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Contributions to Nephrology

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Endothelin in Renal Physiology and Disease

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Preface

‘Those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable.’

Hippokrátēs (460 BC – 370 BC)
ΚΥΡΙΑΚΟΣ, Part VII

The prevalence and incidence of kidney disease has been steadily increasing, mostly due to rising numbers of patients with obesity and/or diabetes, as well as an aging world population. Chronic kidney disease aggravates other conditions, including arterial hypertension, dyslipidemia, and atherosclerosis. Current drug therapies modestly slow progression of chronic kidney disease rather than reversing structural injury. Unfortunately, a large number of patients ultimately require renal replacement therapy through dialysis or kidney transplantation.

Following seminal discoveries in endothelial biology in the early 1980s, several endothelium-derived vasoconstrictor activities were reported, and by 1988 Yanagisawa and his team had succeeded in isolating, cloning, and sequencing a peptide which even today remains the strongest vasoconstrictor known to man. Named ‘endothelin (ET)’ because of its endothelial cell origin, this peptide activates G protein-coupled receptors and exerts a wide variety of effects on almost every organ system. Within the kidney, ET potently regulates physiologic function and contributes to renal injury through multiple mechanisms. Within the past 10 years the ET field has evolved rapidly; we now know that ET plays a central role in renal sodium and water balance, arterial blood pressure regulation, and the development and maintenance of kidney disease. Exciting new studies even suggest that proteinuric renal disease associated with activation of ET is – at least in part – a reversible condition.

Orally active ET receptor antagonists (ERAs) are now available; this new class of drugs exerts renoprotective activity in numerous models of renal disease. In the late 1990s, the first clinical studies suggested therapeutic potential for ERAs in the treatment of kidney injury. Since then, clinical drug development by a number of pharmaceutical companies has led to studies demonstrating
remarkable antiproteinuric effects of ERAs, even in patients already on current standard antiproteinuric therapy.

This book offers timely reviews by acclaimed experts in pharmacology, molecular biology, physiology, cardiovascular medicine, and nephrology covering (1) pharmacology, molecular biology, and physiology of ET in the kidney; (2) preclinical evidence for the role of ET and ERAs in renal disease; and (3) the current state of clinical development of ERA therapy in renal medicine. We hope that this book will be a valuable source of information for nephrologists, clinicians, and other healthcare professionals; renal physiologists and molecular biologists; postdoctoral researchers and students in the life sciences; and scientists and decision-makers in drug research and drug development.

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