interaction of Intrinsic Reactivity and Motion in Implant Capsule Thickness Motion Minimal a Maximal b Material Thickness of Capsule (mean ± S.E.M.) PE 24.3 ± 2.9 μm 31.4 ± 2.7 μm PA 14.1 ± 2.8 μm 25.1 ± 3.5 μm ANOVA Contrasts Hypothesis F Significance H 1 : T pe,min = T pe,max 2.05 p > 0.2 H 2 : T pa,min = T pa, max 3.07 p = 0.125 H 3 : T pe,min = T pa, min 3.01 p = 0.125 H 4 : T pe,max = T pa,max 0.60 p > 0.5 a 0.00 ± 0.07 cm. b 0.18 ± 0.07 cm. Source: Kupp, T. et al., in Advances in Biomaterials, Vol. 3: Biomaterials 1980, Winter, G.D., Gibbons, D.F. and Plenk, H., Jr. (Eds.), John Wiley & Sons, Chichester, 1982, 787.

and spatial distribution of cellular enzymes directly (Salthouse and Williganı

1972; Salthouse and Matlaga 1975).

Even if a refined histochemical evaluation system is not used, it might be

a good idea to evaluate tissue around animal implants in a more detailed

way than simply by measuring capsule thickness. Salthouse (1980) has sug

gested using a scheme that incorporates a number of observations into an

overall index, analogous to the CTI approach of Autian (1977) in his level 1

test scheme. The scheme suggested by Salthouse is a modification of one

proposed by Gourlay et al. (1978), which is based upon the earlier work

of Sewell et al. (1955). An outline of the method is given in Chapter 18,

Appendix 2. The advent of modern image analysis systems now permits the

use of quantitative measures of tissue response (Hunt and Williams 1995);

however, earlier semiquantitative grading scales still remain in use.

In the long run, the most severe criticism of F 981 is its nonfunctional

aspect. Even when this drawback is offset by selecting tissue sites more

typical of the application — for instance, in the rabbit cornea for intraocular

applications — the results remain inferior in providing confidence in pre

diction of human clinical experiences to those obtained from functional tests.

An alternate approach is to isolate the material from the tissue so as to

remove the mechanical features and examine the chemical (and presumably

electrical) effects on cellular aspects of local host response directly. Perhaps

the best known example of this approach is the cage implant system devel

oped by James Anderson and his students (Marchant 1989; Kao and Ander

son 1998). In this case, the implanted material is placed within a wire or

mesh enclosure and, after appropriate sterilization, implanted. This “cage”

will rapidly fill with a mixture of extracellular exudate and inflammatory

cells. The fluid may be sampled from time to time by transdermal puncture

and analyzed for enzymatic and cellular content, and a chronological picture

can be built of the local response to the implant. Although elegant in con

ception and widely applied by its originators, the major criticism of this

approach is that the local host response to the implanted material is that of

cells already exposed to the cage material, which is usually different in

composition and surface condition. Although it is possible to overcome this

problem by fabricating the enclosure from the same material as that of the

test specimen; in the general case this is difficult and costly.

18.2.2 Functional Tests

18.2.2.1 General Requirements and Problems

Functional tests require that, in addition to being implanted, the material,

at least in some degree, be placed in the functional mode that it would

experience in human implant service. This is required to study, for instance,

tissue ingrowth into porous materials for fixation purposes, formation of

neointima in vascular processes, and production of wear particles in load

bearing devices (and possible clinically relevant tissue response to them).

Functional tests are obviously of much greater complexity and cost than

nonfunctional ones. Simple devices have been designed to exert dynamic

loads typical of the desired application on the material. An example of this

approach is the dynamic aortic patch (von Recum et al. 1978) for evaluating

materials for cardiac assist devices in the canine aorta.

Tests of materials for partial or total joint replacements present different

problems. In some cases, small human implants may be used directly, as in

the case of insertion of a phalangeal interphalangeal (PIP) joint in the fore

leg of a cat (Woodman et al. 1983). On the other hand, the design of a

completely functional animal version of the proposed device is frequently

required. Design, fabrication, mechanical testing, and implantation of these

devices may be more difficult than the final production of the device for

human use. In both cases, problems arise from the small size of economically

priced animals, differences in animal anatomy, and the inability of the animal

“patients” to cooperate actively with the experiment.

Despite these difficulties, total hip joint replacement designs, for example,

have been made and tested in rats, cats, dogs, sheep, and goats. Figure 18.1

illustrates the evaluation of a fibrous material for fixation by bony ingrowth.

Initial tests utilized nonfunctional, cylindrical transcortical plugs. This was

followed by implantation of a proximal medullary device that permitted

mechanical “pull-out” testing to evaluate the shear

strength of the interface,

albeit under essentially unloaded conditions. Finally, the material was incor

porated into a custom designed tibial component for a fully functional canine

total knee replacement (Berzins et al. 1994; Rivero et al. 1988).

In some cases, veterinary models of implants exist that can be used as

material test devices. Figure 18.2 is a radiograph of a total hip implanted in

a cat. The femoral component is a modified small size of a canine femoral

(Gorman) prosthesis; the UHMWPE cup was custom designed and is held

in a metallic retainer attached to the iliac crest with bone screws.

In other cases, a human clinical design can simply be scaled down to a suitable

size for an animal. Figure 18.3 illustrates a metallic femoral component designed

for cemented total hip replacement in 450-g rats, maintained at constant skeletal

dimensions by dietary control (Powers et al. 1995). The head diameter is 2 mm;

advantage was taken of rodentine anatomy to implant the devices functionally

(head placed medially) and nonfunctionally (head placed laterally). One of the

advantages of such small implants and test animals is that full histological

sections may be made with the components in place.

Fracture fixation designs have been tested in all of the

species mentioned

earlier, as well as in larger ones such as cows and horses. For such relatively

small devices in larger species, it is often possible to use actual human

dimension prototype models rather than having to produce modified

designs.

Particular problems arise in each of these test methods. Some difficulties,

however, are common to all of them. Considerable interspecies variation is

found in the histological appearance of tissue. Additionally, local tissue

conditions that are abnormal in some species may be chronic in others.

Misinterpretations of test results, insofar as local tissue response and remote

organ condition are concerned, have arisen from the involvement of clinical

(rather than veterinary) pathologists in evaluation of histology from implant

studies. Satisfactory and reliable evaluation of tissue from multispecies tests

can only be achieved by an individual specifically trained in comparative

histology and animal pathology.

The inability of animals to cooperate with treatment has already been

mentioned. Specifically, it is not possible to return an animal to full activity

FIGURE 18.1

Specimens for canine evaluation of fiber metal (titanium) as an ingrowth material. Clockwise

from bottom: transcortical plug, medullary pullout specimen (Ti6Al4V substrate), tibial com

ponent for total knee replacement (Ti6Al4V substrate and pins, ultra high molecular weight

polyethylene articular surface). (From Berzins, A. et al., J. Appl. Biomater., 5(4), 349, 1994; Rivero,

D.P. et al., J. Biomed. Mater. Res., 22, 191, 1988; previously unpublished, used by permission.)

on a planned schedule. The animal will move as it sees fit and set its own

schedule. Similarly, an animal cannot indicate or describe internal problems

of discomfort or pain. Experienced animal handlers may be able to detect

early signs of pain accompanying infection or tissue reaction. More com

monly, these problems are not detected until the animal is systemically ill

or loses function in a limb, or, incidentally, at autopsy. The presence of

culturable infection of any origin at an implant site invalidates any obser

vations on that animal (unless an infectious agent was deliberately intro

duced as part of the experimental plan). Systemic infection imposes a

FIGURE 18.2

Radiography of feline THR. (From author’s research in collaboration with D. Nunamaker.

Implants provided by Richards Manufacturing, now Smith+Nephew Richards, Memphis, TN.)

significant stress on experimental animals, may cause weight loss, and casts

doubts on the validity of observations.

Test animals such as cats, dogs, rats, etc. have shorter life spans and higher

metabolic rates than humans (Brody 1945). Over and above particular vari

ations in physiology, these factors introduce other problems of unknown

magnitude. For instance, what is the appropriate factor by which to scale

down an implant for an animal to experience the same apparent body load

of foreign material as man does (see Section 15.4.4)? Because lifetime as well

as neoplastic transformation induction times are shorter in these animals

FIGURE 18.3

Section of femoral component of a rodentine total hip replacement (~25× magnification). Ma

terial: stem/head F-75 type cast CoCr alloy; cement: F 451 acrylic bone cement. (Component

fabricated by DePuy, Inc., Warsaw, IN; section by L. Smith, Clemson University.)

than in humans, how can these be scaled up to expected human experience?

The importance of this latter point is underlined by occasionally finding

implant site sarcomas in dogs in conjunction with high corrosion rate stain

less steel implants in clinical veterinary practice (see Section 13.5). In dogs,

these have occurred after an average implantation time of

5.8 years. What

is the comparable period in man after which one should expect to see this

type of tumor, if the assumption is that the transformation mechanisms are

the same in both species?

Questions of this type are unresolved and are the subject of continuing

research. A final question related to these interspecies differences is how

long to test before true chronic conditions are realized. Although current

practice is to limit chronic implant models to 1-year duration, this question

remains unresolved on a universal basis. The initial expense of animals and

an annual holding cost for dogs frequently exceeding $2000 per animal make

this last question one of vital importance.

18.2.3 Cardiovascular Functional Tests

18.2.3.1 Material Tests

The previous comments have applied primarily to implants in locations

other than in the cardiovascular system. The nature of such implants is

largely functional and, as in the case of in vitro testing, must be discussed

separately.

In vivo testing in the cardiovascular system is an extension of the ex vivo

or dynamic type of testing previously discussed in Section 17.4.3. The simpler

form of such testing is the use of an implant of an idealized geometry rather

than a full-scale working device. Instead of reproducing the exact functional

design of the implant, a standard design of simple geometry is used to

introduce the material into a vascular process. Patches or daggers may be

attached to the vascular wall in various locations — in some cases with

provision for mechanical loading (von Recum et al. 1978). Sections of blood

vessels may be replaced, often with devices with deliberate flow-disturbing

defects in them such as in the Gott and Kusserow tests.

The Gott or canine vena cava test (Gott and Furuse 1971) is the better

known of these two methods. In this technique, rings 9 mm long by 8 mm

(OD), with a 7-mm-diameter lumen, are surgically inserted to replace a

portion of the inferior vena cava in the dog. The rings may have a small

internal constriction or web to increase blood turbulence. Groups of five

animals are used with implantation periods of 2 hours and, if the initial

group remains patent, 2 weeks. Evaluation is by examining patency of the

rings and degree of coverage by thrombosis on removal.

The Kusserow or renal embolus test (Kusserow et al. 1970) involves replac

ing a portion of the suprarenal aorta with a similar ring. An infrarenal

constriction is produced by partial ligation to force a large portion of the

aortic circulation (an estimated 90%) through the renal arteries into the

kidneys. Groups of five to eight animals are used, with implantation times

of 3 days to 2 weeks. Evaluation is by examination of the rings and histo

logical quantization of kidney infarcts secondary to emboli “shed” by the

implants.

The Gott test appears more severe with respect to adherent thrombi due

to lower flow rates in the canine vena cava than in the aorta, even after

partial ligation. However, the Kusserow test provides better overall evalua

tion because it permits examination of adherent thrombus and remote emboli

(in the kidney primarily), thus more closely modeling human clinical expo

sure.

18.2.3.2 Transitional Tests

A transitional form of this sort of testing may involve the use of a portion

of a clinical design implanted in a different location in an animal. Sawyer et

al. (1976) described an early example. In this study, sections of cardiac cath

eters intended for human clinical use were implanted as segmental replace

ments in jugular and femoral veins of dogs as well as being placed in the

more usual location in the right atrium through right jugular insertion.

This study illustrates a feature common to most cardiovascular tests of the

idealized type; that is, the response at 2 hours after implantation mirrors

and closely predicts that seen at 2 weeks. It is this acute response of the

cardiovascular system to foreign materials that makes functional testing so

difficult. The early events are complicated by the establishment of equilib

rium between material and host and by the events of trauma associated with

implantation, and they are difficult to study due to the requirements to

support the test animal clinically. However, from the point of view of the

test and of the eventual clinical response, the acute response may be the

most important. Thus, it is often said of materials tested in vivo for cardio

vascular applications: “If they will last 2 hours, they will last 2 weeks; if they

will last 2 weeks, they will last 2 years.”

18.2.3.3 Device Tests

The more complex form of functional testing for cardiovascular application

is the evaluation of a material fabricated into a final device design. The costs

and difficulties associated with such tests can be easily appreciated. A major

problem is the same as that which faces evaluation of any human clinical

device: the animal implant site is not the same as the human site, so problems

of comparison and scaling arise. These scaling problems are particularly

acute in the case of blood contact materials because of the relative interspe

cies constancy of the viscosity of mammalian blood. Calves are often used

for such studies; however, their continuing growth usually limits such tests

to 9 months' duration. In the final analysis, materials for cardiovascular

applications can only achieve qualification by tests in actual clinical appli

cations. On the face of it, this may seem to be an insupportable position;

however, it must be recognized that such testing is always based upon two

prerequisites:

- The material must first perform sufficiently well in vitro and in animal tests in which likelihood of success is good and chance of failure is small.

- There must be a real potential benefit to the specific patients involved in this study. (Chapter 19 deals with this point at greater length.)

Functional device tests using typical clinical geometries and methods of

construction and implantation are essential to examine the effects of the

details of construction on response to materials. For

instance, for a new

design, it is difficult to predict the rate of hemolysis that will result from

relative movements of parts in a heart valve and the portion of this that can

be ascribable to materials selection. In this respect, full clinical testing is

highly desirable despite its risks and inherent ethical problems.

18.2.4 Human Tests

In the final analysis, clinical testing is the only technique by which the true

biological performance of implantable biomaterials can be determined. In

short, the only completely valid subject for study is the human being. When

necessary preconditions are met (Chapter 19), human implantation will

begin; the challenge is to obtain data from this experience.

The second consideration cited in the previous section — that is, that any

human clinical experiment must provide a potential benefit to the patients

involved — essentially prevents the use of humans as test subjects for bio

materials per se. There are very rare exceptions to this rule, as in the study

of Hofmann and colleagues (1990) involving patients who were to receive

staged bilateral total knee replacement arthroplasties (TKAs). During the

first surgery, a TKA was performed on one side and plugs of porous implant

materials were inserted in the medial femoral condyle of the opposite knee.

At the second surgery 9 weeks later, the plugs were retrieved and the second

TKA performed without deviation from the technique that would have been

employed in the absence of the experimental implants. This study, which

was approved by a local review committee (see Section 19.2.1) and for which

each patient gave informed consent, probably represents the extreme limit

to which the “potential benefit” principle can be stretched. The need for such

tests is underlined by the observation of the investigators that their results

(ingrowth of bone into porous cobalt- and titanium-base alloy plugs) did not

replicate the responses seen earlier in a canine model (Hofmann 1993).

Although there is a marked lack of study of device function (and biological

performance of the materials involved) in patients (as noted in Interpart 2),

opportunities exist for examination of these issues during device retrieval

studies are provided in Interpart 2; Chapter 22 discusses them in further

detail. Although engineering tests on the device to ascertain, among other

data, the material response are routine, examination of the local host

response is somewhat more difficult. Efforts have been made

to develop

comparative overall scores for local host response in parallel to those used

in animal studies. The “Mirra scale” (Mirra et al. 1976) (Chapter 18, Appendix

3) or modifications of it are still in general use to describe the largely mate

rials-mediated response of patient tissues to partial and total hip and knee

replacement devices. Although it is highly desirable that this scale continue

to be used (so that historical comparisons can be made), more sophisticated

ones are needed, especially as materials and material configurations used in

implanted clinical devices continue to change.

18.3 A Final Comment

As consensus emerges concerning qualification of new materials, better judg

ments about the role that each of the generic test methods will play can be

made. However, animal tests of the functional and nonfunctional type play

a vital part in determining material and host response in the application of

biomaterials. Despite their expense, complexity, and difficulty of interpreta

tion, they will continue to be used for the foreseeable future.

Nevertheless, it is necessary to recognize that the limitations of animal

testing are becoming an increasing problem as clinical experience with estab

lished biomaterials extends. It may be that their use in development and

selection of materials for novel devices and applications should be empha

sized, rather than depending upon them for preclinical qualification for older

materials in established or new devices. For the latter situations, an increased

dependence on studying the actual clinical experience seems preferable.

American Society for Testing and Materials, Standard practice for short-term screening of implant materials, F 763-04, in, 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, 2004a.

American Society for Testing and Materials, Standard practice for assessment of compatibility of biomaterials for surgical implants with respect to effect of materials on muscle and bone, F 981-04, in, 2004 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM International, West Conshohocken, pp. 290ff, 2004b.

Anderson, L.C. and Hughes, H.C., Experimental animal selection, in, Handbook of Biomaterials Evaluation, 1st ed., von Recum, A.F. (Ed.), Macmillan, New York, 1986, 255.

Autian, J., Toxicological evaluation of biomaterials: primary acute toxicity screening program, Artif. Organs, 1(1), 53, 1977.

Bakker, D. et al., Effect of implantation site on phagocyte/polymer interaction and fibrous capsule formation, Biomaterials, 9, 14, 1988.

Berzins, A. et al., Effects of fixation technique on displacement incompatibilities at the bone-implant interface in cementless total knee replacement in a canine model, J. Appl. Biomater., 5(4), 349, 1994.

British Standards Institute, Evaluation of medical devices for biological hazards, BS 5736, Part 2: method of testing for tissue implantation, BSI, London, 1981.

Brody, S., Basal energy and protein metabolism in relation to body weight in mature animals of different species, in Bioenergetics and Growth, with Special Reference to the Efficiency Complex in Domestic Animals, Reinhold, New York, 1945, 352.

Curren, R.D. and Harbell, J.W., In vitro alternatives for ocular irritation, Environ. Health Perspect., 106 (Suppl 2), 485, 1988.

Department of Agriculture, Animal welfare; standards; final rule, 9 CFR Part 3, Fed. Reg. 56(Feb. 15), 6426, 1991.

Department of Health and Human Services, Guide for the Care and Use of Laboratory Animals, NIH Publication 85-23, U.S. Government Printing Office, Washington, D.C., 1985.

Dillingham, E.O., Primary acute toxicity screen for biomaterials: rationale, in vitro/ in vivo relationship and interlaboratory performance, in Cell-Culture Test Methods, ASTM STP 810, Brown, S.A. (Ed.), American Society for Testing and Materials, Philadelphia, 1983, 51.

Escalas, F. et al., MP 35 N: a corrosion resistant, high strength alloy for orthopedic surgical implants: bioassay results, J. Biomed. Mater. Res., 9, 303, 1975.

Ferguson, A.B., Jr. et al., The ionization of metal implants in living tissues, J. Bone Joint Surg., 42A, 77, 1960.

Gott, V.L. and Furuse, A., Antithrombogenic surfaces, classification, and in vivo evaluation, Fed. Proc., 30(5), 1679, 1971.

Gourlay, S.J. et al., Biocompatibility testing of polymers: in vivo implantation studies, J. Biomed. Mater. Res., 12, 219, 1978.

Greenfield, E.M. et al., Does endotoxin contribute to aseptic loosening of orthopedic implants? J. Biomed. Mater. Res., Appl. Biomater., 72B, 179, 2005.

Hofmann, A.A, Bachus, K.N. and Bloebaum, R.D., In vivo implantation of identically structured and sized titanium and cobalt alloy porous coated cylinders into human cancellous bone, Trans. Soc. Biomater., 13, 80, 1990.

Hoffman, A.A., Response of human cancellous bone to

identically structured commercially pure titanium and cobalt chromium alloy porous-coated cylinders, Clin. Mater., 14, 101, 1993.

Howie, D.W. et al., A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles, J. Bone Joint Surg., 70A, 257, 1988.

Hunt, J.A. and Williams, D.F., Quantifying the soft tissue response to implanted materials, Biomaterials, 16, 167, 1995.

Kao, W.J. and Anderson, J.M., The cage implant system, in Handbook of Biomaterials Evaluation, 2nd ed, von Recm, A.F. (Ed.), Taylor & Francis, Philadelphia, 1998, 659.

Kupp, T. et al., Effect of motion on polymer implant capsule formation in muscle, in Advances in Biomaterials, Vol. 3: Biomaterials 1980, Winter, G.D. Gibbons, D.F. and Plenk, H., Jr. (Eds.), John Wiley & Sons, Chichester, U.K.,1982, 787.

Kusserow, B. et al., Observations concerning prosthesis-induced thromboembolic phenomena made with an in vivo embolus shunt test system, Trans. Am. Soc. Artif. Intern. Organs, XVI, 58, 1970.

Marchant, R.E., The cage implant system for determining in vivo biocompatibility of medical device materials, Fund. Appl. Toxicol., 13, 218, 1989.

Matlaga, B.F. et al., Tissue response to implanted polymers: the significance of sample shape, J. Biomed. Mater. Res., 10, 391, 1976.

Mirra, J.M. et al., The pathology of the joint tissues and its clinical relevance in prosthesis failure, Clin. Orthop. Rel. Res., 117, 221, 1976.

National Research Council, Guide for the Care and Use of Laboratory Animals, National Academy Press, Washington, D.C. 1996.

Nunamaker, D.M. and Black, J., Tissue response associated with ingrowth into porous stainless steel, Trans. Orthop. Res. Soc., 3, 160, 1978.

Overgaard, S. et al., Role of different loading conditions on resorption of hydroxyapatite coating evaluated by histomorphometric and stereological methods, J. Orthop.

Res., 14, 888, 1996.

Powers, D.L. et al., The rat as an animal model for total hip replacement arthroplasty, J. Invest. Surg., 8, 249, 1995.

