Edited by
Matthias Epple and Edmund Baeuerlein

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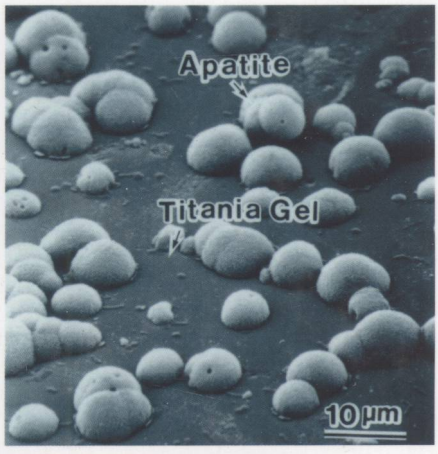
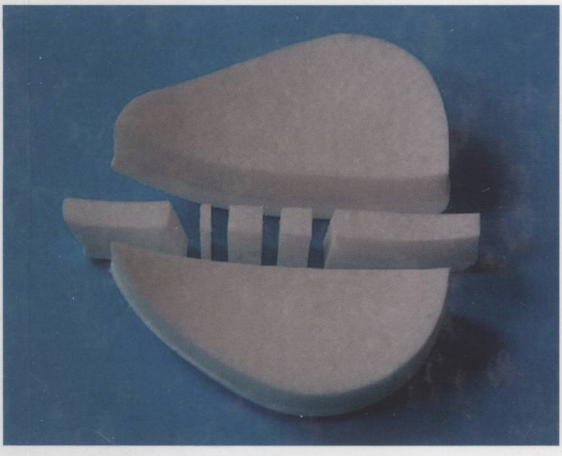
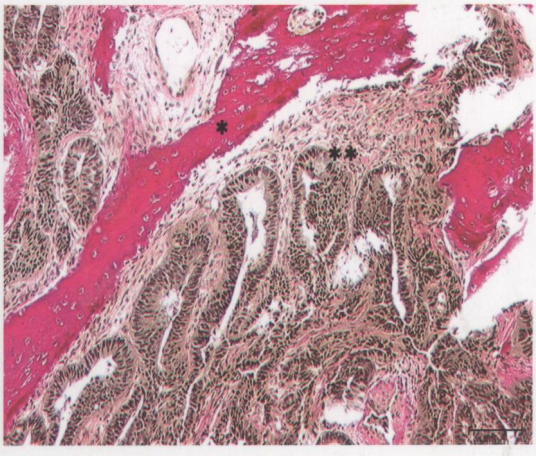
Handbook of Biomineralization

Medical and Clinical Aspects

Foreword by Wolfgang Pompe







Handbook of Biomineralization

Medical and Clinical Aspects

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Matthias Epple and Edmund Bäuerlein

WILEY-VCH Verlag GmbH & Co. KGaA

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Cover Illustration (designed by Felix Bäuerlein)
Top left: Heterodont molar of carnivorous mammals (wolf, no functional wear) with no exposed dentin and very small pulp chamber. (P. Gaengler, W. H. Arnold, Chap. 14, Fig. 14.1c).
Top right: Apatite formed on TiO_2 gel in simulated body fluid (SBF). (T. Kokubo, H. Takadama, Chap. 7, Fig. 7.4(2)).
Bottom left: An implant manufactured by hot pressing and gas flushing for cranial reconstruction with gradients in composition and spatially different porosity. (M. Epple, Chap. 6)
Bottom right: Calcified lung metastases of a primary colorectal adenocarcinoma. Lightmicroscopic image, HE-stain, metastases with typical structure of colon (*), typical lung structure is not present, ossification (**). (Inge Schmitz, Chap. 18, Fig. 18.7)

Handbook of Biomineralization
Biological Aspects and Structure Formation:
ISBN 978-3-527-31804-9
Biomimetic and Bioinspired Chemistry:
ISBN 978-3-527-31805-6
Medical and Clinical Aspects:
ISBN 978-3-527-31806-3
Set (3 volumes):
ISBN 978-3-527-31641-0

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at ⟨http://dnb.d-nb.de⟩.

Printed in the Federal Republic of Germany
Printed on acid-free paper

Typesetting Asco Typesetters, North Point, Hong Kong
Printing betz-druck GmbH, Darmstadt
Binding Litges & Dopf GmbH, Heppenheim
Cover Design Felix Bäuerlein, Munich
Wiley Bicentennial Logo Richard J. Pacifico

ISBN 978-3-527-31806-3

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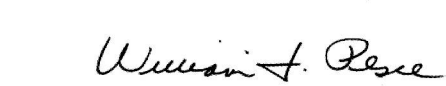

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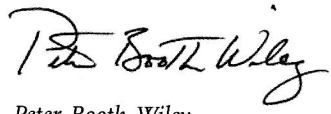

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Preface

When I began my academic career in Hamburg, I worked on the solid-state chemistry of organic compounds. By chance, our group identified a solid-state reaction which led to a polymer (polyglycolide), a class of biodegradable polyesters which a literature survey showed to have many applications in clinical medicine. This finding led in turn to my first contacts with physicians and their ideas about implants, biomaterials, and bone. As a member of a graduate school on bone in the medical faculty, I learned that biomaterials usually depend on biomineralization – that is, the cellular action and similarity to the corresponding hard tissue. I also became aware for the first time of the great importance of pathological calcifications in our society.

