Conclusion

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Here, by Chapter 196 of a volume exploring the endothelium in medicine, it has become clear that this is an astonishingly diverse and far-reaching subject. Identified for the first time only at the end of the nineteenth century, the once seemingly simple and passive cell layer is now understood to represent a dynamic system that reflects and determines much about health and function for humans and other vertebrate species. This collection of chapters shows how far we have come in our understanding, and also how rich the opportunities are for further study and more effective translation of our understanding into clinical practice.

There is great virtue in bringing together all these topics that would normally reside in the archives of separate disciplines. We have gained many different perspectives of what the endothelium is and how endothelial cells (ECs) come together as a functioning system. By reflecting on the way the endothelium develops and by comparing phenotypes across different species, we gain insights into the alternatives available and what any particular developmental pathway means for the organism. This helps us understand the endothelium as a highly evolved, integrated system. The system is by no means perfect. Rather, it is an interlocking “bundle of adaptations,” some of which were born of trade-offs that are no longer applicable. Indeed, the extreme path-dependence of evolutionary change has undoubtedly engendered design flaws that render the modern-day human endothelium highly vulnerable to disease.

The use of metaphors to conceptualize the endothelium is a powerful tool for understanding an otherwise hidden and under-appreciated entity. We hope that the reader will agree that the analogies between endothelium and weather, landscape, and urban design are at the same time provocative and illuminating. While the metaphor of the EC as an input-output device has obvious limitations, not least of which is the risk of overlooking what are often considered to be “emergent properties,” it has nonetheless provided an important organizing theme for the book. Moreover, the use of the input-output device metaphor illuminates how our biological knowledge might be carried into clinical practice. For example, if we consider the remarkable capacity of the endothelium to sense and respond to its extracellular environment it is not a leap to assume that every drug we administer systemically to patients will alter EC phenotypes, for better or for worse. On one hand, such capacity to be modulated may be leveraged to develop novel agents targeted against the endothelium. On the other hand, the exquisite sensitivity of ECs to the extracellular environment may contribute to the adverse effects of many drugs.

When considered collectively, the chapters on endothelium in health and disease provide a clear message: as diverse as the endothelium is in structure and function, it is nevertheless a highly integrated system. The more we learn about the endothelium across the vasculature, the more successful we will be in identifying common or core properties, and the better poised we will be to understand the wider consequences of endothelial-based disease.

The collection of perspectives brings many, many new questions and new directions for research. That is clear. New knowledge together with new ways of knowing will bring richer research results, and we have opportunities to translate those results into clinical practice. But we will not do so without changes in the medical curriculum. In that spirit, it is incumbent upon us to train our physicians, starting in undergraduate programs and medical schools, to think of the endothelium not simply as a collection of cells that passively separate circulating blood from underlying tissue, but rather as an active, interactive, dynamic and directive organ system.

Based on the collective writings in this volume, we conclude that the endothelium is a powerful organizing principle in health and disease. Indeed, endothelial biomedicine is a field that warrants recognition in its own right – at all levels of training and research. In addition, the current book calls for reconceptualizing biological structure and function more generally and extending the same questions and approaches to other biological systems. And it calls for new ways of working, not in isolated and separated specialized disciplinary laboratories, but interactively and collaboratively. Perhaps through our own efforts, we can set an example on how to apply
integrated research strategies to complex systems. Systems biology continues to be inspired for the most part by high-throughput genomic and proteomic approaches. However, as emphasized throughout this volume, complexity is “encoded” not so much in the component parts, but rather in the links or interactions between genes, proteins and cells. Moreover, systems biology is heavily rooted in evolution and development. Hence, an understanding of the phylogeny and ontogeny of complex systems, such as the endothelium, provides invaluable insights into the role of these systems in health and disease.

Finally, we hope to have made a case for the importance of conceptual innovation and clarification for structuring available information in such a way that new perspectives can emerge. History teaches us how the endothelium was conceptualized within certain domineering paradigms and how our ideas about the endothelium have changed in light of new developments. Today, however, this relationship might well be reversed and the focus on endothelium as an integrated complex system might lead to a reconceptualization of other areas of biomedicine.