Rivero, D.P. et al., Calcium phosphate-coated porous titanium implants for enhanced skeletal fixation, J. Biomed. Mater. Res., 22, 191, 1988.

Salthouse, T.N., Personal communication, 1980.

Salthouse, T.N. and Matlaga, B.F., An approach to the numerical quantitation of acute tissue response to biomaterials, Biomater. Med. Dev. Artif. Org., 3(1), 47, 1975.

Salthouse, T.N. and Willigan, D.A., An enzyme histochemical approach to the evaluation of polymers for tissue compatibility, J. Biomed. Mater. Res., 6, 105, 1972.

Sawyer, P.N. et al., Experimental and clinical evaluation of a new catheter material, Trans. Am. Soc. Artif. Intern. Organs, XXII, 527, 1976.

Sewell, W.R., Wiland, J. and Craver, B.N., A new method of comparing sutures of ovine catgut with sutures of bovine catgut in three species, Surg. Gynecol. Obstet., 100, 483, 1955.

Turner, J.E., Lawrence, W.H. and Autian, J., Subacute toxicity testing of biomaterials using histopathologic evauation of rabbit muscle tissue, J. Biomed. Mater. Res., 7, 39, 1973.

von Recum, A.F. et al., Biocompatibility tests of components of an implantable cardiac assist device, J. Biomed. Mater. Res., 12, 743, 1978.

Willoughby, D.A. et al., The use of the air pouch to study experimental synovitis and cartilage breakdown, Biomed. Pharmacother., 40(2), 45, 1986.

Wood, N.K., Kaminski, E.J. and Oglesby, R.J., The significance of implant shape in experimental testing of biological materials: disc vs. rod, J. Biomed. Mater. Res., 4, 1, 1970.

Woodman, J.L., Black, J. and Nunamaker, D.N., Release of cobalt and nickel from a new total finger joint prosthesis

made of vitallium, J. Biomed. Mater. Res., 17, 655, 1983.

Wortman, R.S., Merritt, K. and Brown, S.A., The use of the mouse peritoneal cavity for screening for biocompatibility of polymers, Biomater. Med. Dev. Artif. Org., 11(1), 103, 1983.

Anderson, J.M., Biological response to materials, Annu. Rev. Mater. Sci., 31, 81, 2001.

Berry, C.L. (Ed.), The Pathology of Devices, Springer-Verlag, Berlin, 1994.

Department of Health and Human Services, Guidelines for Blood-Material Interactions, NIH Pub. 85-2185, U.S. Government Printing Office, Washington, D.C., 1985.

Gad, S.C., Safety Evaluation of Medical Devices, 2nd ed., Marcel Dekker, New York, 2001.

Greco, R.S. (Ed.), Implantation Biology: The Host Response and Biomedical Devices, CRC Press, Boca Raton, FL, 1994.

Homsy, C.A. et al., Surgical suture-canine tissue interaction for six common suture types, J. Biomed. Mater. Res., 2, 215, 1968.

Horowitz, E. and Torgesen, J.L. (Eds.), Biomaterials, NBS Special Pub. 415, Washington, D.C., 1975.

Leininger, R.L., Polymers as surgical implants, CRC Crit. Rev. Bioeng., 1, 333, 1972.

Loomis, T.A. and Hayes, A.W., Loomis's Essentials of Toxicology, 4th ed., Academic Press, New York, 1996.

von Recum, A.F. (Ed.), Handbook of Biomaterials Evaluation, 2nd ed., Macmillan, New York, 1998.

Revell, P.A., Pathology of Bone, Springer-Verlag, Berlin, 1986, 215.

Schmidt-Nielsen, K., Scaling: Why Is Animal Size so Important? Cambridge University Press, Cambridge, U.K., 1985.

Skurla, C.P. and James, S.P., Assessing the dog as a model for human total hip replacement: analysis of 38 postmortem-retrieved canine cemented acetabular components, J. Biomed. Mater. Res., Part B. Appl. Biomater., 73B, 260,

2005.

Williams, D. (Ed.), Biocompatibility of Implant Materials, Sector Publishing, London, 1976.

Williams, D.F. (Ed.), Techniques of Biocompatibility Testing, Vols. I and II, CRC Press, Boca Raton, FL, 1986.

19

Clinical Testing of Implant Materials

19.1 Goal of Clinical Trials

After material selection, device design, in vitro tests, and implantation in

animals, a material must eventually be tested in humans. Such tests are

necessary because the goal of implant materials development, selection, and

testing is the alleviation of human disability and disease and because knowl

edge about biological performance of materials is insufficient to predict

clinical success with confidence on the basis of only laboratory and animal

testing. In this chapter, some aspects of the design and conduct of clinical

trials will be briefly considered.

Before considering a clinical trial, it is well to consider the goal of such

evaluation. Unless an implant is designed for acute use, trials cannot extend

beyond a short fraction of intended device life. Furthermore, testing a new

or novel biomaterial in a particular device cannot result in qualification of

the material. Therefore, clinical trials must be regarded as serving primarily

as detectors of bad news; in much the same way that canaries in coal mines

warned of impending life-threatening gas concentrations, a clinical trial rep

resents a limited, controlled, well-observed introduction of a new material

and/or design. The use of the term introduction is deliberate because, unlike

in the case of animal trials, the experimental subjects will continue to be

exposed to the device and its material components even after the period of

observation. The longer the time elapsed is and the greater the number of

patients studied during such limited introduction is, without detection of

adverse results, one is entitled to have greater confidence in acceptable

biological performance following general introduction.

19.2 Design of Clinical Trials

19.2.1 General Requirements

Burdette and Gehan (1970) identify four types or sequential phases of clinical

trials:

- Phase I — early trial: selecting a new treatment from among several options for further study
- Phase IIA — preliminary trial: if the new treatment is not effective in the early trial, this phase examines whether further studies should be performed or the treatment abandoned
- Phase IIB — follow-up trial: estimating the effectiveness

of a new treatment that appears promising based upon phase I or phase IIA trials

• Phase III: comparison of the effectiveness of the new treatment with a standard method of management or some other treatment

In the human testing of materials within devices, phases I, IIA, and IIB

are rarely planned in a formal sense. Their function is usually fulfilled by

the use of individual custom devices for selected patients under the direct

care or supervision of the surgeon member of the research group. Only when

the new material/device (usually in comparison to other material/device

arrangements) is perceived to have relative benefit does formal clinical test

ing begin with a phase III trial. This phase in implant development may be

further subdivided into two subphases (Burdette and Gehan 1970):

• Phase IIIA: examination of clinical outcome of a defined new treatment for a group of patients with defined indications

• Phase IIIB: following success in a subphase IIIA trial, examination of the clinical outcome for a defined (refined) new treatment for a group of patients with defined (refined) indications, usually involving multiple investigators and institutions*

It is standard practice in new drug trials to employ the double-blind

method; that is, a drug and a harmless inactive material (placebo) are used

in a treatment plan for a defined group of patients with a common set of

symptoms. Which patients receive the drug and which the placebo is pre

determined at random. Neither the patients (single blind) nor the treating

physician (double blind) knows whether they are receiving the active drug.

When the experimental trial is complete, an identifying code assigned to the

drug and placebo doses is deciphered and an analysis of effectiveness of the

* A very useful source for up-to-date information on clinical trials in the U.S. can be found at

http://www.clinicaltrials.gov.

treatment is made. A further sophistication is employed in some designs:

the treatments for the two groups are “crossed over” or interchanged half

way through the trial. Thus, each subject has a near equal chance of benefit

from the drug and of adverse effects from the drug or the placebo (because

administering the placebo prevents the use of other [previous] drugs known

to have beneficial effects on the patient’s condition).

When an implant is surgically inserted, whatever the phase of the trial, it

is not possible to pair the implanted patient with a placebo-treated patient.

The case of no insertion is clearly not blind to patient or doctor, and it would

not be ethically or practically acceptable in longer term trials. A study com

paring identical devices made of different materials is at

best blind to the

patient. Differences in appearance, weight, shape, etc. between devices made

of different materials usually render them easily distinguishable to the phy

sician and the patient. Furthermore, as is noted in Chapter 21, the interrela

tionship between materials selection and device design is such that it would

be unlikely that the two devices would differ only in respect to materials of

construction. It is more usual that several factors, including surgical tech

nique, are changed. Although this still permits comparison between the old

and new treatments, the effect of materials change is statistically confounded

and thus cannot be observed with any certainty.

Therefore, clinical trials of implant materials must be based upon different

experimental designs. Comparisons may be made as follows:

- Between the condition of the patient before and after implant surgery. This is useful to detect acute changes that may take place in an individual with underlying disease (for which the implant is indicated) that may be associated with response to the implant material.

- Among patients with similar implants made of different materials. When possible, this is useful to investigate acute and chronic differences in material and host responses.

- Between patients with implants and nondiseased (control) individuals of the same age and sex, and with a similar home/workplace environment. This may be useful for detection of subtle chronic effects of materials (host response). Spousal or partner controls are used in many such studies.

A number of efforts have been made to set standards for selection and

treatment of patients in clinical trials. Some of the general rules that have

emerged are:

• Medical care must be under the direction of a medical professional.

• The patients must give informed consent to any experimental procedure. This consent can only be obtained after a full explanation of possible benefits and risks of the proposed procedure in comparison to alternatives, including no treatment.

• The identity of the patients must be protected and the confidentiality of their medical records must be preserved.

• Perhaps the most important point is that, for the trial to be justified, whatever the phase, there must be a reasonable possibility of specific benefit to the patients in the trial combined with reasonable assurance of the absence of unusual risk.

The governing ethical considerations of which these are a part are the 12

basic principles of the Declaration of Helsinki II, revised and extended by

the 29th World Medical Assembly (Silverman 1985).

It is clear that clinical trial protocols for drugs or devices are difficult to

design and implement. As an aid in such efforts, virtually all medical

research and treatment facilities involved with patients maintain Human

Subjects Committees (also known as Internal Review Boards [IRBs]). These

committees are available to help in preparing protocols and generally must

review the procedures and safeguards in any experimental program involv

ing human subjects before the clinical trial is started. Federal agencies now

make such reviews by IRBs a prerequisite to public funding of clinical

research. In addition, many of the Device Classification Panels of the Center

for Medical Devices and Radiological Health (CDRH) of the Food and Drug

Administration (FDA) have developed guidelines for design of clinical trials

and for statistical treatment and format for reporting results. If relevant

guidelines exist in the area under consideration, they should be consulted

at an early point of protocol development.

Although these detailed guidelines are of use, they have now generally

been supplanted by an FDA control document. This arises from the need to

obtain an exemption from certain provisions of the Medical Device Amend

ments (1976) (see Section 20.2) in order to manufacture, ship interstate, and

implant the quantities of implants required for phase III clinical trials.* The

necessary authorization is obtained through a successful (approved) appli

cation for an investigational device exemption (IDE).** The referenced por

tions of the Code of Federal Regulations describe the procedure for

application for an IDE and the responsibilities of the sponsor, investigators,

and Human Subjects Committees (here called IRBs), as well as set standards

for informed consent, protection of patient confidentiality, and reporting of

study results.

It should be further noted that an IDE would not be granted unless the

supporting tests of the type to be discussed later in this chapter, as well as

others, meet the requirements of the regulations on good laboratory practice

* Devices required for earlier phases are manufactured individually at the surgeon's or physi

cian's prescription and are permitted to be used under the custom devices provisions of the

Medical Device Amendments (1976).

** Federal Register 45(13):3732, 1980. See also Dobelle et al. (1980).

(GLP).* These regulations set forth standards concerning design and docu

mentation of preclinical trials, qualification of personnel, and preservation

and presentation of experimental results. Although the GLP regulations

apply only to aspects of testing to support claims of safety at this time, it is

not improbable that they will eventually be extended to apply to all aspects

of preclinical testing, as well as to a wide variety of biomedical research

efforts not directly associated with direct material and

device development.

Before clinical trials of a new material (in a device configuration) can be

countenanced, at least two preliminary types of nonclinical tests of the

material seem imperative. These are in addition to tests that may be required

to demonstrate the safety and effectiveness of the material and the device

design before phase III clinical trials may begin. However, if GLPs are

observed, these preliminary test results may be used as part of a later IDE

application submission.

19.2.2 Preclinical Tests

The first of these two preliminary tests is acute screening based upon in vitro

and tissue culture techniques as outlined in Chapter 17. This area has no

general standards and many different protocols are in use. Completion of

these acute screening trials should lead to a second type of preliminary test,

the chronic animal demonstration test. The ASTM F 981 protocol (Chapter

18) is such a test. Chronic animal tests should essentially meet or exceed the

requirements of F 981. Equivalency to F 981 involves, as a minimum, the use

of:

- Multiple species
- The same control (reference) materials used in acute

testing

• Group sizes and sacrifice schedules substantially equal to or greater than those required by F 981

• Operative sites similar to those of the intended human application

If a material demonstrates that it is equal or superior to materials in present

use in both of these types of tests and no extraordinary hazards specifically

associated with it arise, the planning and execution of phases I and II clinical

trials seems warranted. The requirements for such clinical trials are probably

more stringent than those needed to demonstrate performance of new device

designs. This is the case due to the subtlety of many materials' problems

and the general "endorsement" that a new material may achieve inferentially

after successfully completing its first clinical trial series.

The question of what tests are necessary and sufficient before phase III

clinical trials of new materials are warranted is extremely controversial in

all aspects. It would be very inviting to develop a consensus viewpoint or

* Federal Register 43(247):59986, 1978.

matrix into which all new materials, material combinations, and material

applications could be classified, thus settling the generic problem once and

for all. A number of groups, including working groups

within various U.S.

and foreign national governmental agencies and national standards-making

organizations, are examining this approach to the question. Progress has

been slow, and the end product is clearly a long way away.

The first step was the development of ASTM F 748: Practice for Selecting

Generic Biological Test Methods for Materials and Devices. The standard

contains a recommended test matrix that distinguishes among external

devices, external communicating devices, and implants, and between tissue

types and contact periods (Figure 19.1). When originally written, generic

host response tests, including an F 981 type chronic implantation test, were

recommended for each exposure class. Although the tests were defined

generically, the ASTM F-4 committee has gone on to recommend specific test

procedures in each area that are now incorporated by reference (Table 19.1).

The success of this voluntary practice, originally adopted in 1982, led to

the so-called Tripartite Biocompatibility Guidance (TBG) (Kammula 1991),

which was ratified on April 24, 1987. This document was developed by a

joint U.S., Canada, and U.K. working group and was intended to assist

manufacturers and government health agencies in the three

countries in

anticipating the information necessary for preclinical evaluation of new

materials. The TBG retained the matrix approach of F 748, deleted the dis

tinction between contact periods (intraoperative, short term, or chronic) and

added several additional possible tests, including determination of the phar

macokinetics of released material (“biological fate”) and of reproductive and

developmental toxicity. Unlike F 748, the TBG does not refer to specific

recommended test methods but simply puts forward recommended aspects

of such tests.

The formation of the European Economic Union (EU), effective at the end

of 1992, led to interest within the International Standards Organization (ISO)

in producing a systematic approach to selection of tests for biological eval

uation of materials. This standard (ISO 10993-1, 1991) was drafted by Tech

nical Committee 194 and draws very strongly on the TBG, which it has

effectively superseded. In fact, it uses a similar matrix and recommended

tests but restores the exposure classes of F 748 by distinguishing among three

conditions:

- Limited exposure (≤24 hours; includes intraoperative)

• Prolonged or repeated exposure (>24 hours but <30 days) (= short term)

• Permanent contact (>30 days) (= chronic)

In addition, the ISO guidance document is somewhat subtler in its

approach in that it distinguishes among nine initial and four supplementary

evaluation tests. This approach recognizes the criticality of nine initial tests,

Recommended Applicable Tests Classification of Material or Device and Application C e l l C u l t u r e C y t o x i c i t y S e n s i t i z a t i o n S k i n I r r i t a t i o n / I n t r a c u t a n e o u s M u c u s M e m b r a n e I r r i t a t i o n S y s . T o x i c i t y — A c u t e / S u b c h r o n i c B l o o d C o m p a t i b i l i t y H e m o l y s i s P y r o g e n i c i t y I m p l a n a t a t i o n — S h o r t T e r m I m p l a n t a t i o n — L o n g T e r m I m m u n o g e n i c i t y G e n o t o x i c i t y C a r c i n o g e n i c i t y

External devices Intact surfaces (all time periods) X X X

Breached surfaces Intraoperative X X X Short term X X X X Chronic X X X X X

External devices communicating with

Intact natural channels Intraoperative X X X X Short term X X X X X X Chronic X X X X X X X X X

Body tissues and fluids Intraoperative X X X X A Short term X X X X A X X Chronic X X X X A X X X X

Blood path, indirect Intraoperative X X X X X X X Short term X X X X X X X Chronic X X X X X X X X X

Blood path, direct Intraoperative X X X X X X X Short term X X X X X X X X Chronic X X X X X X X X X X

Implanted devices principally contacting

Bone/tissue/tissue fluid Intraoperative X X X X Short term X X X X X X Chronic X X X X X X X X X

Blood Intraoperative X X X X X X X Short term X X X X X X X

X X X Chronic X X X X X X X X X X X X

Notes: X: recommended; A: may be considered (especially for central nervous system); intraoperative: < 24 hours; short term: up to and including 30 days; chronic: >30-days. Consult standard for definitions of tissue types.

FIGURE 19.1

Selection of preclinical tests (ASTM F 748 Recommended Practice) (Adapted from ASTM F

748-04, ASTM Annual Book of Standards, Vol. 13.01, ASTM International, West Conshohocken,

PA, 2004 (see Table 20.3).

excluding chronic toxicity and carcinogenicity, for the majority of short- and

intermediate-term applications; it makes no recommendations concerning

testing for reproductive and developmental toxicity and the biological fate

of degradation products, except for an application-by-application consider

ation.

Comparing ISO 10993-1 and ASTM F 748, one observes that the former

emphasizes cytotoxicity, sensitization, and intracutaneous irritation more

than the latter. In addition, ISO 10993-1 is less tailored to differences in

exposure class. This probably reflects the overall EU regulatory outlook that,

in comparison to the U.S. approach, depends less on preintroduction testing

and more on clinical observation of outcomes of materials (and device) use.

Finally, ISO is following the example of F 748 and

developing specific test

methods for many of the 13 generic test categories used in its selection matrix

(published as additional parts of standard ISO 10993).*

Although the matrix approaches taken to date in ISO 10993 and ASTM F

748 are extremely beneficial, the ideal generic test selection matrix should

incorporate the following criteria:

1. Separation of test requirements by the following technical aspects: a. Type of tissue that the implant will contact (muscle, blood, etc.) TABLE 19.1 Test Methods Referred to in F 748-04 Test Type (per F 748-04) Recommended Test Protocol Cell culture cytoxicity F 813, F 895, F 1027, F1903 Sensitization F 720 F 2147, F 2148 Skin irritation or intracutaneous F 719 Mucus membrane irritation F 749 a Systemic toxicity, acute or subchronic USP, F 750 Blood compatibility F 2151 b Hemolysis F 756 Pyrogenicity USP, LAL Short-term implantation F 736, F 1408, F 1904 Long-term implantation F 981, F 1983 Immunogenicity F 1905, F 1906 Genotoxicity c Carcinogenicity F 1439 Notes: For USP, see Section 20.2.1, for F XXX, see Table 20.3. LAL: limulus amebocyte lysate test. a In suitable animal/tssue. b See also tests for complement activation (F 1984, F 2065). c No single test agreed. Sources: Ross, V.C. and Twohy, C.W., Prog. Clin. Biol. Res., 189, 267, 1985; Munson, T.E., Prog. Clin. Biol. Res., 231, 143, 1987.

* Subsequent revisions over the years suggest that eventually no useful distinctions will be pos

sible between F 748 and IS 10993-1. b. Duration of implant, by classes of time intervals (short-term, intermediate-term, etc.) c. Relative exposure of materials to the patient’s body (SA/BW ratio, etc.)

2. Selection of tests by generic description (with minimum requirements) rather than by detailed specification of procedures

3. Specification of levels of certainty (“confidence levels”) rather than setting specific sample or group sizes in individual tests

The ISO standard addresses some but not all of these concerns. In particular,

it fails to deal with 1c and 3. Great care must be taken in defining specific

test methods for host response in this context. Although the intent is clear

to set minimum requirements, the high cost of testing often converts these

minima into maxima. In the case of new classes of materials, this may permit

subtle but deleterious aspects of host response to be overlooked.

In practice, it appears that F 748, the TBG, and ISO 10993 have not been

strictly adhered to; that is, they appear to serve a useful role as benchmarks

by defining the consensus minimum preclinical testing required. Industrial

sponsors tend to develop their own test matrices, involving additional test

ing, based upon these views (Stark 1991).

19.2.3 Clinical Trials

Finally, the time will arrive when confidence in a new material has risen

sufficiently that clinical trials can be begun with caution. Clinical trials must

be performed under the control of a defined (written) prospective protocol

that includes the following provisions:

- Description of the implant device (note that the implant site must be that of the proposed application)

- Outline of indications for the surgical procedure

• Outline of the uniform surgical procedure used

• Outline of postoperative treatment

• Outline of follow-up schedule and postoperative evaluation techniques

The following information is needed for adequate consideration and eval

uation of clinical testing results (with respect to biological performance of

materials):

• Protocol as listed previously

• Identification of 200 patients, by code number, who constitute consecutive individuals seen by the treating physician and meet item 2 of the protocol

• Results of follow-up of these patients for a minimum of 5 years and average of 7 to 10 years for those not lost to follow-up at an earlier date (minimum of 100)*

• Summary of all adverse results (note that a statistical summary is desirable; individual results with code should not be reported)

The last point should be dwelt upon. Presumably, at the time at which the

trial protocol was being developed, consideration was given to each of the

questions to be asked and the statistical measures to be used in answering

them. At the end of the trial, it is thus appropriate to suggest that statistical

measures be employed. Therefore, reports of clinical trials should take care

to:

• Discuss accuracy and precision of all measurements, where possible.