The process of biomineralization is based on the formation of inorganic crystals, and is strongly controlled by organic molecules which are themselves controlled by cells. As a chemist, I was familiar with the first part of this story, but I had much to learn about biomolecules, the different cell types, and also the clinical treatments of diseases. Fortunately, in Hamburg, as well as in the subsequent institutions where I worked – at Bochum and Essen – I met people from the field of medicine who were interested in conducting joint studies. When all parties had learned to communicate – due to the different vocabulary of their disciplines – many fruitful collaborations developed, and in this respect I am deeply indebted to my colleagues (listed in alphabetical order), Prof. M. Amling, Prof. G. Delling, Prof. S. A. Esenwein, Prof. H. Eufinger, Rof. P. Gängler, Prof. W. Jahnen-Dechent, Dr. A. Klocke, Prof. M. Köller, Dr. P. Lanzer, Dr. W. Linhart, Prof. G. Muhr, Prof. J. M. Rueger, Prof. W. Ruether, Dr. I. Schmitz, and Dr. S. Weihe, from whom I learned much about the clinical aspects of biomineralization.

Therefore, I was very excited when Edmund Bäuerlein asked me jointly to edit a volume of the *Handbook of Biomineralization*. We quickly selected the three main topics which are relevant in medicine, namely bone, teeth, and pathological calcifications, and also were fortunate to find many competent authors from all over the world who agreed to contribute. Many aspects of biomineralization in medicine are highlighted in this book, and I sincerely hope that it will contribute to our understanding of this field of research, as it is not only of academic inter-

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ISBN: 978-3-527-31806-3

est but also covers many general aspects of biomineralization. Indeed, it can be said that good health is dependent on correct biomineralization!

Essen, Germany
February 2007 *Matthias Epple*

Foreword

During the past decade, biomaterials research has undergone tremendous change. Ten years ago, the first dialogues were made between physicians searching for artificial materials that could be used for regenerative therapies (for example, in bone surgery), and materials scientists offering a variety of structural and/or functional materials which originally were developed for engineering applications. Today, we can take advantage of the impressive advances in modern biology and biochemistry, and as a consequence we have the chance to follow completely new pathways for solving such problems.

As will be shown in this volume, our current understanding of biomineralization opens up new approaches not only for physicians but also for materials scientists in many medical applications. The key here is provided by the exploration of genetically controlled mechanisms of the biomineralization of hard tissues. The activation and inhibition of biomineralization are two complementary processes which lead to such wonderful structures as bone or teeth, and based on the phenotypic analyses of several mouse models and various diseases causing calcification of soft tissues, we have learned that there is a variety of non-collagenous proteins that control this interplay of activation and inhibition. The following examples will indicate how this knowledge can be used for biomimetic implant development.

As the overall age of our modern-day society continues to rise, bone diseases will become increasingly important, and consequently the successful treatment of the pathological mineralization of bone – for example, in the case of osteoporosis – represents one of the major challenges of the next decade. This general problem in bone research is discussed in Chapter 5, wherein it is clear that, based on an understanding of biomineralization in such pathological situations, new strategies could be derived for biomedical treatments as well as for new materials that may be used in the regenerative therapy of disturbed tissue.

Today, although a large variety of bone substitution materials is applied on a practical basis, an evolutionary process can be foreseen in which a group of artificial engineering materials will be completed by more biologically functionalized materials. Here, one favored strategy is the stimulation of bone growth on implants, and today the development of scaffolds suited to the immobilization of

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living bone cells has been boosted by the recent progress made in stem cell research.

Another exciting feature relating to the biomineralization of bone and teeth is the formation of hierarchical or graded structures. This leads to basic questions concerning structural evolution on the mesoscopic scale. The guiding principle for understanding such structures is related to the biomechanical adaptation of living tissue. In Chapter 13, the author explains how, in the case of teeth, evolutionary pressure has led to the creation of highly optimized structures with respect to the complex mechanical loading situations in a living organism. Based on this theory, many attempts have been made to model such structures, whereby the models describe the formation of the mineralized tissue by combining cellular activity with acting mechanical stresses. However, the predictive power of such numerical simulations based on Finite Element codes remains limited. In particular, the uncertainty of the constitutive laws for materials behavior sets such restrictions, and consequently new experimental approaches are required that will allow the appropriate measurement of the properties of these materials on the micro- and mesoscale. Today, there are growing numbers of promising methods available to perform just this task, and this is demonstrated throughout this volume.

As mentioned above, the unwanted pathological calcification of soft tissue or of vascular systems is an issue which is closely connected with the biomineralization of hard tissues. Today, we know that there are no significant differences between both phenomena, and thus another broad field of research activity is opening up with relevance for biological tissue characterization as well as for the development of artificial materials, for example in vascular prostheses. In the final part of this volume, we show that this phenomenon is also dominated by active cell-mediated processes and not by the simple precipitation of minerals at a given substrate.

In summarizing, it can be said that the exciting interdisciplinary cooperation of biologists, biochemists, materials scientists, and physicians has led us to a challenging new research field of biomineralization, with wonderful perspectives for a better understanding of the beauty of the evolution of living organisms, whilst at the same time making significant contributions to human healthcare.

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ISBN: 978-3-527-31806-3

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ISBN: 978-3-527-31806-3