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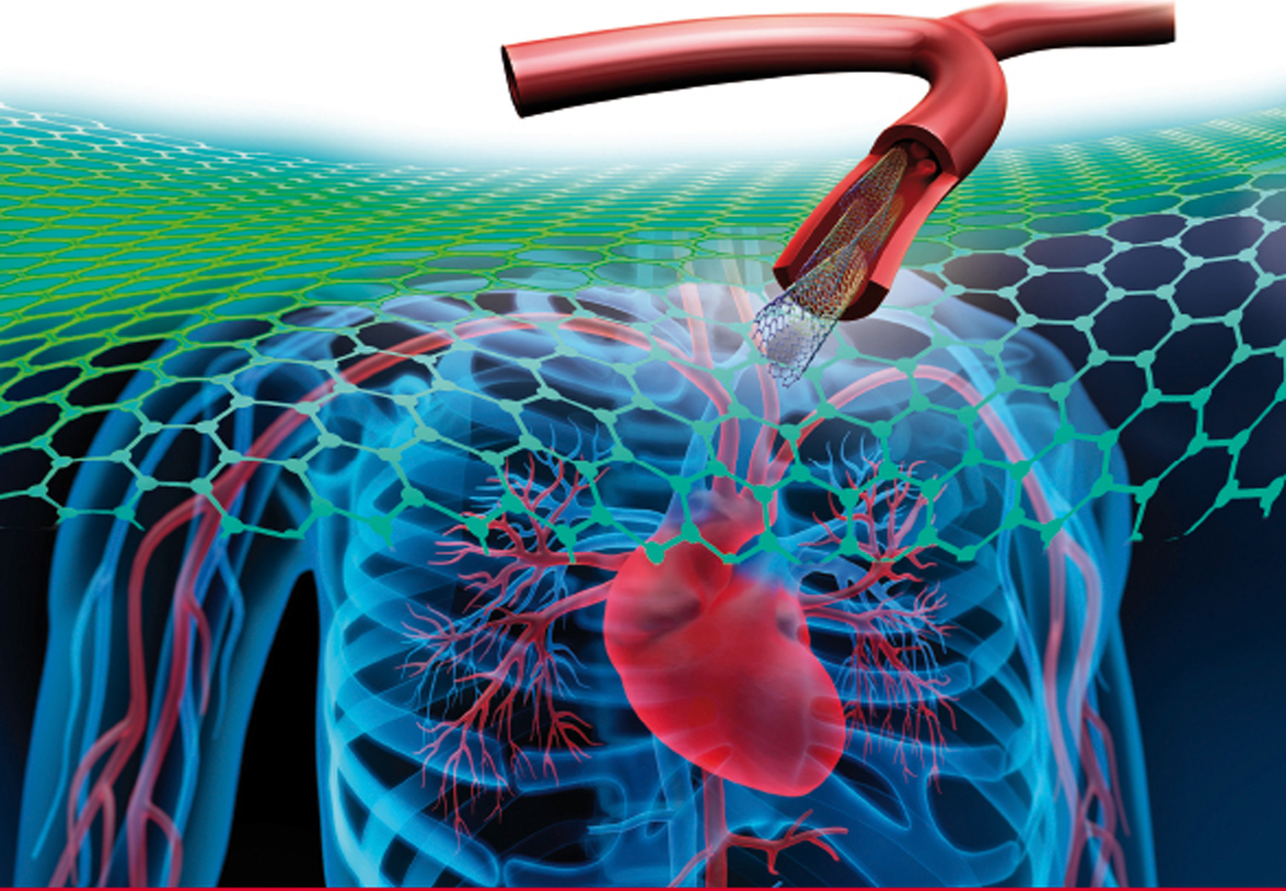

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Thanks to my wife for her patience with me spending
many hours working on the book series through
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and large computer files with many sophisticated scientific
figures is also greatly appreciated.