• Define a minimum confidence level for all statistical measures of the data, usually p <0.05.

• Report confidence intervals or other measures of significance associated with all derived parameters.

• Indicate the significance of any conclusion arrived at by analysis of the trial.

19.3 Conclusions from Clinical Trials

19.3.1 Introduction

As pointed out in Interpart 2, no clinical trial can approach the numbers and

period of exposure that will be experienced when a material enters into

general use. Thus, in a sense, it is imperative that clinical testing never end.

The treating physician and his consultants should distinguish between new

and old materials and should continue to be sensitive to possible biological

performance problems associated with the use of either kind.

A well-designed and conducted clinical trial does not serve to qualify a

material. In addition to design studies, physical measurements, and acute

and animal tests, it provides data that are required for a decision to release

a product for general use. The decisions made along the path to release

* In practice, it is difficult to distinguish material trials from device trials. Unfortunately the de

facto standard for device trials is only 2 years' minimum follow-up, and no additional follow-up

is generally recommended in the case of new materials. This is grossly inadequate for the eval

uation of new materials.

should all be based on appropriate statistical tests at a minimum confidence

level of 95%. Such release, when it occurs with the approval of the appro

priate regulating agencies, is necessarily a risk. That is, the benefits attendant

to the use of the device incorporating the material in question are felt at the

moment of decision to outweigh the risks involved.

Throughout this book, aspects of biological performance, including

material and host response, have been considered. The latter sections of this

work have begun to examine the details of test methods for examining

biological performance leading to clinical use. Two factors are common to

all of these methods:

- Large investments of time and money are required to produce results with reasonable levels of reliability and statistical significance due to the variability of the biological systems involved.

- Large quantities of inductive reasoning must be used to apply the results of in vitro and animal testing to the prediction of clinical performance.

These two general conclusions overshadow all considerations of clinical

testing and introduction into routine clinical use of new materials or old

materials in new designs or applications.

19.3.2 Complication Incidence Rates

In discussions of clinical evidence for materials incompatibility (failure to

exhibit adequate levels of biological performance), time and again, incidence

rates of complications are small. For instance, the “variant poppet” problem

in early heart valve designs probably did not affect more than 3% of patients

receiving the prosthesis. The more adverse experience with an early design

of an anterior cruciate ligament replacement prosthesis (Chen and Black

1980) resulted in failure in a larger percentage of cases, but still probably

less than 20%. In many high-use applications, such as total hip and knee

joint replacement, device-related failures for all causes, including failure of

biological performance, are now appreciably less than 1% per year after

surgery.

Why then is the concern expressed here for examining biological perfor

mance? A manufacturer could fairly argue that modern implant materials

have proven beneficial for 95 to 99%+ of patients receiving them. Similarly,

a study by the Carnegie-Mellon Institute of costs and benefits associated

with research to improve then current orthopaedic prosthetic devices con

cluded that failure/complication rates, even in the 1970s, were acceptably

small and that the investment required to reduce these rates significantly

would be costly out of proportion to the resulting benefits (Piehler 1978).

This remains clearly the case today, with an additional problem: in some

cases, such as total hip replacement, present technology is so successful that,

even if they are actually superior to current choices, newer developments,

such as changes in the materials of the articulating wear pair, cannot rea

sonably be expected to demonstrate statistical superior clinical outcomes due

to practical limitations on size and duration of clinical trials (Black 1996)

Thus, one is faced with the problem that one cannot define a failure or

complication rate during clinical trials and that such a rate, a priori, could

not be judged to be acceptable except in extreme cases. How then is one to

decide when a material has proven itself sufficiently, with respect to biolog

ical performance, to move into general use?

19.4 Aspects of the Decision for General Clinical Use

19.4.1 Current Concerns

I believe that it is necessary to address this question in two frames of refer

ence. The first is the current medical/legal environment. The general argu

ments cited earlier concerning cost of additional testing and the “acceptable”

level of performance of current devices were raised time and again during

the hearings on the Kennedy (U.S. Senate) and Rogers (House of Represen

tatives) bills that resulted in the Medical Device Amendments of 1976 (see

Section 20.2). However, they were more than offset by the force of individual

testimony concerning the human and financial costs to individuals as a result

of device malfunction and failure. Thus, although statistical failure rates are

low, the failure rate in a given individual with a defective device is perceived

as 100%. Despite the implementation of the 1976 legislation, continuing

concerns about the impact of individual device malfunction and failure led

to two subsequent safe medical devices acts (1990, 1992) (see Section 20.2).

This humane view of individuals rather than average statistics has resulted

in a dramatic rise in medical malpractice and damage suits associated with

device failure. A typical early report* summarizes five suits concerning

“defective” heart valves. Only one of the five alleged defects was connected

with the death of a patient; the damage claimed in the other four cases was

disability and the need for additional surgery. Total damages sought in the

five cases were $55 million. Although the final outcome of

such cases will

not be known for some time, malpractice/device failure awards have already

exceeded $1 million in individual nonfatal cases and, by 1990, new cases

were being filed at a rate of 900/day, with average final awards of $300,000

(Kiplinger 1991).

As reflected in congressional testimony and in the results of malpractice

suits, public opinion contributed in no small part to the formula adopted in

the Medical Device Amendments (1976). The test of adequate performance

laid out in this law is that the device be “safe and effective” and expose the

* The New York Times, Dec. 4, 1977.

patient to no “unreasonable” risk or hazard. Thus, decisions on what will

be acceptable failure rates remain subjective and depend on the continued

interaction of public opinion, expert advice, and administrative action.

Individuals are torn between two views. The heart says that no failure is

acceptable, especially if it were to happen to oneself or to one dear to one.

The head says that such a goal may be unattainable and approachable only

at prohibitive cost.

19.4.2 Response to Current Concerns

The search for a defect-free materials technology for

medical and surgical

implants and devices has a precedent. Early in the development of intercon

tinental ballistic missiles, it was recognized that, in the normal course of

events, the complexity of the electronic control systems required would lead

to nonfunctioning systems. That is, the level of reliability of individual elec

tronic components, then exceeding 99.9%, was insufficient to permit systems

with 10 6 to 10 8 components to have any real level of satisfactory performance.

Two approaches were taken to deal with this problem. The first was the

idea of redundancy. Each section of a control system was to have one or

more “backup” sections that operated in support or in parallel and could

take over if the primary system failed. This led to the practice in the present

space shuttle program of having three (and in some cases four) parallel

systems serving each critical function.

The second approach was to adopt the position that no absolute level of

performance for an individual component was definitively acceptable. This

latter view led to a highly successful initiative, first instituted by the Mar

tin-Marietta Company (Denver) and later by the U.S. Air Force and NASA,

called the Zero Defects Program. The basic concept is to

test devices con

tinually, even after they pass into active service, and feed the results back

into product improvement with a view to eventual “100%” satisfactory

performance through evolutionary change. The combination of these two

approaches contributed to the success of the Apollo Lunar Program and

the continued high level of performance of civilian and military aerospace

hardware.

I suggest that both of these concepts and an additional idea of a fail-safe

product can be applied to considerations of biological performance in the

current environment. The idea of redundancy is hard to apply directly

toward the design of devices for a number of reasons. It is applicable to

active devices, such as heart pacers, but far less so to joint replacements,

sutures, etc. However, redundancy can be incorporated into materials and

device testing. The F 981 protocol already does this to a degree in its use of

multiple animal species. Despite efforts to the contrary, multiple, parallel,

and overlapping tests should be continued, driven in part by financial con

siderations and in part by greater, perhaps misplaced, confidence in short

term test results.

The concept of zero defects can be incorporated into clinical evaluation

and experience by refusing to accept any given level of performance as

permanently satisfactory. Thus, one can insist that performance equal to or

better than that of materials in use today be demonstrated before new mate

rials can go into clinical trials and routine use. However, this should not

blind one to the need to examine the performance of current (old) and future

(new) materials constantly with a view toward continual evolutionary

improvements where and when possible — thus the emphasis in Interpart

2 on increased attention to the human epidemiology of biomaterials.

The third idea of a fail-safe product can also be adopted. This is the concept

that the ill effects of the failure of a device to function in its intended mode

may be minimized by design* provisions. An example of fail-safe design in

everyday life is the Westinghouse type AB air brake used on railroad cars.

If the train separates at a coupling or the brake control system fails, the

system is designed to apply the brakes automatically in the individual cars

and to maintain braking until each system is manually released and reset.

In fracture fixation applications, such a concept might

lead to the choice of

a material with lower strength and higher ductility, such as a stainless steel,

over alloys with higher strength but limited ductility. Here the fail-safe

feature is that the observation of permanent deformation of an internal

fixation device can lead to a change in external support prescribed by the

physician. Even though it may result in an angulation in the healed fracture,

the “failed” situation for a device fabricated from a ductile material (that is,

angulation) is far more acceptable to patient and physician than the “failed”

situation for the less deformable device — acute device fracture — that may

lead to additional disability, surgery, and, possibly, legal action.

19.4.3 Future Concerns

The second frame of reference that should be briefly examined with respect

to cost/risk/benefit aspects of material introduction is that of the future.

How can one judge when a new material or device is ready to enter use and

perhaps supplant present, apparently less effective products?

I think the answer is rather simple. If the ideas of safe failure modes in

design, redundancy in testing, and, especially, continual evolutionary per

formance improvement are adopted, a real distinction

between old and new

materials will no longer be present. No one would knowingly substitute an

inferior new product for a current product unless driven by inhumane

motives. With this in mind, I hope that progressive attitudes on the parts of

researchers, manufacturers, surgeons, and regulatory authorities will lead to

a continual upgrading of the performance of current materials and the grad

ual introduction of new materials when subjective levels of safety and effi

cacy, most probably defined by then-current experience, are reached.

* See Chapter 21 for a discussion of the materials' design process.

Critics would suggest the need for some absolute (minimum) level of

safety that must be obtained before introduction of a new material. With

respect to devices, it has been proposed that the following definition be used:

"A device is safe enough to use when it is no worse than others in use and

presents no greater hazard than the condition it is to be used to treat." This

appears clear enough in instances in which large improvements in devices

(and materials) can be demonstrated and the conditions treated are life

threatening. In situations in which a new material represents an evolutionary

change in composition and/or processing and in subsequent behavior and

the aim is to improve the quality of life of the patient by alleviating a

condition of low mortality and morbidity, such a statement is a poor guide.

Hazards may be of a new and noncomparable type. Meaningful comparison

of hazards, in any case, is possible only when potential outcomes differ

greatly. Thus, I suggest that decisions on device and materials introductions

must be made on the individual merits and demerits of each situation and

not shackled by a set of rigid rules.

Except at an early point in this discussion, I have said nothing about the

costs associated with this approach to materials application in the medical

and surgical field. This was deliberate. I suggest that the analyses of the type

made by Piehler (1978) and others fail in the face of the human and emotional

aspects of this field. As long as the financial costs of devices remain a

relatively small component of the true cost of disease and disability, includ

ing the cost of health care (as they currently are in the U.S.), money should

not be an important factor in these considerations. In individual cases, it is

clear that the increased cost of research, development, and testing of mate

rials and devices that is the legacy of the Medical Device Amendments and

the Safe Medical Devices Acts, the increased number and size of malpractice

and product liability suits, and increased public attention will act to stifle

innovation. A situation parallel to that in the drug field has developed: an

improvement in the nature of products newly introduced and a tendency to

move research and development activities “offshore.” It is hard to pass

judgment on this continuing development. Whether it is good or bad, it is

coming about in response to a clear public demand for safe and effective

materials for medical and surgical implants and devices.

One can pass judgment, however, on the increasing trend towards market

driven rather than technology-driven introduction of new devices and mate

rials. Clinical experience with many existing materials now exceeds three

decades; thus, it is very difficult to argue that short-term (2- to 5-year) testing

of new materials is capable of revealing subtle or long-term defects in them

or, more directly, of providing the information needed to determine whether

the new material is equal to or exceeds the performance of the older material

that it may replace simply on a novelty basis. A Gresham’s law appears to

be operating in the development of medical and surgical devices and their

materials through which novelty has a market value. The drive to use new

materials is depriving patients of the proven performance of older ones. In

a free market system that provides many benefits and maximizes individual

freedom, it is hard to see how such a situation can be corrected. Physician

and patient education, more sophisticated regulatory approaches, and eco

nomic restrictions imposed by widespread recognition of the need to curtail

the growth of medical expenses may help. However, one can expect to avoid

future problems associated with inadequate biological performance of mate

rials in patients only through the bioengineer's endorsement of the Hippo

cratic injunction to, in the first place, do no harm.

19.5 Final Comments

One of the chronic problems that the materials scientist or engineer encoun

ters in the medical device clinical literature is an inability to determine from

what materials devices were made and, even if that is possible, the details

of composition, processing, etc. selected within the generic material. For this

reason, I suggest that a radical change is needed in how the clinical use of

materials is viewed. The clinical introduction of a

material should be viewed

more as the beginning of the qualification process rather than the end of it.

Studies of retrieved devices have helped to provide information concerning

biological performance in actual clinical settings. In the last two decades,

such studies have slowly been extended from examination of clinically

retrieved failed devices to study of successful devices obtained at autopsy

or, in some cases, still in use. However, lacking reliable incidence and prev

alence data, such studies tend to be isolated examples of numerators for

which reliable denominators are, as yet, unavailable. Therefore, it seems

advisable to be at least as serious about durable medical devices, especially

chronic (>30-day) implants as one is about motor vehicles and devise some

form of internationally acceptable registration and tracking system. Chapter

22 discusses early efforts towards this goal in the U.S.

To further illuminate this need, consider two situations: the first use of an

adapted or new material as a biomaterial and the subsequent use of that

material in a second design or application. In the first case, the device

designer, surgical developer, IRB, and regulatory agency are all tempted to

ask, “Is the material biocompatible?” The main thrust of

this work is to

suggest that the more appropriate question is, “What is the predicted bio

logical performance of the material in the intended application?” The answer

to this question is then approached through theoretical and practical con

siderations, laboratory testing, and a progression of in vitro and in vivo

biological testing before clinical evaluation, as described in this chapter,

begins. However, the second case is different. The material has been in

clinical use now for some years and the questions that need to be asked and

answered are different. Now actual experience can be drawn upon — unfor

tunately not with the material but with devices fabricated in part or in whole

from it.

Each component of an implant has three elements: a functional element,

a connectional element, and a structural element. That is, each component

has a desired function in relation to its site of implantation, a method of

connecting it to the surrounding tissues so that it remains in the intended

site and orientation, and a structural aspect to preserve the spatial relation

ship between the sites of connection and of function. In some cases, compo

nents may consist of a single material that can constitute

all three elements,

such as a monofilament surgical suture. In other cases, different materials

may be joined in a single component, with each contributing one or more

of these elements. For instance, a femoral component of a hip replacement

may have an articulating ceramic head and a metal intramedullary stem

with a porous ingrowth fixation coating to attach it to bone.

Now suppose that a material has been in use as an articulating (functional)

element in the hip, but using it as an articulating element in the shoulder is

desired. The temptation is to revert to the initial question of biological per

formance. However, this is not logical because there is (or should be) infor

mation on the actual, rather than conjectural, performance of the material in

the biological environment of a human joint — in this case, one fairly similar

to that of the new application (hip vs. shoulder). Then the appropriate initial

question becomes, “What data and clinical experience support the assertion

that the material in question will prove safe and effective in the proposed

(new) clinical application?”

A study leading to answering this question now should have the following

charge: Considering the material in question (a ceramic

used for femoral heads in the hip), in the proposed design in the proposed application (prosthetic replacement of the humeral head), find and analyze the laboratory and clinical predicates that support the assertion that its use will meet appropriate regulatory standards for safety and effectiveness.*

The analysis then proceeds through the following secondary questions:

• For each component of the proposed design fabricated in whole or in part from the material in question, the question is "What are the laboratory and clinical predicates for friction and wear, structural integrity, and fixation (including possible adverse local and systemic reactions to wear debris and other degradation products) that would

* Safe and effective are foundational descriptors in medical device regulation. However, as is the

case for biocompatibility, they cannot be defined or determined on absolute bases. Therefore, sat

isfaction of locally prevailing regulatory definitions and standards provides the usual test, rather

than any intrinsic de novo considerations. Note, however, that in U.S. experience, no legal con

nection exists between a regulatory decision that a device is safe and effective for a given set of

indications and the actual observed clinical performance. This issue has been extensively liti

gated, pro and con. However, this complex topic is beyond the scope of this work. For general

regulatory considerations, see Chapter 20. lead one to conclude that this design in the proposed clinical application will be safe and effective?"*

• For interfaces between such components and other components of the proposed design, the question is "What are the predicates to support the assertion that the use of the material in question will not produce clinical outcomes inferior to those experienced with materials now in general clinical use in the proposed market?"

It should be clear that the ability to answer this progression of questions

depends acutely on the quality and quantity of data that exist concerning

the actual material in question, its material and host responses in patients,

and the overall clinical outcomes as a function of time. In this situation, it

should be remembered and taken to heart that data are not the plural of

anecdote.

F 748-04 Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices, ASTM Annual Book of Standards, Vol. 13.01, ASTM International, West Conshohocken, PA, 2004.

F 981-04 Standard practice for assessment of compatibility of biomaterials for surgical implants with respect to effect of materials on muscle and bone, ASTM Annual Book of Standards, Vol. 13.01, ASTM International, West Conshohocken, PA, 2004.

Black, J., Metal on metal bearings: a practical alternative to metal on polyethylene bearings? Clin. Orthop. Rel. Res., 329S, S244, 1996.

Burdette, W.J. and Gehan, E.A., Planning and Analysis of Clinical Studies, Charles C Thomas, Springfield, IL, 1970.

Chen, E.H. and Black, J., Materials design analysis of the prosthetic anterior cruciate ligament, J. Biomed. Mater. Res., 14, 567, 1980.

Dobelle, W.H. et al., How to comply with the Food and Drug Administration's new "investigational device exemption (IDE)" regulations, including an application form, Artif. Organs, 4(4), 1, 1980.

International Standards Organization, Biological testing of medical and dental materials and devices, Part 1: guidance on selection of tests. ISO/DIS 10993-1:1994. ISO, Switzerland.

Kammula, R.G., Tripartite biocompatibility guidance for

medical devices, in Biocompatibility Workshop Notebook, Duncan, P.E. and Wallin, R.F. (Eds.), Society for Biomaterials, San Antonio, TX, 1991.

Kiplinger, A., The Kiplinger Washington Letter, 68(20), 4, 1991.

Munson, T.E., FDA LAL guideline — update, Prog. Clin. Biol. Res., 231, 143, 1987.

* Note that the question has been specialized for the application: friction and wear reflect the

functional element of this application; structural integrity the structural element, and fixation

the connectional element; the listing of possible adverse observations reflects a general under

standing of clinical performance of joint replacements.

Piehler, H.R., Regulating orthopedic surgical implants, Orthopaedic Rev., 7(1), 75, 1978; effect of FDA Medical Device Amendments on the benefit and cost of implants, (2), 65; better data acquisition and analysis are needed to pinpoint device failure sources, (3), 97; orthopedic implant retrieval studies document a part of failure story, (4), 79; orthopedic surgeon and patient play important roles in success of implant, (5), 99; FDA Medical Device Amendments regulation of orthopedic implants is misdirected, (7),103, 1978.

Ross, V.C. and Twohy, C.W., Endotoxins and medical devices, Prog. Clin. Biol. Res., 189, 267, 1985.

Silverman, W.A., Human Experimentation: A Guided Step into the Unknown, Oxford University Press, Oxford, 1985.

Stark, N.J., How to organize a biocompatibility testing program: a case study, Med. Dev. Diag. Ind., 13(6), 68, 1991.

Fleiss, J.L., The Design and Analysis of Clinical Experiments, John Wiley & Sons, New York, 1986.

Friedman, L.M. et al., Fundamentals of Clinical Trials, 3rd ed., Springer, New York, 1999.

Plantadosi, S., Clinical Trials: A Methodological Approach, Wiley-InterScience, New York, 1997.

Peto, R. et al., Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Design, Brit. J. Cancer, 34, 585, 1976; Part II. Analysis and examples, Brit. J. Cancer, 35, 1, 1976.

Rozovsky, F.A. and Adams, R.K., Clinical Trials and Human Research: A Practical Guide to Regulatory Compliance, Jossey-Bass (John Wiley), New York, 2003.

Whitehead, J., The Design and Analysis of Sequential Clinical Trials, John Wiley & Sons, New York, 1997. 403

20

Standardization and Regulation of

Implant Materials

20.1 Historical Perspective

The manufacture and sale of drugs in the U.S. has been under gradually

increasing federal regulation since passage of the Wiley Act in 1897 and the

first Pure Food and Drug Act of 1906. These acts, as well as subsequent ones,

were adopted against a background of the sale of patent medicines with

exaggerated claims and the production of food with extensive and deliberate

contamination. There are many horror stories about the effects of patent

medicines from the pre-Wiley Act era and the later period of weak legislation

up to the 1930s (see Lamb 1936; Mintz 1965). Perhaps the strongest single

factor in the initiation of federal regulation of food additives and purity was

the publication of The Jungle by Upton Sinclair (1906). This novel describes

the conditions in the processed meat industry in Chicago at the time in

horrifying detail and caused widespread revulsion to and rejection of pro

cessed meats such as sausage, ham paste, etc.

Various legislative acts directed towards regulation of content and safety

of food, drugs, and cosmetics brought the U.S. Food and Drug Administra

tion (FDA) into being. Although legislative authority probably existed from

1923 to regulate implants, practical regulation did not begin until the 1970s.

