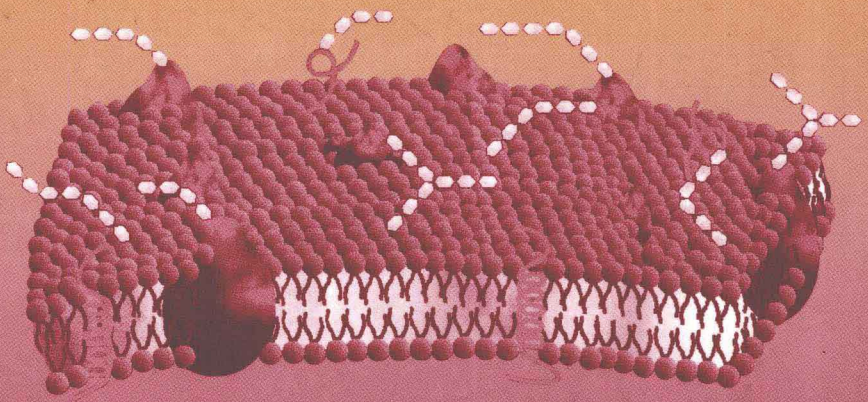
Biomedical and Health Research

New Biomedical Materials

Basic and Applied Studies



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Basic and Applied Studies

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Preface

In recent years there have been tremendous advances in the fields of chemistry, physics and biology which have a direct impact on advances in biomaterials science. These advances have contributed significantly to the improvement of modern health care and continue to influence the practice of medicine. Biomaterials research is an interdisciplinary field that brings together scientists with background in both basic and applied science. Biomedical engineers, materials scientists, synthetic chemists, biochemists, and clinicians are all working together to address a range of problems such as understanding how body fluids respond to biomaterials; developing cellular-based artificial organs; cardiovascular devices; drug delivery systems, artificial bone, and orthopaedic materials. These were amongst a host of topics covered at the First International Conference on Biomedical Materials held in Ancona, Italy in May 1997.

The conference provided a forum for the presentation and discussion of the latest advances in the field of Biomaterials. The scientific programme was organised such that there was adequate coverage of both applied and basic studies. A selection of subjects covered at the conference is presented in this book. The Book is organised in sections I to VI, and contains chapters from scientists who have made numerous innovative and exciting contributions in the field of biomedical materials. The latest advances in the field are covered including our current understanding of factors governing cell interactions with biomaterials. We are grateful to all those authors who submitted their camera-ready manuscripts on time and in a format prescribed by our publisher. In order to meet the tight publication schedule we have been obliged to restrict ourselves to only very light editing.

Our special thanks to Biocompatibles International for their support towards this conference. We would like to thank the generous financial assistance from the following organisations: Dideco S.p.A., Johnson & Johnson Corporate Biomaterials Center and Smith and Nephew Research Ltd. Support from Interdisciplinary Research Centre in Biomedical Materials Queen Mary and Westfield College, University of London and Faculty of Applied Sciences, De Montfort University is also gratefully acknowledged. We are extremely grateful to Professor Enrico Bertoli and his colleagues from the Department of Biochemistry, University of Ancona, for all their enthusiastic help which contributed towards the success of the conference. Finally we would like to thank our publishers for their encouragement which motivated us to produce this book.

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Contents

Section I
Cell-Surface Interaction and Haemocompatible Materials

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Endothelial-Biomaterial Interactions: A Central Role in Haemocompatibility

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Abstract Up until now the topic of the endothelium and biomaterials has tended to centre on the study of how endothelial cells (EC) can colonize a biomaterial surface, such as in vascular prostheses. That EC might be very relevant to other aspects of haemocompatibility has not received much attention. The highly reactive nature of the endothelium, however, makes it an important candidate for a regulatory role in the reactions to intravascular implants, whether in the short-term (e.g. catheters, haemodialysis) or in the long-term, as in prosthetic heart valves or vascular stents. In the present paper the ability of biomaterials to alter the activation state of the endothelium, both in the vicinity of, as well as at a distance from a cardiovascular implant, will be discussed. Among the relevant activating signals affecting EC are metal ions, bacterial toxins and mediators from blood cells and plasma cascade systems, which can elicit EC production of inflammatory mediators and up-regulate cell adhesion molecules (CAM). This in turn can lead to an amplification of the inflammatory response. These complex reactions are intricately involved in the complications associated with such biomaterial applications. Nevertheless, knowledge of these pathomechanisms could offer the possibility of therapeutic control, in order to minimize the negative effects. Targeting signal transduction pathways within the endothelium represents one such approach and will be illustrated in the context of CAM expression. Finally, the problems of inadequate growth of EC on implants will be discussed and the importance of intensive research on biomaterial-induced angiogenesis emphasized. Examples from our own research activities will be presented to illustrate these principles.