Marcel Van de Voorde

Series Editor Preface

Since years, nanoscience and nanotechnology have become particularly important technology areas worldwide. As a result, there are many universities that offer courses as well as degrees in nanotechnology. Many governments including European institutions and research agencies have vast nanotechnology programmes and many companies file nanotechnology-related patents to protect their innovations. In short, nanoscience is a hot topic!

Nanoscience started in the physics field with electronics as a forerunner, quickly followed by the chemical and pharmacy industries. Today, nanotechnology finds interests in all branches of research and industry worldwide. In addition, governments and consumers are also keen to follow the developments, particularly from a safety and security point of view.

This books series fills the gap between books that are available on various specific topics and the encyclopedias on nanoscience. This well-selected series of books consists of volumes that are all edited by experts in the field from all over the world and assemble top-class contributions. The topical scope of the book is broad, ranging from nanoelectronics and nanocatalysis to nanometrology. Common to all the books in the series is that they represent top-notch research and are highly application-oriented, innovative, and relevant for industry.

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The book series appeals to a wide range of readers with backgrounds in physics, chemistry, biology, and medicine, from students at universities to scientists at institutes, in industrial companies and government agencies and ministries.

Ever since nanoscience was introduced many years ago, it has greatly changed our lives – and will continue to do so!

March 2016 *Marcel Van de Voorde*

About the Series Editor

Marcel Van de Voorde, Prof. Dr. ir. Ing. Dr. h.c., has 40 years' experience in European Research Organisations, including CERN-Geneva and the European Commission, with 10 years at the Max Planck Institute for Metals Research, Stuttgart. For many years, he was involved in research and research strategies, policy, and management, especially in European research institutions.

He has been a member of many Research Councils and Governing Boards of research institutions across Europe, the United States, and Japan. In addition to his Professorship at the University of Technology in Delft, the Netherlands, he holds multiple visiting professorships in Europe and worldwide. He holds a doctor honoris causa and various honorary professorships.

He is a senator of the European Academy for Sciences and Arts, Salzburg, and Fellow of the World Academy for Sciences. He is a member of the Science Council of the French Senate/National Assembly in Paris. He has also provided executive advisory services to presidents, ministers of science policy, rectors of Universities, and CEOs of technology institutions, for example, to the president and CEO of IMEC, Technology Centre in Leuven, Belgium. He is also a Fellow of various scientific societies. He has been honored by the Belgian King and European authorities, for example, he received an award for European merits in Luxemburg given by the former President of the European Commission. He is author of multiple scientific and technical publications and has coedited multiple books, especially in the field of nanoscience and nanotechnology.

Contents

Nanomedicine: Present Accomplishments and Far-Reaching Promises

The symbolic dawn of nanotechnology is often ascribed to Richard Feynman's address to the American Physical Society in 1959: "There is plenty of room at the bottom.." Possible applications to medicine rapidly appeared as of major importance encompassing *in vitro* diagnosis, *in vivo* imaging, and therapeutics. It has been, however, necessary to wait until 1995 to have the first nanodrug approved by the US Food and Drug Administration – a liposomal formulation of doxorubicin termed Doxil®. At present, there are over 300 nanodrugs in various stages of clinical development. All of them, that have been already approved, rely on passive targeting: These compounds are accumulated in tumor tissue due to the existence of leaky, abnormally fenestrated blood vessels and also due to altered lymphatic circulation (EPR (enhanced permeability and retention effect)). Nanocarriers conjugated with antibodies or physiological ligands and thus specifically targeted to cells expressing the corresponding markers are the next step in the development of nanotherapeutics. Such drugs are expected to display a markedly increased therapeutic index, that is, increased effect on tumor tissue and decreased general toxicity. Several of them are now in the late stages of clinical studies and should become available soon. Future developments include theranostics and personalized nanomedicine. Theranostics consist in the presence of therapeutic and imaging compounds in the same carriers specifically targeted to tumor cells. A major advantage of this technology would be the possibility of noninvasive monitoring of early response to therapy and thus to rapid adaptation of the treatment. Personalized nanomedicine will allow the selection of nanodrugs specifically for each patient according to molecular markers ("-omics" data). In this respect, RNA interference seems a promising approach. In parallel to this progress, in diagnostics and therapy, it will be necessary to develop toxicology. The toxicity of a compound changes markedly when the latter is reduced at the nanometer scale. Besides toxicity, due to their shape – "asbestos-like" properties of carbon nanotubes – nanoparticle detrimental effects derive from generation of reactive oxygen species, cellular structure disruption, and immunological reactions. A great progress in the clinical development of nanodrugs would be the availability of *in vitro* assays able to predict *in vivo* toxicity.