A series of amendments to the Food, Drug, and Cosmetic Act (1976), collec

tively termed The Medical Device Amendments, was adopted and signed

into law on May 28, 1976. These amendments gave the then recently orga

nized Bureau of Medical Devices and Diagnostic Aids* of the FDA broad

powers to regulate implants, surgical instruments, and medical devices as

articles of commerce. These powers generally parallel the powers afforded

in the regulation of drugs; differences in the law and the regulatory arrange

ments reflect some of the differences between devices and drugs. These

amendments have been supplemented and modified to minor degrees by

* Now called the Center for Devices and Radiological Health.

legislative action; however, they underwent significant recent extension

beginning in 1990 by adoption of the Safe Medical Devices Act.

Numerous efforts at standardization and thus control of medical and sur

gical devices and materials predate these legislative efforts and continue in

a supplementary and parallel fashion today.

20.2 Drug Standardization Activities

20.2.1 The U.S. Pharmacopeia

The idea of standardization of drugs and, more recently, of medical and

surgical devices and materials is quite an old one. The motives involved are

usually the related desires to assure reproducible effect (efficacy) while pro

tecting the patient against hazards associated with adulteration, mislabeling,

misuse, etc. (safety).

The first concrete effort in this area in the U.S. was the proposal by Dr.

Lyman Spalding in January 1817 to establish a national pharmacopeia. The

pharmacopeia was seen as a widely agreed upon and accepted document

that would set out the composition, identity, properties, and, to some extent,

clinical behavior of drugs and other medical substances shown to be useful

— that is, beneficial in action. In response to Dr. Spalding’s proposal, the

First United States Pharmacopeial Convention (USPC) assembled in Wash

ington, D.C., on January 1, 1820. The First U.S. Pharmacopeia was published

on December 15, 1820, in Latin and English. Its 272 pages listed some 217

drugs considered worthy of recognition. At that time, provisions were made

to hold subsequent meetings of the convention and to issue a revised phar

macopeia every 10 years.

The first USPC and the First Revision Committee were composed exclu

sively of physicians. By 1830, pharmacists had been invited to join the con

vention and numbers of them have continued to join over the years. The

present bylaws of the United States Pharmacopeia require, however, that at

least one-third of the members of the Board of Trustees and the Committee

of Revision continue to represent the medical profession.

The initial policy of the USPC was to select the most fully established and

best understood substances from among those that possess medicinal power.

Over the years and through its various revisions, this principle had been

adhered to. The last independent version, The Pharmacopeia of the United States

of America (USP XIX 1975), was the 19th revision, published subsequent to

the USPC of April, 1970. It contains 1284 articles

describing a somewhat

lower number of drugs and other medical agents. Implants and other med

ical devices are not discussed in USP XIX, with two exceptions. The first

and more important of these exceptions is that provision is made for the

definition and testing of glass and plastic containers for drugs. The methods

of test for containers outlined in USP XIX are:*

- Light transmission
- Chemical resistance (glass containers)
- Biological tests (plastic containers): injection of extracts and examination of 72-hour implants in rabbits and mice
- Physiochemical tests (plastic containers): extraction, residue identification, residue ignition, heavy metal content, and buffering capacity

The other medical device described is the absorbable surgical suture. This

is the so-called “catgut” suture, although the basic material is now derived

from other sources. USP XIX sets out methods of test and standards for

length, diameter, tensile strength, content of soluble chromium compounds,

and color of extracts, as well as describing methods of needle attachment

for these sutures.

Although neither of these device areas is directly applicable to implant

materials, many of the methods, particularly those used to qualify container

materials, have been used extensively by biomaterials investigators. Of inter

est is the provision for the use of a standard implant reference material for

evaluation of the 72-hour animal tests. The material is a low-molecular

weight polyethylene fiber that can be inserted through a hypodermic needle.

It is stocked in a supply maintained by the USPC.

In 1974, the USP and the National Formulary (NF) (see next section) were

combined. The current edition (USP 28 2005) continues the USP series as the

28th revision and includes the 23rd revision of the NF. Although they are

now published together, an internal distinction is maintained, with the USP

articles addressing drug composition and dosage (as well as general issues

of testing and packaging) and NF articles dealing with pharmaceutical ingre

dients other than drugs. The combined USP/NF has been published every

5 years since 1975 and is enlarged by annual supplements and by a bimonthly

magazine, Pharmacopeial Forum; with the 2002 edition, it will now be pub

lished annually. The rate of growth can be appreciated by noting the addition

of 112 chapters and monographs as well as 637 revisions of previous ones

in the 28th edition.

The current revision, USP 28 (2005), in addition to continuing the nonbi

ological tests of previous revisions, now lists a total of six host response tests

(Table 20.1). It is of great interest that the in vitro test methods now cite ASTM

* USP XIX, p. 642.

20.2.2 The National Formulary

As mentioned earlier, another compilation of drugs and their properties is

the National Formulary, which first appeared in 1888. This is prepared and

published by the American Pharmaceutical Association, which was orga

nized in 1852. The stated goals of the NF are similar to those of the USP,

with the exception that not only the drugs of the greatest therapeutic merit

are to be included, but also drugs of any demonstrated merit. This factor

and the domination of the NF by the manufacturers rather than the users of

drugs, leads to a somewhat different format and emphasis. The NF was

originally published at 10-year intervals, more recently in 5-year intervals

and, since 2002, annually. The last independent edition (see previous section)

was the 14th edition (NF 14 1975) and includes 1009 articles defining and

describing a somewhat greater number of drugs and medical materials.

NF 14 describes materials, in the nondrug sense, in only

two areas. It makes

provisions for examination and qualification of glass containers for drug

packaging that are similar to and depend upon USP 19 provisions. In addi

tion, special provisions are made for qualification of containers for oph

thalmic preparations. These provisions include a previously mentioned eye

irritation test using saline and cottonseed oil extracts in the eye of the albino

rabbit.

20.3 Biomaterials Standardization Activities

20.3.1 The American Dental Association

A number of efforts have been made in the standardization of biomaterials

(in the sense of materials without primary pharmacological effects). Begin

ning in 1926, the American Dental Association (ADA) has sponsored and TABLE 20.1 Host Response Test Methods in USP 28 General article <82>: biological reactivity tests, in vitro Agar diffusion Direct contact Elution General article <83>: biological reactivity tests, in vivo Systemic injection Intracutaneous injection Implantation Source: USP 28, The Pharmacopeia of the United States of America, 28th revision, incorporating The National Formulary, 23rd revision, The United States Pharmacopeial Convention, Inc., Washington, D.C., 2005.

conducted a program to define the physical and chemical properties of

materials used in restorative dentistry. Over the years a large number of

specifications have been developed for various metal alloys, cements,

impression materials, casting and investment waxes,

plaster, resin, and elas

tomeric products, as well as cutting instruments and equipment for radiation

diagnosis and therapy.

In addition to these specifications, the ADA maintains a program to certify

specific dental material products and manufacturers of these certified prod

ucts. The results of this program, carried out through a cooperative effort

with the National Bureau of Standards (now the National Institute for Stan

dards and Technology [NIST]), was a periodic publication entitled Guide to

Dental Materials and Devices most recently published in a seventh edition

(ADA 1974).* This contains a great deal of technical information as well as

some 25 materials specifications. Today there are about 67 standards; how

ever, they may be obtained only individually from the ADA or from the

American National Standards Institute, Washington, D.C. Table 20.2 lists

dental materials and materials test standards currently in use.

20.3.2 The American Society for Testing and Materials**

An effort of greater generality is that on the part of the American Society for

Testing and Materials (ASTM). This organization was founded in 1898 and

is the principal scientific and technical organization for the voluntary devel

opment of standards on characteristics and performance of materials, prod

ucts, systems, and services in the U.S. It performs its work through 130 main

technical committees with more than 20,000 active members.*** These com

mittees function in prescribed fields under regulations that ensure balanced

representation by producers, users, and general interest participants.

In 1962, the Committee F4 on Medical Devices was organized (Brown and

Cook 1982). More recently, this committee was reorganized and renamed the

Committee F4 on Medical and Surgical Materials and Devices. It includes

within its organization a resources subcommittee with individual sections

devoted to specific materials classes such as polymeric materials, metallur

gical materials, etc., as well as biocompatibility, and a series of subcommit

tees in various surgical specialties such as orthopaedics, cardiovascular

surgery, neurosurgery, etc. The division of areas addressed by these latter

medical subcommittees approximately parallels that of the Device Classifi

cation Panels established by the Food and Drug Administration subsequent

to the passage of the Medical Device Amendments (1976).

* The reason for discontinuation of this publication is unclear; however, the subsequent approval

of these standards by the American National Standards Institute (ANSI) and their joint publica

tion renders the decision moot.

** Since 2004, called ASTM International; however, I have preserved the older name here because

it is more familiar to readers.

*** http://www.astm.org.

The scope of this committee is the development of definitions of terms

and nomenclature, methods of test, specifications, and performance require

ments for medical and surgical materials and devices. By 2004, the committee

had adopted and approved through society vote more than 75 biomaterials

specifications and 50 methods of test for biological response (Table 20.3), as

well as device standards and other methods of test. The biomaterials spec

ifications are consensus documents that describe the results of present prac

tice in the fabrication of these materials. In that they are adhered to and the

incorporated standardized materials are used as reference materials, the

methods of test can be considered as standard tests, within the meaning of

TABLE 20.2

ANSI/ADA Dental Biomaterials Standards and Test Methods

Biomaterials 1 Alloy for dental amalgam 5 Dental casting alloys 6 Dental mercury

11 Agar impression materials

12 Denture base polymers

13 Denture cold-curing repair resins

14 Dental base metal casting alloys

15 Synthetic polymer teeth

16 Dental impression paste — zinc oxide-eugenol type

17 Denture base temporary relining resins

18 Alginate impression materials

19 Dental elastomeric impression material

20 Dental duplicating material

22 Intraoral dental radiographic film

24 Dental baseplate wax

27 Resin-based filling materials

30 Dental zinc oxide–eugenol and zinc oxide–noneugenol cements

32 Orthodontic wires

37 Dental abrasive powders

38 Metal-ceramic dental restorative systems

39 Pit and fissure sealants

42 Polymer-based crowns and bridges

57 Endodontic sealing material

69 Dental ceramic

75 Resilient lining materials for removable dentures — part 1: short-term materials

82 Dental reversible/irreversible hydrocolloid impression material systems

87 Dental impression trays

88 Dental impression alloys

96 Dental water-based cements

Test Methods

41 Biological evaluation of dental materials

82 Dental materials — determination of color stability

97 Corrosion test methods

Source: American Dental Association (ADA)
http://www.ada.org.

TABLE 20.3

ASTM Biomaterials Standards and Methods of Testing for Host and Material

Response a

Biomaterials

F0067-00 Specification for Unalloyed Titanium, for Surgical Implant Applications (UNS

R50250, UNS R50400, UNSR50550, UNS R50700)

F0075-01 Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting

Alloy for Surgical Implants (UNS R30075)

F0086-04 Practice for Surface Preparation and Marking of Metallic Surgical Implants

F0090-01 Specification for Wrought Cobalt-20Chromium-15Tungsten-10Nickel Alloy for

Surgical Implant Applications (UNS R30605)

F0136-02A Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low

Interstitial) Alloy for Surgical Implant Applications (UNS R56401)

F0138-03 Specification for Wrought

18Chromium-14Nickel-2.5Molybdenum Stainless Steel

Bar and Wire for Surgical Implants (UNS S31673)

F0139-03 Specification for Wrought
18Chromium-14Nickel-2.5Molybdenum Stainless Steel

Sheet and Strip for Surgical Implants (UNS S31673)

F0451-99AE01 Specification for Acrylic Bone Cement

F0560-05 Specification for Unalloyed Tantalum for Surgical
Implant Applications (UNS

R05200, UNS R05400)

F0562-02 Specification for Wrought
35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy

for Surgical Implant Applications (UNS R30035)

F0563-00 Specification for Wrought
Cobalt-20Nickel-20Chromium-3.5Molybdenum

3.5Tungsten-5Iron Alloy for Surgical Implant Applications
(UNS R30563)

F0602-98AR03 Criteria for Implantable Thermoset Epoxy
Plastics

F0603-00 Specification for High-Purity Dense Aluminum Oxide
for Medical Application

F0604 Specification for Silicone Elastomers Used in Medical
Applications

F0620-00 Specification for Alpha plus Beta Titanium Alloy
Forgings for Surgical Implants

F0621-02 Specification for Stainless Steel Forgings for
Surgical Implants

F0639-98AR03 Specification for Polyethylene Plastics for
Medical Applications

F0641-04 Specification for Implantable Epoxy Electronic
Encapsulants

F0648-00E01 Specification for Ultra-High-Molecular-Weight
Polyethylene Powder and

Fabricated Form for Surgical Implants

F0665-98R03 Classification for Vinyl Chloride Plastics Used in Biomedical Application

F0688-05 Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy

Plate, Sheet, and Foil for Surgical Implants (UNS R30035)

F0702-98AR03 Specification for Polysulfone Resin for Medical Applications

F0745-00 Specification for 18Chromium-12.5Nickel-2.5Molybdenum Stainless Steel for Cast

and Solution-Annealed Surgical Implant Applications

F0754-00 Specification for Implantable Polytetrafluoroethylene (PTFE) Polymer Fabricated

in Sheet, Tube, and Rod Shapes

F0755-99R05 Specification for Selection of Porous Polyethylene for Use in Surgical Implants

F0799-02 Specification for Cobalt-28Chromium-6Molybdenum Alloy Forgings for Surgical

Implants (UNS R31537, R31538, R31539)

F0899-02 Specification for Stainless Steels for Surgical Instruments

F0961-03 Specification for 35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy Forgings

for Surgical Implants (UNS R30035)

F0983-86R05 Practice for Permanent Marking of Orthopedic Implant Components

F0997-98AR03 Specification for Polycarbonate Resin for Medical Applications (continued)

TABLE 20.3 (CONTINUED)

ASTM Biomaterials Standards and Methods of Testing for Host

and Material

Response a

Biomaterials (continued)

F1058-02 Specification for Wrought
40Cobalt-20Chromium-16Iron-15Nickel-7Molybdenum

Alloy Wire and Strip for Surgical Implant Applications (UNS
R30003 and UNS R30008)

F1088-04A Specification for Beta-Tricalcium Phosphate for
Surgical Implantation

F1091-02 Specification for Wrought
Cobalt-20Chromium-15Tungsten-10Nickel Alloy

Surgical Fixation Wire [UNS R30605]

F1108-04 Specification for Titanium-6Aluminum-4Vanadium
Alloy Castings for Surgical

Implants (UNS R56406)

F1185-03 Specification for Composition of Hydroxylapatite
for Surgical Implants

F1251-89R03 Terminology Relating to Polymeric Biomaterials
in Medical and Surgical

Devices

F1295-05 Specification for Wrought Titanium-6 Aluminum-7
Niobium Alloy for Surgical

Implant Applications (UNS R567000)

F1314-01 Specification for Wrought Nitrogen Strengthened 22
Chromium/N 13 Nickel/N 5

Manganese/N 2.5 Molybdenum Stainless Steel Alloy Bar and
Wire for Surgical Implants

(UNS S20910)

F1341-99 Specification for Unalloyed Titanium Wire UNS
R50250, UNS R50400, UNS R50550,

UNS R50700, for Surgical Implant Applications

F1350-02 Specification for Wrought
18Chromium-14Nickel-2.5Molybdenum Stainless Steel

Surgical Fixation Wire (UNS S31673)

F1377-04 Specification for Cobalt-28 Chromium-6 Molybdenum
Powder for Coating of

Orthopedic Implants (UNS-R30075)

F1472-02A Specification for Wrought
Titanium-6Aluminum-4Vanadium Alloy for Surgical

Implant Applications (UNS R56400)

F1537-00 Specification for Wrought Cobalt-28 Chromium-6
Molybdenum Alloy for Surgical

Implants

F1538-03 Specification for Glass and Glass Ceramic
Biomaterials for Implantation

F1579-02E01 Specification for Polyaryletherketone (PAEK)
Polymers for Surgical Implant

Applications

F1580-01 Specification for Titanium and Titanium-6
Aluminum-4/tVanadium Alloy Powders

for Coatings of Surgical Implants

F1581-99 Specification for Composition of Anorganic Bone
for Surgical Implants

F1586-02 Specification for Wrought Nitrogen Strengthened 21
Chromium/M10 Nickel/M3

Manganese/M2.5 Molybdenum Stainless Steel Alloy Bar for
Surgical Implants (UNS

S31675)

F1609-03 Specification for Calcium Phosphate Coatings for
Implantable Materials

F1713-03 Specification for Wrought
Titanium-13Niobium-13Zirconium Alloy for Surgical

Implant Applications (UNS R58130)

F1813-01 Specification for Wrought Titanium/N 12 Molybdenum /N 6 Zirconium/N 2 Iron

Alloy for Surgical Implant (UNS R58120)

F1839-01 Specification for Rigid Polyurethane Foam for Use as a Standard Material for

Testing Orthopedic Devices and Instruments

F1855-00R05 Specification for Polyoxymethylene (Acetal) for Medical Applications

F1873-98 Specification for High-Purity Dense Yttria Tetragonal Zirconium Oxide Polycrystal

(Y-TZP) for Surgical Implant Applications

F1876-98R03E01 Specification for Polyetherketoneetherketoneketone (PEKEKK) Resins for

Surgical Implant Applications (continued)

TABLE 20.3 (CONTINUED)

ASTM Biomaterials Standards and Methods of Testing for Host and Material

Response a

Biomaterials (continued)

F1925-99R05 Specification for Virgin Poly(L-Lactic Acid) Resin for Surgical Implants

F2005-00 Terminology for Nickel-Titanium Shape Memory Alloys

F2026-02 Specification for Polyetheretherketone (PEEK) Polymers for Surgical Implant

Applications

F2038-00R05 Guide for Silicone Elastomers, Gels and Foams Used in Medical Applications

Part I/M Formulations and Uncured Materials

F2042-00R05 Guide for Silicone Elastomers, Gels, and Foams Used in Medical Applications

Part II/M Crosslinking and Fabrication

F2063-00 Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical

Devices and Surgical Implants

F2066-01 Specification for Wrought Titanium-15 Molybdenum Alloy for Surgical Implant

Applications (UNS R58150)

F2146-01 Specification for Wrought Titanium-3Aluminum-2.5Vanadium Alloy Seamless

Tubing for Surgical Implant Applications (UNS R56320)

F2210-02 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered

Medical Products

F2211-02 Classification for Tissue-Engineered Medical Products (TEMPs)

F2224-03 Specification for High-Purity Calcium Sulfate Hemihydrate or Dihydrate for

Surgical Implants

F2229-02 Specification for Wrought, Nitrogen-Strengthened 23Manganese-21Chromium

1Molybdenum Low-Nickel Stainless Steel Alloy Bar and Wire for Surgical Implants (UNS

S29108)

F2257-03 Specification for Wrought Seamless or Welded and Drawn 18 Chromium-14Nickel

2.5Molybdenum Stainless Steel Small Diameter Tubing for Surgical Implants (UNS S31673)

F2311-03 Guide for Classification of Therapeutic Skin Substitutes

F2312-04 Terminology Relating to Tissue-Engineered Medical Products

F2313-03 Specification for Virgin Poly(glycolide) and Poly(glycolide-co-lactide) Resins for

Surgical Implants with Mole Fractions Greater than or Equal to 70% Glycolide

F2315-03 Guide for Immobilization or Encapsulation of Living Cells or Tissue in Alginate

Gels

F2386-04 Guide for Preservation of Tissue-Engineered Medical Products (TEMPs)

F2393-04 Specification for High-Purity Dense Magnesia Partially Stabilized Zirconia (Mg

PSZ) for Surgical Implant Applications

Methods of Test for Host and Material Response

F0561-05 Practice for Retrieval and Analysis of Implanted Medical Devices and Associated

Tissues

F0619-03 Practice for Extraction of Medical Plastics

F0624-98AR03 Guide for Evaluation of Thermoplastic Polyurethane Solids and Solutions for

Biomedical Applications

F0719-81R02E01 Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation

F0720-81R02E01 Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig

Maximization Test

F0732-00 Test Method for Wear Testing of Polymeric Materials Used in Total Joint Prostheses (continued)

TABLE 20.3 (CONTINUED)

ASTM Biomaterials Standards and Methods of Testing for Host

and Material

Response a

Methods of Test for Host and Material Response (continued)

F0746-04 Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials

F0748-04 Practice for Selecting Generic Biological Test Methods for Materials and Devices

F0749-98R02E02 Practice for Evaluating Material Extracts by Intracutaneous Injection in the

Rabbit

F0750-87R02E01 Practice for Evaluating Material Extracts by Systemic Injection in the Mouse

F0756-00 Practice for Assessment of Hemolytic Properties of Materials

F0763-04 Practice for Short-Term Screening of Implant Materials

F0813-01 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices

F0895-84R01E01 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity

F0897-02 Test Method for Measuring Fretting Corrosion of Osteosynthesis Plates and Screws

F0981-04 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with

Respect to Effect of Materials on Muscle and Bone *

F1027-86R02 Practice for Assessment of Tissue and Cell Compatibility of Orofacial Prosthetic

Materials and Devices

F1408-97R02E01 Practice for Subcutaneous Screening Test for Implant Materials

F1439-03 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of

Implant Materials

F1635-04 Test Method for in Vitro Degradation Testing of Hydrolytically Degradable Polymer

Resins and Fabricated Forms for Surgical Implants

F1801-97 Practice for Corrosion Fatigue Testing of Metallic Implant Materials

F1830-97 Practice for Selection of Blood for in Vitro Evaluation of Blood Pumps

F1841-97 Practice for Assessment of Hemolysis in Continuous Flow Blood Pumps

F1877-98R03E01 Practice for Characterization of Particles

F1903-98R03 Practice for Testing for Biological Responses to Particles in vitro

F1904-98R03 Practice for Testing the Biological Responses to Particles in vivo

F1905-98R03 Practice for Selecting Tests for Determining the Propensity of Materials to Cause

