Edited by
Martin J. Leahy

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2. The working principles of sidestream dark-field (SDF) imaging (for more details, see Fig. 2 in Chapter 2 by M.J. Milstein et al.).
3. Three-dimensional image of an experimental tumor (KHT) growing in a mouse (for more details, see Fig. 6 in Chapter 13 by Stuart Foster).
4. Blood flow changes during stroke: relative cerebral blood flow 10 min after occlusion of the middle cerebral artery in a rat (for more details, see Fig. 12 in Chapter 8 by Bryers et al., with kind permission by SPIE and A.K. Dunn, University of Texas).
5. Micro-CT image data (20 µm isotropic voxels) of the vascular bed of a rat heart, which was filled with a contrast agent (Microfil) and was imaged in situ. For more details, see Fig. 15 in Chapter 14 by Timothy L. Kline and Erik L. Ritman.)
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Preface

This book brings together the main techniques used for imaging the small blood vessels, which supply nutritional oxygen and remove waste products from the cells of the body. The rapid development of new techniques to image the microcirculation (vessels <100 µm in diameter) in two and three dimensions was the main driver for publishing this book. The macrocirculation of the cardiovascular system enjoys a special place in medicine and is well catered for with imaging modalities that are ever present in our hospitals. X-ray CT, ultrasound, MRI, and PET all play an important role in diagnosis and treatment of the disorders of the large vessels. However, there is growing realization that some of the diseases that most threaten the quality and quantity of life in the developed world, such as diabetes and cancer, have their origins in the microcirculation. Therefore, new techniques with appropriate resolution were required to image these smaller vessels, and these largely depend on the rapid developments in photonics.

It is impossible to present all techniques that have been applied to microcirculation in this book. The editor is grateful to the (unknown) reviewers of the original proposal for their suggestion to supplement the biophotonics techniques well known to him with MRI and high-frequency ultrasound. The result is a more thorough covering of the field, although I am open to further suggestions for additions in future editions. Researchers, practitioners, and professionals in the fields of diabetes, cancer, wound healing, biomedical optics, and biophotonics, as well as professionals in other disciplines, such as laser physics and technology, fibre optics, spectroscopy, and biology, will find the book a useful resource. Graduate and undergraduate students studying biomedical physics and engineering, biomedical optics and biophotonics, and medical science would benefit greatly from consulting this reference.

Several Irish and international grants supported this project, particularly the National Biophotonics & Imaging Platform Ireland, funded by the Irish Government under the national development plan (NDP) 2007–2013 HEA PRTLI IV. I greatly appreciate the cooperation, contributions, patience, and support of all the contributors, my colleagues from the School of Physics at NUI Galway, the Department of Physics at the University of Limerick, the Royal College of Surgeons, and the
Preface

National Biophotonics and Imaging Platform. Last, but not least, I would like to thank my family for their support and understanding during my work on this book.

NUI, Galway

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A Historical Perspective of Imaging of the Skin and Its Gradual Uptake for Clinical Studies, Inclusive of Personal Reminiscences of Early Days of Microcirculation Societies

Terence J. Ryan and Martin J. Leahy

Modern microscopy of microcirculation was conceived by the observers of especially the seventeenth century, but gestation was in the hands of the national and continental Microcirculatory Societies that began in the decade 1954–1964. They were a meeting point between the laboratory investigator of microcirculation and the clinician. Zweifach [1] reviewing historical aspects of microcirculation research wrote “The usage of the term ‘microcirculation’ in an organic context is of comparatively recent vintage, first appearing consistently in the literature during the 1950s.” Global collaboration with a strong clinical input began with World Congresses of Microcirculation first held in Toronto in 1975, then in San Diego in 1979, next in Oxford in 1984, and every four to five years since then. As an Oxford clinician specializing in care of the skin, T. J. R. was roped in at the deep end of nonclinical pursuit of microcirculation on several occasions. However, this began by a chance observation that if one pushes tissue fluid away by indenting the skin with a steel probe, one gets much better visualization of the skin capillary bed [2, 3]. It has long been known that one sees at the surface of the skin only what its optical properties allow. Excised epidermis from white skin placed over a printed page is transparent enough to read through it. Melanin of pigmented skin prevents such visualization. The redness of blood provides in vivo pinkness, but blue blood in veins is a consequence of blue light being scattered more than red. This does not stop the practised clinician from easily recognizing the condition when black skin is flushed. Newton [4] discussed the decomposition of white light, and Doppler [5] made known that the effect of movement toward or away from the observer influenced the color observed. For several centuries, any observation of complex surfaces reflecting light was clarified by applying transparent oils to that surface.

1.1 Early History

George P. Fulton [6], Professor of Biology at the Boston University, writing on the historical perspective of the founding of the American Microcirculatory Society, lists Harvey and Lord Lister amongst the early influences on microcirculation, but it
was interest in microscopy and improved microscopes in the seventeenth century that led to the first observations of blood flow by better imaging. The discoverers and forerunners of imaging were fascinated when they applied their new magnifying devices, and detecting transparency in some living tissues saw for the first time the movement of the content of the small capillaries. These early observations especially on red cells were well reviewed for the journal Blood Cells by Bessis and Delpechi [7]. As stated in that review, three men, Malpighi, Leeuwenhoek, and Swammerdam, made the most of the improvements in magnifying lenses in the early seventeenth century and noted red particles in blood capillaries in transparent tissues. Of these, van Leeuwenhoek of Delft (1632–1723) gained the most publicity by getting his observations published by the Royal Society of London [8]. Indeed, it was the tax collector, van Leeuwenhoek, who contributed one of the greatest innovations through his hobby by producing a very short focal length lens. This avoided chromatic aberrations, which plagued compound microscopes of the day, and yet produced sufficient magnification to reveal the structure of the blood cell (Figure 1.1) and its movement within organs and organisms if they were sufficiently transparent. It was this innovation that allowed Malpighi to confirm Harvey’s theory that blood circulates from the arterial to the venous side via these small capillaries, and indeed, it can be considered the discovery of the microcirculation.

Figure 1.1 The discovery of the circulation of the blood, the shape of the red blood cell, and, most importantly, the microcirculation (after The Discovery of the Circulation of the Blood, Charles Singer, G. Bell and Sons Ltd., London, Ref. [9]).