1. Current Trends in Haemocompatibility

In addition to vascular prostheses there are many blood-contacting biomaterials and applications in medical practice, both in the short term, as in catheters and haemodialysis, and in the long term, as in stents and prosthetic heart valves. Up until now, most attention has been paid to the negative aspects of biomaterial interaction with blood cells, especially platelets, monocytes and granulocytes, as well as the plasma coagulation system [1]. Less attention had been given to the role of endothelial cells (EC) in these interactions, although the high biological activity of the endothelium makes it a significant factor in biomaterial interactions with the cardiovascular system. Important aspects of this theme will be discussed in the following, which will emphasize the central pathogenetic principle that *biomaterials can significantly modulate the activation state of the endothelium.*

2. Role of Pre-existing Endothelial Cells (EC)

It is instructive to regard the endothelium as a dynamic balance, in which opposing functions are strictly controlled under physiological conditions, but which may be altered to such an extent that a pathological event may result. The embodiment of this paradoxical situation has prompted us to regard the endothelium as the „face of Janus", a biological metaphor which stresses the high reactivity of the endothelium. There are (at least) four elements of this paradox, which involve haemostatic control, a central role in regulation of the inflammatory response, vascular tone modulation and growth-regulating signals [2].

The endothelium is nature´s most efficient anti-thrombogenic surface, the maintenance of which depends on the production of numerous factors, acting either as anti-coagulants or as promoters of fibrinolysis. These include the synthesis of potent anti-platelet factors, such as prostacyclin and nitric oxide (NO), thrombomodulin, heparan sulphate proteoglycans, as well as plasminogen activator of tissue and urokinase type (t-PA and u-PA resp.). Tissue factor must rank as one of the most important endothelial pro-coagulant factors. In addition, through the production of plasminogen activator inhibitor-1 (PAI-1), the endothelium can prevent initiation of the fibrinolytic cascade. Further pro-thrombogenic products of EC are the coagulation factors V and VIII, as well as the receptors for factors IX and X. Concerning the endothelium and the inflammatory response, the physiological role of the endothelium can best be described as a modulator of inflammation and involves stringently controlled interactions between EC and blood cells, as well as between EC and mediator cascades in the plasma fraction of blood. The endothelium makes an important contribution by its own production of pro-inflammatory agents, including interleukin-1ß (IL-1ß), IL-6, IL-8 and platelet-activating factor (PAF), as well as by acting as the stage on which the sequence of cellular events occurs. This includes the processes of leukocyte margination, adhesion and emigration out of the vascular bed into the extravascular space. A major contribution is made by the endothelium itself via its expression of various groups of cell adhesion molecules (CAM), capable of being recognized by corresponding ligands on circulating blood cells [3].

a. EC in the vicinity of cardiovascular implants

Because of the insufficient inertness of biomaterials in current use, there is very often protein adsorption and platelet adhesion and activation, with the resulting release of mediators which can alter the *activation state* of adjacent endothelium. The latter includes tipping of the haemostatic balance in favour of pro-coagulant activity, and induction and up-regulation of various groups of CAM, promoting EC interactions with blood cells. This could have an amplifying effect on both thrombogenesis and the inflammatory response. A further contribution to the negative effects of EC in the biological microenvironment around the biomaterial could be made by divalent metallic cations, such as nickel, leaching from components of a biomaterial (e.g. heart valve, vascular stent). We have shown that even micromolar concentrations of such metal ions can up-regulate CAM involved in inflammation (E-selectin, ICAM-1)[4]. A third factor may become operative in the case of bacterial contamination of a biomaterial, as endotoxins can both damage EC and induce their pro-coagulant and pro-inflammatory activity [5,6]. These factors and their effects are presented schematically in Fig. 1. Activated EC can produce, for example, cytokines, which in turn can feed back on the same EC to stimulate further production of cytokines. A classical example of this is IL-1ß, which can be produced by blood monocytes, activated by a biomaterial. Il-1ß is known to stimulate EC to synthesize the same cytokine [7] and thus initiate a so-called autocrine loop. The cytokines released by activated EC can, however,