Immunotoxicity

F1906-98R03 Practice for Evaluation of Immune Responses in Biocompatibility Testing Using

ELISA Tests, Lymphocyte Proliferation, and Cell Migration

F1926-03 Test Method for Evaluation of the Environmental Stability of Calcium Phosphate

Coatings

F1983-99R03 Practice for Assessment of Compatibility of Absorbable/Resorbable

Biomaterials for Implant Applications

F1984-99R03 Practice for Testing for Whole Complement Activation in Serum by Solid

Materials

F2003-02 Practice for Accelerated Aging of Ultra-High Molecular Weight Polyethylene after

Gamma Irradiation in Air

F2025-00 Practice for Gravimetric Measurement of Polymeric Components for Wear

Assessment

F2027-00E01 Guide for Characterization and Testing of Substrate Materials for Tissue

Engineered Medical Products

F2064-00 Guide for Characterization and Testing of Alginates as Starting Materials Intended

for Use in Biomedical and Tissue/Engineered Medical Products Application

F2065-00E01 Practice for Testing for Alternative Pathway Complement Activation in Serum

by Solid Materials

* See Appendix 1 in Chapter 18. (continued)

TABLE 20.3 (CONTINUED)

ASTM Biomaterials Standards and Methods of Testing for Host and Material

Response a

Methods of Test for Host and Material Response (continued)

F2102-01E01 Guide for Evaluating the Extent of Oxidation in Ultra-High-Molecular-Weight

Polyethylene Fabricated Forms Intended for Surgical Implants

F2103-01 Guide for Characterization and Testing of Chitosan Salts as Starting Materials

Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications

F2129-04 Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements

to Determine the Corrosion Susceptibility of Small Implant Devices

F2131-02 Test Method for in Vitro Biological Activity of Recombinant Human Bone

Morphogenetic Protein-2 (rhBMP-2) Using the W-20 Mouse Stromal Cell Line

F2147-01 Practice for Guinea Pig: Split Adjuvant and Closed Patch Testing for Contact

Allergens

F2148-01 Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine

Local Lymph Node Assay (LLNA)

F2149-01 Test Method for Automated Analyses of Cells/The Electrical Sensing Zone Method

of Enumerating and Sizing Single Cell Suspensions

F2150-02E01 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue

Engineered Medical Products

F2151-01 Practice for Assessment of White Blood Cell Morphology after Contact with

Materials

F2183-02 Test Method for Small Punch Testing of Ultra-High Molecular Weight Polyethylene

Used in Surgical Implants

F2212-02 Guide for Characterization of Type I Collagen as Starting Material for Surgical

Implants and Substrates for Tissue Engineered Medical Products (TEMPs)

F2255-05 Test Method for Strength Properties of Tissue Adhesives in Lap-Shear by Tension

Loading

F2256-05 Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension

Loading

F2258-05 Test Method for Strength Properties of Tissue Adhesives in Tension

F2259-03 Test Method for Determining the Chemical Composition and Sequence in Alginate

by Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy

F2260-03 Test Method for Determining Degree of Deacetylation in Chitosan Salts by Proton

Nuclear Magnetic Resonance (1H NMR) Spectroscopy

F2347-03 Guide for Characterization and Testing of Hyaluronan as Starting Materials

Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications

F2382-04E01 Test Method for Assessment of Intravascular Medical Device Materials on

Partial Thromboplastin Time (PTT)

F2392-04 Test Method for Burst Strength of Surgical Sealants

Note: F-999-02R03E02 means standard F999, adopted 2002, revised 2003, two editorial changes (to 2003 version).

a ASTM standards are routinely revised on a 5-year cycle. A number of those listed here

have been reprinted more recently with minor or editorial changes only. Please refer to

most recent editions of ASTM annual standards books for current texts and explanatory

notes.

Source: 2005 Annual Book of ASTM Standards, Vol. 13.01. ASTM International, West Consho

hocken, PA, 2004, xi–xv.

Section 1.2. Individual standards are available from ASTM, as well as annual

collections. Most technical libraries maintain recent full sets of ASTM stan

dards in their reference collections; biomaterials standards are in annual

volume 13.01.

It is worth noting that, although ASTM F-4 standards for test methods are

consensus documents and have wide support in government, academia, and

industry, they are rarely used. That is, most investigators derive variations

of these procedures; however, when care is taken to meet the requirements

of the parent procedure, the revised and extended procedure is properly said

to adhere to the ASTM standard or recommended method of test.

20.3.3 Other Efforts

A number of other organizations have entered into the specification and

standardization of medical materials and devices. However, none are as

advanced in their efforts as the ADA and the ASTM. Perhaps the best known

of the remainder of these organizations is the Association for Advancement

of Medical Instrumentation (AAMI). This organization has been involved

for a number of years in developing specifications for active medical devices

such as heart pacers and neurostimulators. A number of these specifications

are coming into general use.

Outside the U.S., other countries have made progress in this field. Some,

like Canada, have decided to follow the progress of American groups such

as the ASTM and ADA. As standards have been adopted as American

National Standards (by the American National Standards Institute [designa

tion: ANSI]), they are also being adopted after review as Canadian standards.

For instance, all of the ADA standards listed in Table 20.2 are now ANSI

standards, as are many ASTM standards. Some countries, such as Germany,

France, and England, have developed, relatively independently, their own

national standards for implant materials and devices. An international stan

dards-making group, the International Standards Organization (ISO),* has

organized two committees with broad international representation:

- ISO TC 150 is evaluating national device and material standards and attempting to adopt common international versions. This effort is under way in the fields of orthopaedic, cardiovascular, and neurosurgery and will eventually spread to encompass all medical disciplines.

- ISO TC 194 is conducting similar activities in the area of measurement of biological response.

Subject to approval by the European Commission, ISO standards began

to supplant or override national standards with the formation of the Euro

* http//www.iso.org.

pean Common Market in 1992 and, as a result, are becoming de facto stan

dards for firms involved in international trade in medical and surgical

materials and devices.* Table 20.4 lists the ISO standards currently in force

for biomaterials and methods of test for host response. Individual AAMI

and ISO standards are available from the Association for Advancement of

Medical Instrumentation.**

Trade associations such as the Orthopedic Surgical Manufacturers Associ

ation (OSMA) and the Health Industry Manufacturers Association (HIMA)

have taken active roles in developing standards on their own or through

activity of their representatives in standards-writing organizations such as

ASTM, ISO, etc. Traditional professional organizations in the health and

engineering professions also have standards committees that act as focal

points for technical input into standards preparation by standards-making

organizations.

20.4 U.S. Federal Regulation of Medical Devices and Biomaterials

20.4.1 Medical Device Amendments (1976)

Although the various standardization efforts described in previous sections

continue through today, they were not generally perceived to be sufficient

to provide safe and effective medical and surgical materials and devices for

the public and to control unsafe and ineffective materials and devices. The

result in the U.S. was a legislative mandate for the executive branch of

government to control and regulate medical device manufacturing in the

public interest. The initial chosen legislative tool was the Medical Device

Amendments (1976) whose overall goal is to assure the safety and efficacy

of devices. This legislation provides for classification of devices, which will

be considered later in this chapter. They also lay out a scheme of general

controls including provisions for dealing with adulterated and misbranded

devices, for registering device types and device manufacturers, for premar

ket notification of the introduction of new devices, and for dealing with

banned devices. Details of manufacturers' obligations to repair, replace, or

refund in the case of defective devices are also included. The amendments

also permit the establishment of regulations to define "good manufacturing

practices" and of performance standards as well as premarket product devel

opment protocols for new materials and devices.

* For a detailed idea of how these various standards and specifications interact generically with

the process of federal regulation of medical materials and devices, the reader is referred to Every

thing You Always Wanted to Know about the Medical Device Amendments…and Weren't Afraid to Ask,

HHS, FDA, Rockville, MD, FDA 92-4173.

** http://www.aami.org.

TABLE 20.4

ISO Biomaterials Standards and Methods of Testing for Host Response a

General Biomaterials

ISO 5832-1:1997 Implants for surgery — metallic materials — part 1: wrought stainless steel

ISO 5832-2:1999 Implants for surgery — metallic materials — part 2: unalloyed titanium

ISO 5832-3:1996 Implants for surgery — metallic materials — part 3: wrought titanium

6-aluminum 4-vanadium alloy

ISO 5832-4:1996 Implants for surgery — metallic materials — part 4:

cobalt-chromium-molybdenum casting alloy

ISO 5832-5:1993 Implants for surgery — metallic materials — part 5: wrought

cobalt-chromium-tungsten-nickel alloy

ISO 5832-6:1997 Implants for surgery — metallic materials — part 6: wrought

cobalt-nickel-chromium-molybdenum alloy

ISO 5832-7:1994 Implants for surgery — metallic materials —

part 7: forgeable and cold

formed cobalt-chromium-nickel-molybdenum-iron alloy

ISO 5832-8:1997 Implants for surgery — metallic materials —
part 8: wrought

cobalt-nickel-chromium-molybdenum-tungsten-iron alloy

ISO 5832-9:1992 Implants for surgery — metallic materials —
part 9: wrought high-nitrogen

stainless steel

ISO 5832-10:1996 Implants for surgery — metallic materials
— part 10: wrought titanium

5-aluminum 2,5-iron alloy

ISO 5832-11:1994 Implants for surgery — metallic materials
— part 11: wrought titanium

6-aluminum 7-niobium alloy

ISO 5832-12:1996 Implants for surgery — metallic materials
— part 12: wrought

cobalt-chromium-molybdenum alloy

ISO 5833:2002 Implants for surgery — acrylic resin cements

ISO 5834-1:1998 Implants for surgery — Ultrahigh molecular
weight polyethylene — part 1:

powder form

ISO 5834-2:1998 Implants for surgery — ultrahigh molecular
weight polyethylene — part 2:

molded forms

ISO 10334:1994 Implants for surgery — malleable wires for
use as sutures and other surgical

applications

ISO 13356:1997 Implants for surgery — ceramic materials
based on yttria-stabilized tetragonal

zirconia (Y-TZP)

ISO 13779-1:2000 Implants for surgery - part 1 — ceramic hydroxyapatite

ISO 13781:1997 Poly (L-lactide) resins and fabricated forms for surgical implants — in vitro

degradation testing

ISO 13782:1996 Implants for surgery — metallic materials — unalloyed tantalum for surgical

implant applications

Dental Materials

ISO 1561:1995 Dental casting wax

ISO 1563:1990 Dental alginate impression material

ISO 1564:1995 Dental aqueous impression materials based on agar

ISO 1567:1988 Dentistry — denture base polymers

ISO 6871-1:1994 Dental base metal casting alloys — part 1: cobalt-based alloys

ISO 6871-2:1994 Dental base metal casting alloys — part 2: nickel-based alloys

ISO 6872:1995 Dental ceramic

ISO 6874:1988 Dental resin-based pit and fissure sealants

ISO 6876:2001 Dental root canal sealing materials (continued)

TABLE 20.4 (CONTINUED)

ISO Biomaterials Standards and Methods of Testing for Host Response a

Dental Materials (continued)

ISO 6877:1995 Dental root-canal obturating points

ISO 7491:2000 Dental materials — determination of color stability of dental polymeric

materials

ISO 8891:1998 Dental casting alloys with noble metal content of 25% up to but not including 75%

ISO 9333:1990 Dental brazing materials

ISO 9693:1997 Metal-ceramic dental restoration systems

ISO 9694:1996 Dental phosphate-bonded casting investments

ISO 9917:1991 Dental water-based cements

ISO 9917-2:1998 Dental water-based cements — part 2: light-activated cements

ISO 10139-1:1991 Dentistry — resilient lining materials for removable dentures — part 1:

short-term materials

ISO 10139-2 Dentistry — resilient lining materials for removable dentures — part 2: long

term materials

ISO 11244:1998 Dental brazing investments

ISO 11245: 1999 Dental restorations — phosphate-bonded refractory die material

ISO 11246:1996 Dental ethyl silicate-bonded casting investments

ISO 12163:1999 Dental baseplate modeling waxes

ISO 16744:2003 Dentistry — base metal materials for dental restorations

ISO 24234:2004 Dentistry — mercury and alloys for dental amalgam

Methods of Test for Host Response

ISO 7405:1997 Dentistry — preclinical evaluation of biocompatibility of medical devices used

in dentistry — test methods for dental materials

ISO 10993-1:2003 Biological evaluation of medical devices —

part 1: evaluation and testing

ISO 10993-2:1992 Biological evaluation of medical devices —
part 2: animal welfare

requirements

ISO 10993-3:2003 Biological evaluation of medical devices —
part 3: tests for genotoxicity,

carcinogenicity and reproductive toxicity

ISO 10993-4:2002 Biological evaluation of medical devices —
part 4: selection of tests for

interactions with blood

ISO 10993-5:1999 Biological evaluation of medical devices —
part 5: tests for in vitro

cytotoxicity

ISO 10993-6:1994 Biological evaluation of medical devices —
part 6: tests for local effects after

implantation

ISO 10993-10:2002 Biological evaluation of medical devices
— part 10: tests for irritation and

delayed-type hypersensitivity

ISO 10993-11:1993 Biological evaluation of medical devices
— part 11: tests for systemic toxicity

ISO 10993-12:2002 Biological evaluation of medical devices
— part 12: sample preparation

and reference materials

ISO 10993-16:1997 Biological evaluation of medical devices
— part 16: toxicokinetic study

design for degradation products and leachables

ISO 10993-17:2002 Biological evaluation of medical devices
— part 17: establishment of

allowable limits for leachable substances

ISO 11979-5:1999 Opthalmic Implants — intraocular lenses — part 5: biocompatibility

ISO 12891-1-4:1998, 2000 Retrieval and analysis of surgical implants

a In some cases, ISO standards have multiple designations, reflecting texts identical with

national standards (such as ANSI); however, only ISO designations are listed here.

Source: International Standards Organization (ISO) http://www.iso.org.

If the Medical Device Amendments can be said to have a central theme,

it is one that closely parallels the ideas of the safety and effectiveness of

drugs, cosmetics, and food additives. That is, the legislation foresaw a pat

tern in which materials and devices would be developed, tested, and dem

onstrated to be safe and efficacious before being offered for sale. Once this

point was reached, their future safety and effectiveness would then be con

trolled by the institution of general standards and controls or by the provi

sions of specific performance standards.

20.4.2 Safe Medical Devices Act (1990)

The Safe Medical Devices Act (1990) was the first major revision of the

Medical Device Amendments and occurred largely as a result of public

dissatisfaction with the implementation (rather than the content) of medical

and surgical device regulations envisioned at the time of

passage of the 1976

legislation. The many provisions of the act (Kahan et al. 1991) are intended

largely to strengthen, streamline, better define, and speed up regulatory

activities. Thus, the provisions primarily enlarge on and modify rather than

replace those of the earlier Medical Device Amendments. However, several

new provisions are introduced, including lifetime tracking of permanently

implanted life-supporting or life-sustaining devices, more and improved

reports of life-threatening device malfunction, regulatory authority to order

mandatory recalls and allow seizure of defective devices, rules for postmar

ket introduction surveillance of experience with permanent implants, and

creation of a humanitarian device exemption, similar to an “orphan” drug

provision within drug regulation, to simplify and reduce the cost of devel

opment of devices for diseases or conditions affecting fewer than 4000 indi

viduals in the U.S.

20.4.3 FDA Modernization Act (1997)

At the time of the adoption of the Medical Device Amendments (1976), no

one could predict the vast increase in number and complexity of medical

and surgical devices that would occur in the 1980s and 1990s. The result was

a gradual slowdown of FDA review and approval activities and a growing

frustration on the part of manufacturers and the public. Various small

changes were made to FDA procedures, including a second Safe Medical

Devices (1992) act; however, the major change came about in 1997 with the

adoption of a widely heralded and long awaited “modernization” act. This

act (Kahan et al. 1998a, b) is complex and its effects are still just beginning

to be felt. Perhaps the most important aspects of its intentions are:

- To reduce the arbitrary and unpredictable nature of FDA device regulatory activities by clarifying previsions of the 1976 amendments and spelling out procedures previously left to administrative definition

- To make the FDA a partner with industry and physicians during the device design, development, and qualification process, rather than merely a judge of the end product performance, thus improving chances of a new device’s release for use after an initial application; this is to be brought about by development and approval of a product design protocol early in the design process

- To require a higher level of professional achievement within the FDA regulatory staff by providing for better training, liaison, and reporting

Review times, which had in some cases stretched out to years, are appar

ently shortening significantly and the FDA’s role in medical device devel

opment seems less threatening to manufacturers as a consequence of this

act. More recently, subsequent to yet another effort to provide legislative

relief,* various efforts have been made to speed up the review process fur

ther, in some cases by raising fees or imposing special charges on the man

ufacturers. However, these have come under significant criticism from

industry because they appear to embody the old political principle of “pay

to play.” The longer term consequences of these many changes and the

continuing influence of the political leadership of the FDA remains to be

seen.

20.5 Regulation of Materials for Implants

20.5.1 Requirements of the Medical Device Amendments

The need for regulatory standards arises from the requirements of the Med

ical Device Amendments (1976) and the Safe Medical Devices Act (1990).

These are embodied in a classification system that attempts to distinguish

among various generic types of devices on the basis of risk to the patient.

The general pattern of device classification is as follows. Devices are classi

fied into three categories by one of 14 specialty-oriented Device Classification

Panels:

- Class I, general controls: a device for which controls other than standards and premarket approval are sufficient to assure safety and effectiveness

- Class II, performance standards: a device for which

general controls are insufficient to assure safety and effectiveness but for which information is sufficient for the establishment of a performance standard to provide such assurance

* Medical Device User Fee and Modernization Act, PL 107-250.

• Class III, premarket approval: a device for which insufficient information exists to assure that general controls and performance standards would provide reasonable assurance of safety and effectiveness and that is represented to be life sustaining, life supporting, or implanted in the body or that presents a potential unreasonable risk of illness or injury

Devices classified as class III and any new device that comes on the market

after May 28, 1976 must pass through some form of scientific premarket

review before market introduction. At the point at which these products are

judged to be reasonably safe, effective, and controllable by a performance

standard, they may be reclassified into class II. Thus, the existence of stan

dards can be seen to be critical to the introduction of new materials and

devices into general use. It is hoped that many of the voluntary standards

developed by the various organizations mentioned here, as well as others,

can be adapted to be regulatory standards.

To date, very few regulatory standards have been approved for devices

and none for materials. However, many permanent implants have been

reclassified from class III to class II on the basis of long pre- and postenact

ment experience. The need for regulatory standards, particularly for mate

rials of construction, will become more acute as more devices achieve such

reclassification.

As a consequence and in line with similar changes throughout the U.S.

government, the effort to substitute voluntary standards (see Section 20.5.2)

for regulatory standards is continuing. This effort is driven by a directive of

the Office of Management and Budget (OMB-119*) (Kono 1998). The basic

provision of OMB 119 is permission (and encouragement) to substitute a

consensus standard, such as those developed by ASTM or ISO, for a specially

drawn regulatory standard if the provisions of the voluntary standard are

appropriate to meet the needs of the regulatory agency, in this case the FDA.

This directive was recognized in a provision of the FDA Modernization Act

(1997) (section 204) to make conformance with an appropriate (preaccepted)

standard the basis for approval for the sale and use of certain devices.

20.5.2 Voluntary vs. Regulatory Standards

It should be clear to the reader that a voluntary standard and a regulatory

standard are not necessarily the same thing. Voluntary standards, whether

consensus derived or otherwise, are designed to describe

the content, design,

construction, and performance of existing devices, as well as to set forth

methods of verifying compliance with these aspects of the standard. By their

nature, regulatory standards are designed to regulate — that is, to assure

specific attributes of products. In the case of the (regulatory) performance

* OMB 119: Federal Participation in Development and Use of Voluntary Consensus Standards

and in Conformity Assessment Activities. Fed. Reg. 61:8548, 1998.

standards required by the Medical Device Amendments (1976), the specific

attributes to be regulated are safety and efficacy. It is not clear at this time

what combination of standards on content, design, and construction, as well

as simulation tests in vitro and in vivo, are necessary and sufficient to meet

such a general requirement for (in vivo) patient performance. Thus, although

it is possible to prepare a voluntary standard for an existing device or for

its materials of construction, the relationship of this standard to a future

generic regulatory standard is tenuous, at best.

It seems safe to presume that as genuinely new materials come under

consideration as candidate biomaterials, they will be qualified in a similar

way to that envisaged specifically for devices. In the

course of selection and

development, they pass through series of tests along the lines of those dis

cussed in Section 19.2. As their behavior becomes better understood and

devices incorporating them pass into clinical trials, the process of voluntary

standards preparation begins. The results of these tests and the proposed

form of the standard then constitute the body of material, with supporting

clinical reports, that can be submitted for initial review by a regulating

agency such as the FDA.

In that case, the use of the words “performance standard” in the 1976

enabling legislation harmonizes well with the ideas of biological perfor

mance laid out here in earlier chapters. Thus, a performance standard for

an implant material is one that describes the chemical, physical, and pro

cessing requirements for a material that are needed to assure a reproducible

level of biological performance, as well as to meet the engineering require

ments, of a proposed application. As soon as it is possible to prepare such

a document, the material becomes in an important sense a known material.

Its biological performance can be examined objectively and its suitability

(and admissibility) for specific applications can be

determined. At this point,

as embodied in devices, it should pass easily into class II and be a natural

competitor for use in future specific medical and surgical device applications.

Perhaps the recent revision of OMB 119 (Kono 1998) will encourage this

evolution and lead to materials “generally recognized as safe” for specific

groups of applications.