Nanoparticles are rapidly extending their use in industry: paints, electronics, tires, sport equipment, sunscreens, and so on. The possible toxicity of these compounds present in our environment should be examined. We should also keep in mind and try to prevent the possibility of most dreadful developments: the weaponization of the processes and compounds. The future of nanomedicine is obviously bright. It is bound to become one of our most important tools for diagnosis and therapy.

Member of the French Academy of Medicine *Edwin Milgrom*

Part One
Introduction to Nanoscience in Medicine of the Twenty-First Century

1
Challenges and Opportunities of Nanotechnology for Human Health

Bert Müller

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Medical doctors have a wide variety of experiences with patients. Therefore, they are generally fast in the evaluation of the entire human body. For example, looking at the morphology of the human body, they can identify the chronic inflammatory disease of the axial skeleton, termed ankylosing spondylitis, previously known as Bekhterev's disease. For many natural scientists and engineers, these abilities are fascinating and surprising, at once.

For the diagnosis of an increasing number of diseases, however, a more detailed evaluation, for example, on the basis of radiological data, is necessary. The amount of high-resolution data obtained is huge and usually overburdens the medical experts. Interdisciplinary cooperation with computer scientists to (semi)automatically analyze the imaging data becomes more and more common. These assessments are often expensive and time-consuming. Nonetheless, the available clinical imaging modalities even with the best spatial resolution do not reach the resolution needed to visualize individual biological cells with sizes of about 10 μm. To this end, it appears dubious, why patients can benefit from nanotechnology.

Reading the instruction leaflets of currently available sun crèmes or sensitive toothpastes, we realize, however, that nanotechnology has reached our daily routine. This book will hardly deal with these well-established, systemic applications, we have known from pharmacy for decades, but with the impact of nanotechnology on dedicated future therapies for the most important diseases.

The leading cause of death in our society relates to cardiovascular diseases [1]. Therefore, the first part of this book, which consists of four chapters from medical experts, that is, cardiologist, internist, immunologist, and natural scientists, targets current research activities toward nonsystemic treatments. For example, nitroglycerin is currently administered to widen the constricted atherosclerotic arteries in a systemic fashion. The vasodilator widens all arteries and veins with serious side effects, including a drastic blood pressure drop. Therefore, the nitroglycerin dose has to be kept limited. Specific biomarkers

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for this prevalent inflammation do not exist. Consequently, researchers proposed to exploit the wall shear stress increased at constricted arteries with respect to the healthy parts as purely physical trigger to release drugs from mechanosensitive containers or particles of nanometer size [2,3]. These nanotechnology-based innovations are sweeping the established cardiovascular treatments, especially before the patients reach the operating room and endovascular devices for intra-arterial clot lysis, stent implantation, or arterial balloon dilatation could become effective [4].

Second most common cause of death is cancer. It is, therefore, not surprising that the second part of the book is dedicated to alternative diagnoses and treatments of cancer. Although one can cleverly combine pharmaceutical, surgical, and radiation treatments to heal patients, alternative strategies to fight against cancer are more than desirable. The four related chapters depict how contemporary methods and sophisticated materials can contribute to a reliable diagnosis and, more important, to powerful treatments of cancerous tissues even deeply inside the human body difficult to reach. Here, the deep understanding of the physical interactions between the probes such as photons or protons and the biological matter is essential for the selection and the future development of treatment strategies for the general public.

The third part of the book relates to the most common diseases, which are caries, musculoskeletal diseases, incontinence, and allergies. Although they often do not result in death, they massively influence our quality of life.

