Endothelium-Derived Relaxing Factors


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125 figures and 17 tables, 1990

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Library of Congress Cataloging-in-Publication Data
International Symposium on Endothelium-Derived Vasoactive Factors
Contains the first part of the proceedings of the First International Symposium on Endothelium-Derived Vasoactive Factors.
Includes bibliographical references.
[DNLM: 1. Endothelium-Derived Relaxing Factor - congresses. 2. Endothelium, Vascular - physiology
- congresses. QV 150 I5915ea 1989]
ISBN 3-8055-5091-X
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ISBN 3-8055-5091-X

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Acknowledgements

The success of the International Symposium of Endothelium-Derived Vasoactive Factors and the publishing of this book were made possible by the support and efforts of many organizations and individuals.

We would like to thank the professional staff of International Business Communications, Inc., for the highly competent organization of the symposium with special thanks to Ms. Kim Todd, who was the driving force behind the organizational effort.

We wish to acknowledge the valuable sponsorship of the Physiological Society of Philadelphia and the generous support of Schering AG, West Berlin, and Berlex Laboratories, Inc., Cedar Knolls, N.J. (USA).

The outstanding contribution of the Scientific Advisory Board in preparing the program and the excellent and exciting presentations and chapter contributions by the speakers and chairpersons to the symposium and to this book are gratefully appreciated.

We would like to express our gratitude to Mrs. Susan Packie for her help in the organization of the symposium and editing of this book.

Finally, the editors would like to thank the staff of S. Karger, Basel.
The discovery that endothelial cells play a pivotal role in the relaxation evoked by acetylcholine in isolated rabbit aortas [Furchgott and Zawadzki, Nature 299: 373, (1980)], has initiated a true revolution in the world of cardiovascular sciences. This finding, and its extension to other arteries, and other vasodilator agents has forced the cardiovascular physiologists, pharmacologists and even pathologists to rethink the ways by which local vascular tone and the interaction between the platelets and the blood vessel wall are regulated. Ten years later, one is forced to admit that the importance of the discovery by Dr. Furchgott equals that of the recognition of the role played by sympathetic nerves in controlling vascular tone. It has become impossible to envisage the local regulation of blood flow, whether due to changes in physical conditions, to autacoids produced in the tissues, to circulating vasoactive hormones, or to platelet products, without implicating endothelium-dependent changes in blood vessel diameter. In the first paper describing the phenomenon of endothelium-dependent relaxation, convincing evidence has already been presented showing that the role of the endothelial cells could not be explained by cell-to-cell conduction of signals, but had to relay on the release of a vasoactive substance. The latter was termed ‘endothelium-dependent relaxing factor’ and readily abbreviated EDRF. Although the abbreviation sounded scientific, it masked a lack of knowledge for many years. EDRF appeared to be very labile, and this evanescent nature considerably delayed its proper identification. However, considerable progress has been made in that regard. It now appears that the major EDRF represents nothing else but nitric oxide or a labile nitroso compound, the terminal activator of guanylate cyclase released by exogenous nitrates. It also is obvious that EDRF/nitric oxide alone cannot explain all endothelium-dependent relaxations. Thus, prostacyclin triggers a renewed interest as an endothelium-derived relaxing substance, but yet unidentified endothelial mediators (e.g. endothelium-derived hyperpolarizing factor, EDHF) also can contribute to endothelium-dependent relaxations. The scope on EDRF has widened since it became obvious that the factor
not only affects the underlying smooth muscle, but also platelets, breaking their adhesion and aggregation. The latter effect is particularly pronounced in the presence of prostacyclin, and the view emerges progressively that the combined release of EDRF and the vasodilator prostaglandin may well represent a major physiological mechanism aimed at preventing the coagulation of blood in healthy blood vessels. Hence, it is not surprising that the repeated observation that diseased blood vessels release less EDRF has led to the proposal that the dysfunction of the endothelium may not only lead to abnormal vasoconstriction, but may also facilitate thrombotic episodes. Thus, the burgeoning area of endothelium-dependent relaxation is currently of great interest to understand the events leading to vascular disease. This monograph contains the proceedings of the first part of the International Symposium on Endothelium-Derived Vasoactive Factors which was held in Philadelphia from May 1 to May 3, 1989. The first part focuses on endothelium-dependent relaxations and their mediation by endothelium-derived relaxing factors (EDRF, EDHF and prostacyclin). The monograph discusses the chemical nature (e.g. nitric oxide as EDRF) of the factor(s), the cellular events leading to the release, and the ways by which relaxation of smooth muscle and inhibition of aggregation of platelets are achieved. Special attention is paid to recent data concerning the pharmacology of prostacyclin and its stable analogue, iloprost. This book will be of interest not only to the cardiovascular pharmacologist and physiologist, but also to the physician engaged in the treatment of cardiovascular disease, as it may help his/her understanding of how vascular disease comes about and how a more rational therapy can be initiated.

November 1989 Gabor M. Rubanyi, MD, PhD
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