As an initial step in responding to OMB-119, the FDA maintains an online

registry of standards that it recognizes in regulatory submissions.* In large

part, these standards remain consensus standards that reflect current indus

trial practice and carry with them no assurance of safety and efficacy of the

devices designed and constructed utilizing them.**

*

** For completeness, it is worth noting also that product liability litigation has failed to establish

that FDA approval for sale and use implies a guarantee of safety and efficacy; such regulatory

action only establishes that the then current FDA requirements for such approval have been met.

The converse is also true: lack of FDA approval for a specific indication does not de facto render

a medical device and its materials of construction unsafe and/or ineffective.

Safety will continue to be a relative rather than an absolute attribute

because it will always be related, as I have pointed out, to a balance between

risk and benefit (Black 1995).

20.6 The Biomaterials Supply “Crisis”

Largely as a consequence of litigation associated with the use of silicone gel

in breast augmentation implants and polytetrafluoroethylene in tempero

mandibular joint (TMJ) replacements, concern about future availability of

many biomaterials rose during the 1990s (Hallab et al. 1997). The problem

was apparently that materials suppliers, whose products contribute only a

few cents or dollars to the cost of medical devices selling for thousands of

dollars, have repeatedly been named by plaintiffs in actions alleging injury

through malperformance of the device or merely maloutcome of the overall

procedure. For some materials producers, the result has been legal defense

costs — even in the absence of adverse judgments against them — that far

exceed any reasonable profit. As a consequence, some manufacturers have

ceased to provide materials to medical device manufacturers. The end effect

is unclear; in the case of medical-grade silicones, the withdrawal of Dow

Corning from the marketplace led to the entry of several new small compa

nies that now provide a wider range of well characterized

materials, albeit

at significantly higher prices, than were previously available (Hallab et al.

1997).

This situation, still regarded by some as an impending "crisis," seems

unfortunate on two grounds. In the first place, because the device manufac

turer makes the selection of the material and then tests it as a material and

indirectly during preclinical and clinical device evaluation, the so-called

"learned intermediary" principle seems sufficient to protect the material

manufacturer as long as the materials supplied are made to identified stan

dards (Harper 1996). That is, the responsibility of the material manufacturer

is to assure that the material is what it is represented to be and that of the

device manufacturer (the "learned intermediary" between the material sup

plier and the patient) is to make the judgment that the material selected has

suitable biological performance in the intended application.

Although this concept is clear in U.S. litigation experience, it does not

overcome the problem of paying for legal defense before and until the

material manufacturer is discharged from the plaintiff's action. Numerous

attempts have been made, led by then Rep. Lieberman (D-Conn), to embody

this principle in a federal statute. Despite widespread resistance to product

liability reform, the Biomaterials Access Assurance Act (1998)* was finally

* PL 105-230. See http://www.advamed.org/publicdocs/legal021599.htm for an extensive legal

analysis.

passed and signed into law. The provisions of this legislation parallel the

arguments of Harper (1996) and provide for summary (immediate) discharge

from medical product liability litigation for any materials supplier that meets

appropriate standards and conditions of general salability for its medical

grades of materials.

In the second place, the idea that withdrawal of medical grades of materials

will make those materials unavailable is, to a degree, naive. Although some

biomaterials are specifically manufactured for medial and surgical applica

tions, many, such as ultrahigh molecular weight polyethylene and many

titanium- and cobalt-base alloys, are simply selected batches or modest vari

ants of very large quantity production commercial materials. Thus, because

the FDA does not explicitly regulate biomaterials manufacture or manufac

turers, it is quite possible that intermediaries or the device manufacturers

could continue to procure suitable materials from commercial sources and

qualify them (i.e., determine their conformance with relevant standards) for

use in medical devices and implants.

An unforeseen negative result of the 1998 act has begun to emerge.

Recently, biomaterials and process suppliers named with device manufac

tures as plaintiffs in cases in which failure modes appear to center on mate

rials' properties rather than device design have begun to assert the defense

that the device manufacturer is, de facto, a learned intermediary and, as a

result, they share no possible liability for clinical maloutcome as long as their

product meets the representations (specifications, etc.) for which they make

it. This defense theory is novel enough that it has not yet been definitively

tested in U.S. courts.

At this time, the situation remains very unclear. However, more than a

decade after the specter of future biomaterials unavailability was seriously

raised, the U.S does not appear to have any important shortages. Suppliers

have changed and materials substitutions have been made, albeit at

increased cost, but device availability to patients appears not to have been

adversely affected so far.

American Dental Association, Guide to Dental Materials and Devices, 7th ed. ADA, Chicago, 1974.

American Society for Testing and Materials, 2005 Annual Book of ASTM Standards, Vol. 13.01: Medical Devices and Services, ASTM International, West Conshohocken, PA, 2005.

Black, J., "Safe" biomaterials (editorial), J. Biomed. Mater. Res., 29, 791, 1995.

Brown, P. and Cook, A.G., The background, formation, and maturation of committee F-4, ASTM Standardization News, October, 10, 1982.

Department of Health and Human Services, Everything You Always Wanted to Know about the Medical Device Amendments…and Weren't Afraid to Ask, HHS, FDA, Rockville, MD, FDA 92-4173, 1992.

Hallab, N.J. et al., Biomaterials crisis looms, AAOS Bull., 45(1), 13, 1997.

Harper, G.L., An analysis of the potential liabilities and defenses of bulk suppliers of titanium biomaterials, Gonzaga Law Rev., 32(1), 195, 1996.

Kahan, J.S., The Safe Medical Devices Act of 1990, Med. Dev. Diag. Ind., 13(1), 66, 1991.

Kahan, J.S. and Holstein, H.M., The FDA Modernization Act of 1997: part 1, Med. Dev. Diag. Ind., 20(3), 105, 1998a.

Kahan, J.S. and Holstein, H.M., The FDA Modernization Act of 1997: part 2, Med. Dev. Diag. Ind., 20(4), 77, 1998b.

Kahan, J.S. et al., The implications of the Safe Medical Devices Act of 1990, Med. Dev. Diag. Ind., 13(2), 44, 1991.

Kono, K., OMB A-119 revised, ASTM Stand. News, June, 1998, 19.

Lamb, R. DeF., American Chamber of Horrors: The Truth about Food and Drugs, Farrar & Rinehart, New York, 1936.

Mintz, M., The Therapeutic Nightmare, Houghton-Mifflin Co., Boston, 1965.

NF XIV, The National Formulary, 14th ed., American

Pharmaceutical Association, Washington, D.C., 1975.

Sinclair, U., The Jungle, New American Library, New York, 1906.

USP XIX, The Pharmacopeia of the United States of America, 19th revision, The United States Pharmacopeial Convention, Inc., Washington, D.C., 1975.

USP 28, The Pharmacopeia of the United States of America, 28th revision, incorporating The National Formulary, 23rd revision, The United States Pharmacopeial Convention, Inc., Washington, D.C., 2005.

U.S. Congress, Medical Device Amendments, PL 94--295, 1976.

U.S. Congress, Safe Medical Devices, PL 101-629, 1990.

U.S. Congress, Safe Medical Devices, PL 102-300, 1992.

U.S. Congress, FDA Modernization Act, PL 105-15, 1997.

Black, J. and Hastings, G., Handbook of Biomaterial Properties, Chapman & Hall, London, 1998.

Cangelosi, R.J., Device standards: the view from the FDA, Clin Eng., Jan-Mar, 5(1), 9, 1980.

Department of Health, Education, and Welfare, Federal Food, Drug, and Cosmetic Act, as Amended, Food and Drug Administration. U.S. Government Printing Office, Washington, D.C., 1972.

Food and Drug Administration, Medical Devices Standardization Activities Report. CDRH, FDA, HHS, Washington, D.C. FDA 94-4219. 1994.

Food and Drug Administration, Standards Survey, National Edition, Bureau of Medical Devices, Washington, D.C., 1979.

Health Industry Manufacturers Association, Guidelines for the Development of Voluntary Device Law Standards, Report No. 79-6, Health Industry Manufacturers Association, Washington, D.C., 1979.

Health Industry Manufacturers Association, Guideline for Evaluating the Safety of Materials Used in Medical Devices, Report No. 78-7. Health Industry Manufacturers Association, Washington, D.C., 1978.

Morton, W.A. and Veale, J.R., Regulatory Issues in Artificial Organs: A Primer, J.B. Lippincott, Philadelphia, 1987.

Ratner, B.D. et al., Biomaterials Science: An Introduction to Materials in Medicine, 1st ed., Academic Press, San Diego, 1996, 457. 427

21

Design and Selection of Implant Materials*

21.1 Introduction

21.1.1 What Is Design?

Design is what engineers do: they apply scientific knowledge and principles

to the solution of practical problems. The object of their design may be a

process, a new material, or a novel device. The process of design is artistic

and creative, drawing from the same well at which the painter, sculptor, or

writer does. What distinguishes the objects of engineering design from those

of other artistic activities is the extent to which technological factors come

into play in their realization (Asimow 1962).

As Cross (2000) points out, the separation between design and fabrication

of man-made artifacts is a relatively recent event. When hand artisanship

was the rule, design and fabrication were not separated: the maker designed

as the final form of the artifact emerged. For the artist, there is still no

separation in function: the design is the object. For the surgeon, the separa

tion is incomplete: although surgical procedures are planned prospectively,

detailed and complex decisions are made during the performance of the

operation. However, for the engineer, the separation has become nearly total:

today those who design rarely make and vice versa. This separation has led

to vocational self-selection that produces significant problems for engineers

involved in design. Engineering has become a linear analytical process,

seeking the shortest distance to a solution. Engineers thus often have great

difficulty in dealing with the creative, synthetic aspects of design that require

attempts to devise as many alternative solutions as possible.

Even more than the creative aspects of design, the concept of a design

process must be emphasized. Solutions to engineering design problems

rarely, if ever, spring full blown from the mind of their creator. On the

contrary, what is required is a systematic, dogged, iterative process stretching

from exploration of initial requirements to evaluation of the preferred solu

tion. In a sense, the design process and its necessary iterative design cycle

* Portions of this chapter appeared in an earlier form as Chapter 13 in Black (1988) and are repro

duced by permission (Churchill-Livingstone Inc.).

represent attempts of engineering designers to deal with synthetic problems

in an analytic fashion, rather in the manner of using digital computers to

create analog models of systems. The use of a design process also has ethical

implications: the iterative nature of design conducted in this fashion requires

a continuous and repeated testing of goals and assumptions, thus introduc

ing a system of checks and balances reflected as an inherent safety factor in

the final product.

21.1.2 Introduction to the Orange

Engineers unfamiliar with design often have the same problem as a begin

ning art student: faced with a blank sheet of paper and an overall conception,

they have no idea where to start. A useful exercise is a consideration of an

orange in a process often referred to as reverse engineering. That is, given

an object or finished artifact, one attempts to understand its rationale and

determine details of the materials and processes of its construction retro

spectively rather than design it prospectively. In this case, the use of an actual

orange is a useful aid. The exercise proceeds in three steps:

1. From observation and physical examination, make a list of all the things that it is possible to know about an orange. In doing so, one usually begins with simple

attributes, such as color, weight, size, etc., and moves to more complex ones, such as shape, number of seeds, amount of sugar contained, etc.

2. For as many as possible of the quantitative attributes listed in step 1, estimate the value. The benefit of this step is particularly seen when a number of individuals do the exercise separately or in groups and then compare their answers.

3. For as many as possible of the attributes listed in step 1, propose as many methods as possible for finding their true or actual value. This step provides clues to the later stages of design by requiring problem solving based upon estimates and other incomplete information.

The three steps of this exercise help to prime the creative pump. In form,

they replicate steps 1, 2, and 4 of the design cycle, respectively (see Section

21.2.2). The first step teaches observation, the second estimation, and the

third creation of alternatives.

This exercise also can be used to illustrate another point about design: it

is better played as a team sport than as solitaire. This point may easily be

demonstrated by setting the “orange exercise” for an individual and for a

group to perform; the members of the group, no matter what its makeup,

will always be more productive on average, let alone collectively, than the

individual. Design can and often is performed by a single individual. How

ever, it is far more productive if it is a group project; the resulting synergy

increases in proportion to the variety of people involved.

21.2 The Design Process

21.2.1 The Phases of Design

Asimow (1962) defines design as a seven-phase process arising from a prim

itive need (Table 21.1). Materials design and selection, in the sense in which

they are discussed in this chapter, fall within Asimow's phases I to III,

depending upon the depth and detail required of the design process. In each

instance, a structured design process or cycle (see the next section) is desir

able. Device design is more likely to have to deal with all of Asimow's seven

phases. In either case, a single phase may require a number of design cycles

within its process. Design may be required for the development of manu

facturing processes and design of devices, of surgical procedures and even

of experiments. With suitable modifications, the same structured process

may be utilized.

21.2.2 The Design Cycle

A structured design process consists of the consecutive execution of a repet

itive design cycle. The design of a simple device, such as a tongue depressor

and its dispensing container, may be achieved in as little as three or four

such cycles; however, a complex design, such as a powered wheel chair, may

require hundreds of such cycles, some in parallel and others in series.

The design of materials is a simpler problem, in general, than the design

of devices. Materials design is rarely addressed directly because device

designers tend to view themselves as expert in materials and to assume that

materials design is merely a matter of selection from among the options

available. This approach is illustrated by Lewis' (1990) otherwise excellent TABLE 21.1 Seven Phases of Design Primitive Need → Preliminary Phases I: Feasibility design II: Preliminary design III: Detailed design Phases Related to Production/Consumption Cycle IV: Planning for production V: Planning for distribution VI: Planning for consumption VII: Planning for retirement Source : Asimow, M., Introduction to Design, Prentice Hall, Englewood Cliffs, NJ, 1962, 1.

discussion of the design of a femoral medullary stem for a total hip replace

ment prosthesis.

It is true that the selection of materials, with and without modification, has

dominated biomaterials design until recently. It is possible to use a formal

design process for selection and/or modification of materials, but this may

seem clumsy and unwarranted except for teaching purposes. However, today

the advancing popularity of composite materials or, more properly, engineered

materials makes necessary the use of a design process for the prospective

selection of biomaterials properties for medical and surgical devices. The evo

lution of biomaterials as a field into the prospective design of interactive

materials, such as resorbable ceramics and polymeric matrices subject to

postimplantation cellular remodeling, further emphasizes this point.

The design of materials may require several cycles in series: first, selection

of materials properties; then selection of processing methods and param

eters, followed by consideration of the interaction of various biomaterials

selected. These cycles cannot take place in isolation from the considerations

involved in the design of the device (for which the biomaterials are

designed/selected) because device requirements impose materials require

ments and materials selections affect design choices.

A number of models may be utilized to develop a design cycle. The

approach in this chapter is derived from that of Love (1986) and is shown

in schematic form in Figure 21.1. The next section is devoted to a step-by

step discussion of this cycle.

21.2.3 Steps in Design

21.2.3.1 Beginning the Design

Design within a given cycle arises from a primitive need. This need may be

an external statement (if the cycle is the first in the process) or may be the

output of a previous cycle. The example in this chapter will take as the

primitive need this possible statement by a product salesman for an ortho

paedic implant company: “My customers are interested in a better total hip

replacement (THR) system for younger patients.” The engineering design

group takes up the challenge and develops a concept for a novel femoral

component. However, the group reports that none of the biomaterials in

their handbooks and reference sources provide the appropriate combination

of stiffness, strength, and fatigue life required to realize the preferred design

approach. In Asimow’s terminology, this finding, a result of a preliminary

phase, becomes the input that begins the material design cycle to be exam

ined here.

21.2.3.2 Step 1: Analyzing Needs

The first formal step in the design cycle is to examine the input statements,

often in collaboration with those who made them, and to develop an

objective summary statement that expresses the needs in an analytic way

and represents a rational objective. For example, development of copper with

a higher melting point is an irrational objective and seeking a higher

strength-to-modulus ratio in the copper–silver binary alloy system is a

rational one. In this case, after careful consultation and deliberation, the

design objective is stated as: “The objective is the design of a new material

suitable for use in fabrication of THR components that combines optimum

FIGURE 21.1

The design cycle. (Adapted from Love, S.F., Planning and Creating Successful Engineering Designs:

Managing the Design Process, Los Angeles, Advanced Professional Development, Inc., 1986.) From last cycle Description Analyze Needs Define Goals Develop Target Specifications Create Alternatives Screen for Feasibility Select the Solution Complete the Design Step 1 Step 2 Step 4 Step 5 Step 7 Step 6 To next cycle Step 3 < S R e e v a l u a t i o n S

stiffness (modulus) with greater strength and a higher endurance limit than

that for presently available materials.”

Note that the act of stating the objective limits the inquiry: a new material

will be designed rather than a present one modified. It also completes the

translation of the primitive need to a defined materials need, with three

attributes: optimum (to be defined) modulus, increased strength, and higher

fatigue endurance. In the same way that an experimental question (and its

hypotheses) can be tested, this statement can be tested at the end of the cycle

to see whether the objective has been realized.∗

21.2.3.3 Step 2: Defining Goals

Design is not a simple process that leads to a unique output. Thus, objectives

must be refined to limit the number of choices at each step and to guide the

design cycle. This is achieved by selecting goals whose attainment (1) is

necessary to reach the desired objective; or (2) represents generally “good”

attributes of engineering design or reflects the desires of the designers. The

first type are called specific goals (demands; Cross 2000) and the second type

are called general goals (wishes; Cross 2000). An initial list of specific and

general goals that might follow from the previously stated summary objec

tive statement is given under the heading “initial” in Table 21.2.

The initial list of goals arises from a discussion with the customer — in

this case, the device design group — and represents the definitive starting

point of the material design cycle. It embodies the customer’s concepts of

what is desired as an end product of the design process. The material design

team must now put its talents to work to understand these desires and to

satisfy them. Some of the initial goals may come from other sources: the

engineering manager is always worried about manufacturing costs; the color

was suggested by the marketing manager because yellow is widely used in

the company's packaging and has come to be identified positively with its

products in the mind of the retail customer, the surgeon.

The material design team must actually go through two substeps to pro

duce the refined set of goals shown in the lower part of Table 21.2. The first

of these, the production of an initial set of goals, is the first creative act in

the design cycle. The question posed at this point is, "What should a new

material for a THR component look like?" As previously noted, the creation

of ideas is not an easy process for engineers. The tendency is to "freeze": to

be unable to produce ideas or, more commonly, to have an initial thought

and then to proceed to develop it without consideration of further alterna

tives. The general solution for the individual designer is to produce a situ

ation that is stimulatory and nonself-critical.**

* Discussion of the design and conduct of experiments is outside the scope of this work. How

ever, the reader should note that this phase is identical to the statement of an experimental ques

tion.

** In this section, I refer to a single designer. In Section 21.2.3.5, the situation of creative effort by

a group will be considered.

In this case, the designer may decide that “I’m going to set the problem

aside, go for a 5-km run, and when I come in, write down the first ten things

that come into my head.” Such a procedure, with variants, has been adopted

frequently by many if not most creative persons and is sometimes referred

to as creative avoidance of the problem: undertaking other activities to

distract the conscious mind (probably the analytic left brain function) and

using the products of subconscious deliberation (probably the synthetic right

brain function), without self-criticism or censoring.

The initial list is then reviewed for reasonableness and duplication and

perhaps the process is repeated or extended until the sense is that all of the

immediately possible options — in this case, design goals — have been

acquired. Often the review triggers new ideas not previously considered.

The designer in this example has added two specific goals and no general

goal to previously cited desires. Note that this is an abbreviated example;

step 2 of an actual design cycle might produce dozens of specific and general

goals. TABLE 21.2 Design Goals: New THR Material Initial Specific Modulus < 0.5 × Ti6Al4V Strength as high as possible Endurance limit as high as possible Corrosion/release rate “low” No wear against UHMWPE a Color: yellow General Minimum cost No limit on source of supply Simplicity of fabrication Refined Specific Modulus <

0.5 × Ti6Al4V (H) Strength as high as possible (M) Endurance limit as high as possible (H) Corrosion/release rate as low as possible (H) Wear rate (against UHMWPE) as low as possible (M) Color: yellow (L) Formability in the operating room (M) Release of wear particles > 25 μm in size only (H) General Minimum cost per kilogram (L) No limit on source of supply (M) Simplicity of fabrication (M) a Ultrahigh molecular weight polyethylene

The second substep is the assignment of a priority to each of these initial

goals to produce a set of refined goals. This is necessary because, in an actual

design case, the number of goals very rapidly grows to a point at which it

is obvious, a priori, that all cannot be met simultaneously. Thus, a ranking

of relative importance is necessary. In this case, the designer employed a

common practice and selected three levels of priority:

- High (H): must be met for successful design
- Medium (M): would like to meet during design cycle
- Low (L): desirable to meet but may be sacrificed

Therefore, the material’s modulus is identified as a much more important

attribute than its color, although the desire to satisfy the marketing manager

is still considered as part of the later steps in the cycle. In a more subtle

distinction, it is recognized that in the intended application, the endurance

limit is a more important material attribute than the tensile strength,

although both are important. During this substep, the sets of goals are also

screened to eliminate absolute statements; statements of goals should not

include the terms “never,” “always,” “none,” etc.

21.2.3.4 Step 3: Developing Target Specifications

Setting specific and general goals and then refining the list and assigning

priorities produce considerable clarification of the problem in hand but do

not provide details necessary for later steps in the design cycle. To achieve

this, it is necessary to translate the refined goals of step 2 into measurable

quantities.

These measurable quantities are called specifications. They must be nec

essary, thus not setting limits unrelated to performance. They must also be

sufficient: taken as a group, their satisfaction must be sufficient to produce

a successful design and to assure that the formal requirements of the Medical

Device Amendments (U.S. Congress 1976) of safety and efficacy are met.∗

Finally, they must be conservative: setting too high values or too stringent

criteria will elevate cost unacceptably or possibly make the design unreal

izable.