Caries is the most common infectious bacterial diseases in the world [5]. The disease first destroys the human enamel, which is a unique biologically ordered material with hydroxyapatite crystallites being organized into a fibrous continuum. In healthy state, it remains stable for decades and centuries or even millennia. Currently, no engineering process exists to biomimetically repair this unique biological material with a well-defined nanostructural organization. Therefore, the burden of dental caries lasts for a lifetime. Once the tooth structure is destroyed, it will usually need restoration and additional maintenance throughout life. In addition, the economic impact of such therapeutic approaches is enormous. The World Health Organization estimated that the dental treatment costs accounted for 5–10% of healthcare budgets in industrialized countries and additional costs are caused through absences from work [6,7]. So far, treatments rely on mechanical replacement of decayed tissue by inert biomaterials such as isotropic polymers or composites. Recently, the analysis of the healthy and diseased crowns down to the nanometer scale has led to the necessary anatomical knowledge to develop biomimetic dental fillings, which contain elongated nanostructures with the orientations present in dentin and enamel [8]. Furthermore, the detailed analysis of the caries pathology using X-ray scattering has shown that while bacterial processes dissolve the minerals in enamel and dentin, the dentinal collagen network remains unaffected, enabling the development of treatments to remineralize the dentin [9,10].

The musculoskeletal system demands increasingly frequent treatments with metallic load-bearing implants, which include artificial hips, knees, and dental implants. In general, these metals integrate well into the bone because the sand-blasted and etched oxide surface contains a multiplicity of features on the micro- and nanometer scale, which exhibit similarities to the nanometer-size minerals in bone. Therefore, it has been stated that the morphology of the implant's surface tends to have a greater effect than chemical patterns, when both chemical patterns and topographic ones are offered to biological cells [11]. The vital role of the nanostructures in avoiding inflammatory reactions and in reaching cytocompatibility was demonstrated using nanopyramids naturally formed in heteroepitaxy of semiconductors [12,13]. In contrast to metals, high-performance polymers are radiolucent and magnetic resonance imaging compatible, which allow the diagnostic examination of tissues in implant's vicinity. Only recently, the systematic polymer structuring on the nanometer scale for centimeter-size implants was explored [14]. It is relatively easy to produce micro- and nanostructures with a preferential orientation, which better mimic the anisotropy of the bony tissues within our body [15]. Therefore, one can reasonably expect that polymeric load-bearing implants will be employed in near future at least for dedicated cases.

The aging of our society has led to the increasing prevalence of social and economic burdening by age-related diseases, including urinary and fecal incontinence. In comparatively simple cases, conservative therapy is successful. Surgical therapy is advisable for more complex cases, where the extent of surgery depends on the severity. In severe cases, artificial sphincter systems are applied, which currently rely on fluid-filled cuffs. So far, they are not part of everyday surgical treatments owing to the large number of complications, including wound infection, postoperative pain, and consecutive resurgeries. One of the main drawbacks is the constant pressure acting on the hollow organ. The natural counterpart, however, adapts to external factors such as climbing stairs or resting in bed, so that the function is guaranteed and the tissue can regenerate. Hence, sensor-controlled devices with the necessary time response have to be developed [16]. As dielectric elastomer actuators (DEA) not only provide the necessary forces, strains, and response time but can also simultaneously be operated as sensors, these artificial muscles have a huge potential to become the basis of future active implants [17]. There are, however, several challenges to be solved, mainly related to the high voltages required to drive micrometer-thin DEA. Sandwiched nanometer-thin elastomer films with ultrathin compliant electrodes have to be made available to fabricate biomimetic artificial sphincters and finally to successfully treat incontinence.

The book *Nanotechnology for Human Health* should promote the prosperous use of nanotechnology in prevention, diagnosis, and therapy of the most relevant diseases of our century. It should comparably become a tool for research-interested medical doctors as well as natural scientists and engineers with a strong affinity to support curing patients [18,19]. In this manner, patients concerned will benefit from this collaborative initiative of an interdisciplinary team of researchers.

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