Consider the refined goal (Table 21.2):

• “Corrosion/release rate as low as possible (H)” This might be translated into these specifications: • Corrosion rate in vivo shall not exceed 0.1 mg/cm 2 /year. • Release rate in vivo shall not produce a concentration of products

≥ 5 ppb at a distance of 1 cm from the implant–tissue interface.

* Note that materials used in medical devices are not explicitly regulated but are subject to this

requirement indirectly because they perform in a device. See Section 20.5 for a further discussion

of this point.

The attainment of minimum corrosion/release was judged to be of high

importance; this is reflected in the use of design margins, multipliers of

minimum values. In practice, these may vary between 10 (for extremely

critical attributes) and 1.1 (for low importance or optional attributes). In this

case, the actual allowable values might have been 1 mg/cm 2 /year and 50

ppb, respectively, but were reduced by application of a 10× design margin.

There are no objective criteria for deriving design margins: they reflect cur

rent practice in similar designs.

This is a good time to conduct a design conference to review the project

because completion of phase 3 marks the boundary between defining the

problem and, in a strict sense, solving it. It is worthwhile determining

whether the team is on the right track before the really hard, time-consuming

and costly parts of the cycle are undertaken.

21.2.3.5 Step 4: Creating Alternatives

Development of design concepts or alternative possible solutions is the heart

of the design process and the point at which most fatal mistakes are made.

It requires, again, a suspension of self-criticism and a source of external

stimulation. For most people, concepts and alternatives evolve more readily

in a group situation in which one person’s ideas trigger another’s imagina

tion. This is the time in the design process when the prior formation of a

multidisciplinary design team really pays dividends. The goal is the same

as in step 2: to develop as many independent approaches to realization of

the design goals as possible.

As an introduction to this step, the material’s designer begins to gather

supporting information on past and present materials used in THR prosthe

ses components as well as on current progress in materials design and

processing. Information acquired at this time serves the subconscious as a

source of ideas and, if a design team is in existence, all members should

have access to this resource information. This information will also be needed

for the next step.

The primary tool in creating alternatives is the brainstorming or “blue sky”

meeting. Cross (2000) lists the following essential rules

for such a session:

- Offer no criticism during the session.
- A large number of ideas is wanted.
- Seemingly crazy ideas are welcome.
- Keep all ideas short and snappy.
- Try to combine and improve on the ideas of others.

Citing William J. Osborne, Love (1986) provides many practical suggestions

on how to organize and run a successful session to create alternatives.

Table 21.3 presents a list of ideas that might arise from such a step 4

exercise. The initial list was developed in two creative sessions: a break was

taken between the sessions, and the first part of the list was reviewed by the

group to initiate the second session. The final list was developed some days

later by review and analysis of the initial list.

In this hypothetical case, the creative sessions produced an initial list of

18 ideas that was then reduced to four concepts. The last of these was

eliminated by reference to the objective summary statement (it was not

judged to be able to lead to a new material) and the other three, which focus

primarily on processing leading to new materials, could each be continued

in parallel through later stages of the process. Trouble arises at this point or

at a later point in the process when alternatives are not fully constrained

and/or decisions are made that circumscribe the later steps too narrowly.

Reduction in scope can occur later; what is needed at this point is to have

created a maximum range of possibilities.

21.2.3.6 Step 5: Screening for Feasibility

It is now necessary to examine the alternatives created in the preceding step

(Table 21.3) and select those with which to continue the process. In the TABLE 21.3 Design Alternatives: New THR Material Initial List Animal tusk Modified wood Cloned tree with new properties Petrified wood Coral Metal impregnated coral Woven ceramic fiber/resin impregnated Carbon fiber/graphite Carbon/silicon carbide powder composite Carbon/polyethylene powder composite Hydroxyapatite/polyethylene powder composite Break Taken at this Point Metal-fiber-reinforced silicon nitride Alumina/polymer composite Woven sapphire fiber/metal impregnated Sapphire beads with spring connectors Whisker-reinforced polymer New titanium alloy Titanium/polymer powder composite Final List Modified natural material Fiber-reinforced composite Powder composite New titanium alloy

example given, after analysis of the possibilities proposed, only three alter

native approaches emerged; it might be reasonable to continue with all three.

However, each would need to be screened for feasibility. If more than three

approaches had resulted from the previous step, feasibility screening could

be used to select the two or three most likely to lead to success.

Feasibility is the process of applying rational criticism, which was sus

pended in the previous step, to enable estimates to be made of the relative

chance for success of each proposed approach. The primary aspects of each

idea to be examined are: technical, economic, supply, and parsimony. These

are justified as follows:

• Technical: the designer must avoid attempting to violate laws of nature.

• Economic: cost and resulting price are powerful considerations, even in materials design. This may refer to the final cost of the material and of its design and qualification.

• Supply: there should be no reasonable intrinsic or imposed barrier (through protection of intellectual property, etc.) to provision of sufficient material for the intended application.

• Parsimony: the simple is preferred over the complex.

Secondary attributes, including the designer’s intuition, and political,

legal, and/or perceptual issues (which may be unrelated to technical func

tion) may also come into play. The specifications may be used to drive the

screening process by attempting to estimate values for each of the material’s

physical attributes (identified in step 4) and using the apparent ease of

achieving the specified values as an index of feasibility. The screening process

may be qualitative — each alternative is ranked with respect to each aspect

— or it may be made quantitative, with values assigned to rank and an

overall score derived for each approach.∗

21.2.3.7 Step 6: Completing the Design

Completing the design of the alternatives created in step 4 that survive

feasibility screening in step 5 is the final pure design step of the design cycle.

Not much needs to be said in that it involves traditional engineering pro

cesses of analysis, calculation, and simulation and may even require some

pilot experiments to verify design and manufacturing concepts. Parametric

studies, in which the effects of varying controllable independent variables

are tested, are of great value in later considerations. The specifications must

explicitly drive design choices because they will be the basis for testing the

final design in the next step.

When alternative approaches were selected (step 5), design completion

usually results in a definitive ranking in order of preference or in the elim

∗ Ranking the three approaches selected in the last step is left as an exercise for the reader.

ination of one or more owing to an inability to realize a complete design.

However, cost and time considerations may result in a decision to complete

the design for only the most promising (most feasible) alternative.

21.2.3.8 Step 7: Selecting the Solution

Design selection (or evaluation) is a simple process of comparing the

attributes of the final design to the specified values developed in step 3 and

determining how well they have been met. If no design conferences have

been held (with the “customers”) since the one at the end of step 3, now is

the ideal time to do so. The customers (and outside reviewers, if possible)

may serve as a board of review to complete this step. Ideally, all high- and

medium-priority goals should be met, through satisfaction of their depen

dent specifications (≥S, Figure 21.1), for the design to be said to be acceptable

and for it to advance to the next cycle of the overall (device, etc.) design

process.

If, in the opinion of the reviewers, the design is unacceptable (fails to meet

one or more key specifications, <S, Figure 21.1), several options are open.

These include reviewing design concepts to see whether additional ones can

be developed, reviewing the specifications to see whether they (or their

design margins) can be relaxed, and reviewing the goals to see whether they

are all necessary and have appropriate priorities. If changes can be made

retrospectively at any of these three steps, the cycle can be resumed at that

point to determine whether a satisfactory design results.

21.3 The Value of Prospective Design

21.3.1 Why Have a Design Process Anyway?

The design process or even a single design cycle will not always yield a

satisfactory result. Objectives may be unrealistic or even forbidden by basic

physical principles or the goals selected may not be technologically achiev

able or financially feasible at the time. However, it is clear that, in the majority

of cases, a structured design process does produce satisfactory results with

well-articulated foundations and justification. In most cases, within the

boundaries of assumptions and choices made at various steps, the resulting

designs will represent optimum solutions. Thus, prospective design is to be

preferred to inspired guesses in designing biomaterials, as in other areas of

engineering.

21.3.2 Design in the Real World

The process elaborated here, based upon ideas put forward by Asimow

(1962), Love (1986), and Cross (2000) as well as my experience in academic

and industrial settings, reflects the ideal. The names of the seven steps

encapsulate the central ideas: analysis of need, proposals for solution, elab

oration of proposals, and testing of results against the

original need. This

cyclic, iterative approach is critical, whether it exists within a fully articulated

process as described here or merely guides more informal considerations.

In the biomedical context, useful new materials and devices can result

neither from pure analytical considerations of engineers and developers nor

from pure synthetic suggestions of physicians and surgeons. What actually

happens is that there is a continuing, interactive collaboration, made difficult

at times by the necessary conflict between analysis and synthesis. Groups

and companies that have been successful in bringing novel materials and

devices incorporating them into clinical use have managed to preserve bal

anced collaboration. Robertson and Hyatt (1998) illustrate this interaction in

the idealized development of spinal instrumentation hardware.

However, developments dominated by either party have been seen, in

particular cases, to lead to unfortunate consequences. Engineers often

express frustration in working with medical personnel who generally have

difficulty in providing quantitative measures of their clinical observations.

Clinicians tend to be overly impressed by engineering rigor, as exemplified

by finite element analysis, and then disappointed when performance, which

may have been based on inadequate inputs, fails to meet expectations.

As bioengineering matures professionally and clinical experience with

existing materials now extends to periods of decades in some applications,

additional barriers to successful design of materials have emerged. Although

extensive testing protocols have been devised in the laboratory and in animal

models (Chapter 17 and Chapter 18), it is still extremely difficult to predict

biological performance of materials in the long term. Furthermore, the exist

ence of an increasing range of materials with known host and materials

responses in highly successful devices raises real ethical and practical issues

concerning substitution of novel materials in such applications.

Success in design of materials or of devices requires an understanding of

history as well as cultural and professional differences and all parties' will

ingness to be flexible and remain focused on the real goal: a better outcome

for present and future patients.

Asimow, M., Introduction to Design, Prentice Hall, Englewood Cliffs, NJ, 1962, 1.

Black, J., Orthopaedic Biomaterials in Research and Practice, Churchill Livingstone, New York, 1988, 303.

Cross, N., Engineering Design Methods: Strategies for Product Design, 3rd ed., John Wiley & Sons, Chichester, U.K., 2000.

Lewis, G., Selection of Engineering Materials, Prentice Hall, Englewood Cliffs, NJ, 1990, 179.

Love, S.F., Planning and Creating Successful Engineering Designs: Managing the Design Process, Los Angeles, Advanced Professional Development, Inc., 1986.

Robertson, J.T. and Hyatt, D., Concepts and issues of spine device development and regulation, in Capen, D.A. and Haye, W. (Eds.), Comprehensive Management of Spinal Trauma, St. Louis, C.V. Mosby, 1988, 414.

U.S. Congress, Medical Device Amendments. PL 94-295, 21 USC 301, 1976.

Ashby, M.F., Materials Selection in Mechanical Design, 2nd ed., New York, Butterworth Heinemann (Elsevier), 1999.

Bronikowski, R.J., Managing the Engineering Design Function, Van Nostrand Reinhold, New York, 1986.

Collins, J.A., Failure of Materials in Mechanical Design: Analysis, Prediction, and Prevention, 2nd. ed., John Wiley & Sons, New York, 1993.

Norman, D.A., The Design of Everyday Things, Basic, New York, 2002.

Petroski, H., The Evolution of Useful Things, Vintage, New York, 1994.

Shackelford, J.F., Alexander, W. and Park, J., CRC Practical Handbook of Materials Selection, CRC Press, Boca Raton, FL, 1995. 441

22

Clinical Performance of Biomaterials*

22.1 Historical Aspects

Implants used for the alleviation and treatment of human disability and

disease are derived from natural (biological donor) sources or are manufac

tured from organic and/or inorganic materials. The failure and success of

live cell, tissue, and organ transplantation have been studied extensively.

However, the study of the consequences of the use of manufactured biom

aterials in implants, in their actual service setting, has been spotty at best

and based primarily upon complications seen in reported clinical series or

on local, intermittent study of devices retrieved at surgical revision (replace

ment) or at autopsy.

The use of manufactured implants in medicine has its roots in antiquity;

however, the practice has only become prevalent in the last century and has

gained widespread success only since World War II. Early efforts were dis

tinguished by high rates of complications and failures and thus the use of

nonbiological implants was long regarded as experimental. Historically,

improved biomaterials and devices emerged from short-term animal studies

and clinical observations that eliminate undesirable material and/or design

related performance on a case-by-case or small-group-study basis.

The result is that now a small group of biomaterials is, by and large, highly

successful when used in a broad variety of designs; its use for many indi

cations has become routine (see Interpart 1 for typical examples).** Heart

valve replacements, heart pacemakers, and total hip and knee replacements

are examples of devices incorporating such materials for which clinical expe

rience of more than 10 years allows prediction of a high likelihood of success

(>90 to 95%) for individual patients who meet appropriate indications. It is

hard to estimate how many chronic (intended to remain in situ for more than

30 days) implants are in use today in the U.S., but national data (Moss 1991)

* Many of the ideas in this chapter were developed and elaborated during contractual studies

for the USFDA, CDRH, whose support is gratefully acknowledged.

** However, there is no list of “generally recognized as safe” biomaterials, due to the modern,

and correct, emphasis on biocompatibility being related to specific application requirements and

to the resulting risk/benefit ratio.

suggest that the number was at least 11 million by 1988 with annual increases

since then most probably of about 10%. Non-U.S. experience probably equals

or slightly exceeds these figures; the 2005 worldwide total of chronic

implants probably now exceeds 75 million.

However, success has produced a new set of problems, which can be

summarized as follows:

• Large-scale, routine clinical use of implants, even with low failure rates, produces significant numbers of patients whose procedures fail to meet expectations.

• Clinical confidence in implants results in pragmatic extension of the indications for their use, especially to more difficult medical problems and to earlier intervention in disease processes.

• Routine use and earlier intervention produce an increasing mismatch between typically short development and evaluation cycles and longer intended (and actual) service periods.

Together, these factors have produced needs for certain types of data con

cerning the biomaterials from which implants are manufactured:

• Long-term effects of in vivo environments on biomaterials properties

• Chronic (including systemic and remote site) effects of manufactured biomaterials on human physiological processes

• Comparative service experience of different biomaterials in similar or different device designs used for the same clinical application/ indication

The response to these needs has been an effort, led primarily by bioengi

neers, to study implants and explants (retrieved devices) in a field that has

come to be termed device retrieval and analysis (DRA). Early DRA efforts

tended to focus on the disease state and view the device generically (medical

or clinical pathology model) or to study the device closely, with little atten

tion given to the generic disease or to individual patient conditions and use

(engineering failure analysis model).

Since 1976, at least six major U.S. technical conferences* on DRA have had

a primary, if unstated, goal to bring these two models together and thus

produce a unified approach (using a single analytical model) to the study

of biological performance (host and implant response) of devices (and the

biomaterials from which they are fabricated) in human clinical use. Numer

ous professional societies, commercial concerns, and U.S. government

* Retrieval and Analysis of Orthopedic Implants, Bethesda, MD, 3/5/76; Corrosion and Degra

dation of Implant Materials, Kansas City, MO, 5/22-23/78; Implant Retrieval and Biological

Analysis, Bethesda, MD, 5/1-3/80; Corrosion and Degradation of Implant Materials: Second

Symposium, Louisville, KY, 5/9-10/83; Symposium on Implant Retrieval, Snowbird, UT, 8/12

14/88 and Implant Retrieval Symposium, St. Charles, IL, 9/17-20/92.

agencies have been involved in the sponsorship of these conferences and in

support of numerous smaller symposia and workshops as portions of larger

engineering and medical professional meetings.

Of outstanding note have been the efforts of the ASTM F-4 Committee on

Medical and Surgical Materials and Devices, which, since 1972, has been

codifying procedures and practices for the physical

retrieval and analysis of

individual implants. Although not believed to be widely used exactly as

written, these procedures, such as F-561-05,* provide important and useful

guidance to DRA activities. The American National Standards Institute

(ANSI) and the International Standards Organization (ISO) have more

recently begun to develop standard procedures for DRA. Of note is the work

of Working Group 5 of ISO Technical Committee 150 that is developing

standards for retrieval and analysis of implantable devices.**

However, despite early and continuing perceptions that the data and the

knowledge that can be gained from study of retrieved devices are of vital

importance, most of these efforts continue to focus on the implant and on

the implications of its physical condition (engineering failure analysis

model). The seven major parties to DRA (patient, physician, manufacturer,

treating institution, insurer, regulatory agency, and society at large) recognize

a shared common interest in DRA and its outcomes; however, individual

benefit/risk calculations by each concerned party are in constant conflict

(Black and Fielder 1992) and have stood in the way of emergence of a unified

analytical model or of comprehensive and/or multi-institutional DRA pro

grams. Table 22.1 briefly highlights the benefits and risks perceived by each

party involved in DRA.

Notwithstanding this continued conflict, it is important for the advance

ment of the field of biomaterials and the practice of medicine that DRA

efforts continue to advance and mature. The following sections outline some

applicable methodology.

22.2 Procedures for Device Retrieval and Analysis

DRA today is of necessity a “team sport” brought about by the complexities

of medical practice and of the social and legal setting of the early 21st century.

Before one undertakes such activities, it is necessary to establish a supporting

organization and for the parties involved to agree on a number of assump

tions. The issues to be dealt with include goals, responsibility, methodology,

and reporting.

* F-561-05 Practice for Retrieval and Analysis of Implanted Medical Devices, in 2005 Annual Book

of ASTM Standards, Vol. 13.01: Medical Devices; Emergency Medical Services, ASTM Interna

tional, West Conshohocken, PA, 2005.

** ISO/DIS 12891-1: Retrieval and analysis of surgical implants — part 1: retrieval and handling.

22.2.1 Goals

DRA is a general term that can cover a wide variety of activities, each of

which has specific goals, such as:

• Premarket approval clinical evaluation: goals may include determining normal and abnormal device and/or material performance, meeting regulatory requirements for reporting adverse outcomes, and providing feedback for device and/or surgical technique modification.

• Routine clinical use of a device: goals may include monitoring of appropriateness of device/patient matching, determining specific device-related “failure” rates as part of survivorship calculations, establishing mechanisms underlying survivorship estimates, and planning future treatment for individual patients.

• Autopsy retrieval: goals may include investigation of local and systemic host response, long-term material property changes, and distribution and storage of implant degradation products.

In any of these or other activities, there should be formal written statement

of and agreement to goals because such goals strongly affect the design and

conduct of DRA studies.

TABLE 22.1

Benefits and Risks in Device Retrieval and Analysis Party Benefit Risk

Patient Improved medical care Increased cost Increased concern related to device performance

Physician Improved service to patient Possible malpractice liability

Manufacturer Increased knowledge of device performance Increased administrative burden Possible increased cost Possible tort liability

Treating institution Improved service to patient Increased cost Possible liability

Insurer Increased knowledge of device performance Reduced cost through use of “better” devices Possible increased cost

Regulatory agency Increased knowledge of device performance Increased administrative burden

Society at large Increased knowledge of device performance Reduced cost through use of “better” devices Improved health care Possible alarm about device malfunction

22.2.2 Responsibility

Any DRA study should be conducted under the direction of a group of

interested, appropriately trained, and committed individuals. The issues

raised by DRA are such that careless or unplanned activities can produce

extremely adverse outcomes for many of the parties involved. There should

be a written, agreed upon set of procedures and methods. One individual,

preferably a Ph.D.-trained person with experience in DRA, should have final

responsibility for the program and should be designated as the custodian

for the devices between their surgical recovery and their discharge from

DRA study.

22.2.3 Methodology

In its most general form, DRA is an example of discovery science. Thus, it

is inappropriate, except in very small, tightly focused studies, for all recov

ered devices to undergo a fixed set of procedures. Such an approach, espe

cially in the usual setting of routine clinical practice, would produce

insupportable costs without returning commensurably valuable informa

tion. Thus, it is good practice to classify devices prospectively before study.

Three generic classes can be easily recognized. These are briefly described

next, with examples of each type of device and of possible response within

a DRA study:

• Class 3: no frank evidence of physical damage to the device pre- and postexplantation and no implication of involvement of device malfunction in clinical outcome • Example: routine (nonsymptomatic) removal of fracture fixation hardware • Response: positive identification of device, cataloging, discharge from recovery system*

• Class 2: frank evidence of physical damage to the device post- and possibly pre-explantation but no implication of involvement of device malfunction in clinical outcome • Example: component of total hip replacement, showing surface defects, recovered from site of early postoperative infection

* It is assumed in this chapter that any institution in which a DRA study is planned already has

a working device recovery system in place. Most simply stated, a device recovery system is a set

of procedures, parallel to those used for clinical pathology specimens, that dictate how a device

is collected from the surgical field or clinic, handled postrecovery, examined for routine iden

tification and evaluation purposes and then “discharged” (given to patient, retained for

research, discarded, etc.) (see Section 22.3.4). It is difficult and ill advised to conduct DRA studies

in the absence of such a recovery system; one of the first

steps in designing and implementing a

DRA program may have to be working with the host institution to install or improve a device

recovery system. • Response: as for class 3 with additional procedures to examine and document noted device defects (see Table 22.2)

• Class 1: frank evidence of physical damage to the device pre- and postexplantation and implication of involvement of device malfunction in clinical outcome • Example: cardiac pacer lead with broken conductor • Response: as for class 2 with additional procedures to determine origin and/or cause of noted effects* (see Table 22.2)

22.2.4 Reporting

Timely reporting of results is the key to sustained and useful DRA studies.

Reporting should take the following forms:

• Rapid reports should be made to the treating physicians, on a time schedule parallel to that in the treating institution for clinical TABLE 22.2 Conduct of DRA Studies Steps Removal Class Recovery Procedure Retrieve Package Identify Sterilize a Classify Class 1 Class 2 Class 3 Evaluate Photographs X X X Culture reports X X Histology X X Metallography X Mechanical analysis X Chemical analysis X Special tests X X Mechanical testing (device portions) X Hardness X Specific histologic stains X Metal analysis (AAS) (fluids, tissues) X Case disposition X X X Prepare report X X X Store/dispose of device X X X a Specific studies may require devices to be studied in unsterilized conditions; this may require deviations from routine recovery practice.

* Note: Clinical institutions frequently elect to deal with class 1 cases in a different manner than

class 2 and 3 cases because the former involve devices that may become physical evidence in

malpractice and/or product liability proceedings. pathology studies. In addition to a personal report to the primary physician, a note should be placed in the hospital chart, over the signature of the DRA supervising professional. Although it is unusual for such individual studies to have an impact on the further treatment of the patient in

question, such reporting is simply good manners and helps to maintain the professional relationships needed for DRA studies.

• In the case of class 1 and 2 devices, reports should be made directly to the manufacturer. This is especially necessary if more than one set of similar findings occurs during a study. Sensitivity should be shown to studies of class 1 devices: because of the possibility of litigation in such cases, reports should focus on physical findings and descriptions but omit theories of causation, unless they are supportable by peer-reviewed, published studies.

• Depending upon the nature of the findings and, in the case of a class 1 device, the degree of patient involvement, timely reports may need to be filed with a regulatory agency, such as the FDA in the U.S. Because this is a legal requirement, the treating institution should have already established an approved procedure for submitting such reports as a part of its device recovery system. DRA personnel should be aware of such a system and provide rapid access to their findings for the individuals responsible for making the report.

• Finally, there is a responsibility to make results of studies of groups of retrieved devices available to the scientific and engineering community. Such reports might include publication, presentation at professional meetings, and participation in workshops and instructional courses.

It cannot be too strongly emphasized that, except in reports to physicians

within the treating institution, great care must be taken to preserve the

privacy and identity of the patients involved. This is an ethical and legal

requirement (Black and Fiedler 1992).

22.3 Common Concerns about Device Retrieval and Analysis

22.3.1 Cost

Costs for study and analysis of implants are extremely difficult to identify

due to the varied nature of individual implants and the present indications

for analysis. Survey results and anecdotal experience suggest ranges of direct

costs as follows:

- Class 3: $5 to 25
- Class 2: $25 to $250
- Class 1: $250 to $10,000

These costs certainly are subject to economy-of-scale effects and can be

expected to be nearer the lower ends of each range in large-scale and/or

routine clinical retrieval and analysis studies.

22.3.2 Device Ownership

Central to any functioning DRA program is the concept of rapid availability

of enrolled (recovered) devices, when selected, for nondestructive and

destructive studies. It is good practice that all custodial and other procedures

for handling implants and other medical devices satisfy minimum legal

“chain of evidence” standards; however, the assumption* that patients may

“own” devices removed from their bodies continues. It is suggested that

concern for property rights may be satisfied in one of three ways:

- Institutions that conduct DRA studies beyond routine logging and discharge of recovered devices should probably alter their standard permission for treatment forms to include permission to study devices, including destructive testing. Possible language, as previously proposed,* is: I understand that part of my treatment may require removal of an artificial implant. If an implant is removed, I give

permission for any studies of it related to my treatment. I understand that I and my doctor will be informed of the results of these studies in a timely fashion and that I will be consulted before the implant is discarded or if the implant is desired for other studies.

• In the case of individual (authorized by IRB) prospective studies, an additional approved permission form may be developed that explains the study's goals and conduct and asks for the patient's permission for any necessary destructive testing.

• Alternatively, because devices may already be in institutional custody at the time that they are selected for a study, treating institutions may elect to obtain permission for study retrospectively, using a form such as that described in the previous option (second bullet). This option is less desirable than the first (routine permission) because it may raise the patient's concern over possible device malfunction.

* Black 1996.

22.3.3 Patient Confidentiality

There is a clear need to retain a defined linkage between DRA data, which

are devoid of patient identification, and medical records of each patient. This

linkage is required because studies of device function and biomaterials prop

erties may require correlation with disease state, mechanical environment,

etc. encountered by the device during service. A possible linkage, as pro

posed in Section 22.4, is a coded identification number generated at the time

of recovery of the device. The manual or electronic ways of generating such

unique codes will not be discussed here. However, the key to the coding

system will be deemed to be confidential and related to the

patient, thus not

accessible under Freedom of Information Act inquiry. The keys would be

disclosed only to DRA study supervisors and then only after suitable assur

ances concerning maintenance of patient confidentiality were obtained and

the “need-to-know” established on a patient-by-patient basis.

22.3.4 Recovery System

Repeated recommendations from many sources make it clear that all clinical

facilities in which devices are explanted should possess and maintain recov

ery systems to deal with removed devices. The need for recovery systems

has been frequently noted in individual hospital accreditation committee

reports and exists independently of DRA studies or of the proposed imple

mentation of a NIDRA structure (see Section 22.4).

A recovery system should, at a minimum, provide for the following docu

mented steps:

1. Collection of the device from the surgical field

2. Entry into the patient’s clinical record of a minimum data set

3. Handling and transport of the device to (1) minimize postexplantation damage to the device; and (2) minimize health risk* to support personnel

4. Examination and identification of the retrieved device

5. Discharge of the device from institutional care

(adequate decontamination, disposal, or discharge to physician, patient, or third party)

* It is routine practice in DRA studies to assume that all explanted devices are contaminated with

human pathogens unless positively sterilized. Because postexplantation sterilization procedures

may affect materials' properties, routine sterilization is often not performed, during recovery or

retrieval, and devices may need to be handled through some steps of the recovery process in an

unsterilized state.

22.4 Proposed National Implant Data Retrieval and Analysis Program (NIDRA)

A 1981 conference* attempted to focus on data and knowledge resulting

from DRA rather than on material and design aspects of implants. However,

it primarily dealt with codification and standardization processes without

addressing the need for an overall knowledge structure with defined internal

data flows.

Notwithstanding this pioneering effort, little progress has been made in

generalizing and unifying the intellectual product of DRA efforts and in

making it accessible in real time. Contemporary DRA programs are still

scarce and tend to be based in hospitals and academic research groups.

Strongly influenced by liability considerations, the medical device industry,

by and large, has elected to react to individual cases of

apparent device

malfunction rather than to study the general successful or unsuccessful

performance of its products. Data interchange reflecting case or selected

group studies performed largely without controls continues to be primarily

by podium presentation and paper publication. Two further defects of many

of these studies are that:

• They are performed in large centers that provide secondary or tertiary care and thus have nonrepresentative patient populations.

• They frequently involve or are directed by surgeons and engineers involved in development of the devices or device classes under study, without adequate third-party supervision, oversight, or quality control.

It was apparent by 1992 that a new effort needed to be made to gain

necessary data from the vast human experience of routine clinical use of

implants. The U.S. Food and Drug Administration commissioned me to

develop a design specification for a national data management system. A

questionnaire was developed, widely distributed and the results codified.

The results of that survey clearly supported the need for development of a

national knowledge structure and contain a number of recommendations

that were drawn upon in preparation of this specification. Five guiding

principles were proposed and, validated by the survey, can

now be stated

as system requirements for a national effort to study clinical performance of

biomaterials:

• The emphasis should be on understanding biomaterial performance in vivo as it relates to biomaterials' composition and processing, individual patient variables, and device design classes.

* Medical devices: measurements, quality assurance, and standards, Gaithersburg, MD, 9/24

25/81.

• The program should be structured to provide early and continuing publicly utilizable data on device survival and biomaterial performance.

• The system design should embody low-level uniform data retrieval (for statistical results) combined with focused case studies related to perceived or possible clinical problems (for biomaterials' properties).

• The resulting database should be prospectively linked, in an interactive way, with existing and planned engineering, biological, and clinical databases.

• The system should be decentralized and extramural (nongovernmental) insofar as possible, with central intramural activities involving only planning, direction, data analysis, and audit functions.

The final design specification described the database and its associated

device- and data-acquisition and management systems (termed collectively

the "NIDRA structure") needed for low-cost, reliable production of bioengi

neering data from current clinical implant experience to meet the needs of

expanding use of implants.

22.5 Elements of a NIDRA System

The aim of the NIDRA proposal is to describe a system capable of generating,

in a timely fashion, a number of minimum data sets. The driving idea of this

approach is to make the implantation and removal of chronic (>30 days)

implants statistical events much as births and deaths or, for that matter,

purchase and scrapping of automobile tires are. A secondary goal is to make

recovered implants available for larger scale DRA studies than are now

possible within single institutions.

22.5.1 Data Sets

Three data sets are proposed:

• A minimum explantation data (EDATA) set containing no more than six items: • Date of removal • Identification number (ID number) of medical facility where explantation occurred (per HSS FDA 92-4247*)

* HSS FDA 92-4247: Medical device reporting for user facilities, December 1991. • Coded ID number creating link to patient hospital records (may include previous two items) • Device identity (per HSS FDA 91-4246*) • Retrieval grade: recommended codes (referring to device rather than to clinical outcome)**: • RG1: no pre- (diagnostic imaging, functional test result, etc.) or postremoval (naked eye, functional test result, etc.) defects • RG2: preremoval defects; no postremoval defects • RG3: pre- and postremoval defects • RG4: no preremoval defects; postremoval defects • Device serial/model number (when available) (optional)

• An expanded explantation data set (expanded EDATA): this data set would include the EDATA set as well as information on implantation (e.g., original anatomical location), service (e.g., implantation duration), and analysis (e.g., lipid content of silicone rubber) as well as the minimum IDATA set (when available). Although it is clear that the use of standardized analytical procedures would simplify comparison of expanded EDATA sets, the careful definition

of test methods and the use of control (reference) materials would permit full data merger in the envisioned data base.

• A minimum implantation data (IDATA) set containing no more than six items: • Date of implantation • ID number of medical facility where implantation occurred (per HSS FDA 92-4247) • Coded ID number creating link to patient hospital records (may included previous two items) • Device identity (per HSS FDA 91-4246) • Indication for use (per DRG) • Device serial/model number (when available) and/or coded ID number creating link to manufacturing records

22.5.2 Organizational Elements

The proposed NIDRA structure designed to generate, collate, and analyze

these data sets has four principal elements:

⁎ HSS FDA 91-4246: Classification names for medical devices and in vitro diagnostic products.

August 1991.

⁎⁎ These correspond, respectively, to DRA classes (section 22.2): RG1: class 3, RG2: class 2, RG3:

class 1 (possibly class 2), RG4: class 2.

• Clinical institutions

• Study centers

• Data analysis and device management center (DADMC)

• Steering committee

The proposed responsibilities of each element and their manner of interac

tion are briefly outlined next.

22.5.2.1 Clinical Institutions

Any participating clinical institution would be expected to modify its

(informed) “consent for treatment” procedure to enable off-site analysis of

devices, to operate a recovery system, and to enroll each device by informing

the DADMC (see later section) by FAX transmission of a minimum EDATA

set on the day of explantation of each device. The clinical institution would

then hold the device for a set period (2 to 10 days; recommendation: 3

working days) and subsequently:

• If informed affirmatively (during the holding period) of a need for the device for an approved DRA study in another center and, upon receipt of a prepaid shipping container, ship the device to a specified study center, or

• If not informed affirmatively, dispose of the device in accordance with recovery system routine practice

The costs for a clinical institution to participate in this program would be

minimal and deviation from conventional recovery practice would in many

cases not be necessary beyond NIDRA case enrollment (FAX preparation

and transmission).

22.5.2.2 Study Centers

The principal public need is for an accessible flow of uniform, high-quality

data concerning properties and clinical performance of implants. It is pro

posed to support present analysis programs and, if needed, to encourage

the establishment of new ones in academic, medical, or industrial settings,

by defining and funding a set of prospective studies. Support would be

provided from traditional public funding sources as well as from a fund to

be established in relation to the DADMC.

Briefly, experimental questions would be proposed by the NIDRA Steering

Committee and advertised through traditional RFP/RFC channels for

response by interested groups. Examples of such areas of study are in vivo

degradation of silicone elastomers and fatigue processes in spinal fixation

devices. A study center with a funded NIDRA study would have real-time

access to the device enrollment data flowing into the DADMC so that devices

meeting the criteria defined for each experimental program could be

retrieved rapidly in large numbers. The study center would, as part of its

responsibilities, design and fabricate appropriate shipping containers. It

would identify devices that met the criteria of its study, cause DADMC to

make an affirmative selection of these devices on its behalf, and dispatch

appropriate prepaid shipping containers to the clinical institutions that

enrolled the selected devices. The study center would also bear the respon

sibility (and cost) of directly contacting the clinical institutions from which

it received selected devices to obtain supplementary data, laboratory test

results, etc. as needed for the specific study. As the study progresses, the

study center would transmit results in real time to the DADMC.

Although many highly capable interdisciplinary research groups are cur

rently active in the analysis of device materials and performance, as men

tioned previously, it may sometimes prove necessary to establish dedicated

study centers focusing on a particular perceived device related clinical prob

lem, on a class of devices in a particular medical/surgical field, or on a

particular biomaterial class. The need for such centers would be defined by

the NIDRA Steering Committee and conventional center support funds

would be sought from NIH, NSF, and other public sources as well as funds

provided from the central fund.

22.5.2.3 Data Analysis and Device Management Center (DADMC)

The DADMC would be the only new permanent federal element of the

proposed NIDRA data management system. Its principal responsibility

would be the creation of the software and hardware to host a publicly

accessible relational database to house the minimum EDATA sets and the

integrated results of focused studies by the study centers, on a grouped basis

as well as through generation of an expanded EDATA set for each specific

device studied. This relational database would be provided with functional

linkages to present databases, such as the MDR system, and proposed bases

such as the proposed FDA-based Biomaterials Compendium.* The

DADMC's secondary roles would include management and oversight of

clinical institutions' recovery and enrollment systems, recruitment of new

clinical institutions to the program, performance of statistical analyses on

the database, and design and provision of products for electronic access and

hard-copy publication.

22.5.2.4 Steering Committee

It is intended that the NIDRA Data Management System be coordinated and

directed by a nationally organized steering committee. This committee

would be responsible for further design of NIDRA, for field test and

* At the time of the original NIDRA study (1992), the FDA (CDRH) was compiling data base of

clinically used biomaterials, including properties and relevant standards, from various forms of

pre-approval applications. This effort has apparently been abandoned.

implementation, and for scientific oversight and management in the steady

state. Initially, this committee should be staffed by invitation; however, it

might be reasonable for a definitive committee to have identified seats to be

filled by representatives from various professional, scientific, and industrial

organizations. As of today, NIDRA remains a proposal, although limited

efforts are under way in the U.S. and elsewhere to develop and test various

elements of such a national system.

22.6 Autopsy Retrieval Studies

Conventional DRA programs, however well conceived and executed, will

continue to be studies of “failure”; that is, they focus on the few devices for

which the outcome has been unexpectedly less than desired and/or frank

damage is noted on retrieved implants. For a long time, researchers have

recognized this problem and have attempted to compensate for this by in

situ studies and recovery of successful implants after death.

In situ studies have so far been largely limited to the use of conventional

imaging techniques, such as x-ray, CT, and MRI, and occasional sampling

and analysis of fluids and tissues. However, ethical and practical consider

ations have severely limited the scope and utility of these studies. This is a

still primitive field of effort when compared to the in situ study of natural

systems, but it can be expected to develop in the future.

A number of investigators, such as Sir John Charnley, have recognized the

need to study success and have asked patients prospectively to “return”

their devices when they are no longer needed — that is, after death. The

success of the studies of such devices and the important insights that they

have provided have encouraged a wider approach to autopsy retrievals of

successfully functioning devices and associated tissues, as well as tissues

and fluids from systemic and remote locations.

Involvement in one such program since 1990 (Jacobs et al. 1999) has high

lighted the benefits and the inherent difficulties of its operation. Several

comments can be made about such programs in general:

• Patients and their close relations are generally interested in their medical condition and have an inherent willingness to take part in studies, if they have a fairly low impact on their day-to-day lives, in order to benefit others. However, individuals have social, religious, and ethical standards and principles that must always be honored. Thus, programs must be flexible enough to accommodate a wide variety of individual concerns.

• Permitting study of one’s body after death for scientific purposes is a personal decision, much like agreeing to donate organs. As a result, successful autopsy retrieval programs depend to a great extent on continuing, repeated contact with the prospective subjects and their families by caring, concerned personnel with minimum interference after death.

• Death rarely arrives on schedule or at a convenient time and the window of opportunity for satisfactory, uncontaminated retrieval of device components and tissue

specimens is usually quite brief. Therefore, successful programs require well defined and established protocols, previously prepared instrument and sample recovery kits, trained one- to three-person retrieval teams on 24-hour standby (with adequate coverage for sick leave, vacations, holidays, etc.), and a reliable communication system to alert all parties as quickly as possible after death occurs.

In general, autopsy retrieval programs function much as more conven

tional DRA studies do. However, as the previous comments suggest, costs

are considerably higher. On balance, the scientific results from the few in

operation today have more than repaid the effort required. and they repre

sent one of the frontiers of biomaterials research.

22.7 Concluding Remarks

It should be a truism that one can only really learn about the clinical per

formance of biomaterials by actually examining that clinical performance. A

vast human experiment is under way; significant numbers of patients now

have had chronic devices in situ for more than 20 years. The time when

important new discoveries about the biological performance of biomaterials

can be made in the laboratory or in limited animal studies without primary

reference to this clinical experience has probably passed. Device retrieval

and analysis studies, national data systems, and autopsy retrieval programs

will come to play important roles in obtaining data and

insight to benefit

future generations of patients.

It is clear that the failure of such systems to emerge, for whatever reasons,

has profound impacts on the quality and cost of health care. In 2000, a

U.S.-NIH-sponsored national consensus development conference* con

cluded in part that:

• “Implant retrieval and analysis is of critical importance in the process of improving care of patients…”

* Improving medical implant performance through retrieval information: challenges and oppor

tunities, Bethesda, MD, January 10-12, 2000.

• “The [continuing] failure to appreciate the value of…retrieval and analysis is a serious impediment to medical device research… [R]etrieval will lead to the acquisition of information necessary to improve the quality of future devices.”

In other words, better understanding of biological performance of devices

(and their materials of construction) in actual clinical settings is and remains

important and necessary.

Black, J. and Fielder, J.H., Ethical aspects in device retrieval, Proc. Implant Retrieval Symposium, Society for Biomaterials, St. Charles, LA, 9/17-20/92, 14-1.

Jacobs, J.J. et al., Postmortem retrieval of total joint replacement components, J. Biomed. Mater. Res. (Appl. Biomat.), 48(3), 385, 1999.

Moss, A.J., Advance Data from Vital and Health Statistics, No. 191, National Center for Health Statistics, 1991, 1.

Anderson, J.M., Procedures in the retrieval and evaluation of vascular grafts, in Kambic, H.E., Kantrowitz, A. and

Sung, P. (Eds.), Vascular Graft Update: Safety and Performance, STP 898, American Society for Testing and Materials, Philadelphia, 1986, 156.

Anderson, J.M., Cardiovascular device retrieval and evaluation, Cardiovasc. Pathol., 2(3)(suppl.), 199S, 1993.

Black, J., An overview of goals and perspectives of implant retrieval, Int. J. Risk Safety Med., 8, 99, 1996.

Brooks, C.R. and Choudury, S.A., Metallurgical Failure Analysis, McGraw-Hill, New York, 1992.

Collins, J.A., Failure of Materials in Mechanical Design, 2nd ed., John Wiley & Sons, New York, 1993.

Das, A.K., Metallurgy of Failure Analysis, McGraw-Hill, New York, 1997.

Engel, L. et al., An Atlas of Polymer Damage: Surface Examination by Scanning Electron Microscope, Prentice Hall, Englewood Cliffs, NJ, 1981.

Fraker, A.C. and Griffin, C.D. (Eds.), Corrosion and Degradation of Implant Materials: Second Symposium, STP 859, American Society for Testing and Materials, Philadelphia, 1985.

Scheirs, J., Compositional and Failure Analysis of Polymers: A Practical Approach, John Wiley & Sons, New York, 2000.

Syrett, B.C. and Acharya, A. (Eds.), Corrosion and Degradation of Implant Materials, STP 684. American Society for Testing and Materials, Philadelphia, 1979.

Weinstein, A., Horowitz, E. and Ruff, A.W. (Eds.), Retrieval and Analysis of Orthopaedic Implants, NBS Special Publication 472, U.S. Government Printing Office, Washington, D.C., 1977.

Glossary

FDA 91-4246: Classification Names for Medical Devices and in Vitro Diagnostic Products. U.S. Government Printing Office, Washington, D.C., 1991.

Maquet, P. and Furlong, R., The Law of Bone Remodeling, Wolff, H. (1892), Springer-Verlag, Berlin, (transl.), 1986.

Newman Dorland, W.A., Dorland's Illustrated Medical Dictionary, 30th ed., W.B. Saunders, Philadelphia, 2003.

Szycher, M., Szycher's Dictionary of Biomaterials and Medical Devices, Technomic Publishing Co., Lancaster, PA, 1992.

Williams, D.F. (Ed.), The Williams Dictionary of Biomaterials, Liverpool University Press, Liverpool, U.K., 1999.

Williams, D.F. (Ed.), Definitions in Biomaterials: Proceedings of a Consensus Conference of the European Society for Biomaterials, Chester, England, March 3-5, 1986. Elsevier, Amsterdam, 1987.

Williams, D.F., Black, J. and Doherty, P.J., Definitions in biomaterials, Second Consensus Conference on Definitions in Biomaterials, in Doherty, P.J., Williams, R.L., Williams, D.F. and Lee, A.J.C. (Eds.), Biomaterial-Tissue Interfaces. Advances in Biomaterials Vol. 10, Elsevier, Amsterdam, 1992, 525.