

# Table of Contents

|                  |                                                                                                                                         |           |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Chapter 1</b> | <b>The Juxtaglomerular Apparatus – History of a Concept.....</b>                                                                        | <b>1</b>  |
| <b>Chapter 2</b> | <b>Morphology of the Juxtaglomerular Apparatus .....</b>                                                                                | <b>5</b>  |
| 2.1              | Components and Definitions .....                                                                                                        | 5         |
| 2.2              | Afferent Arteriole.....                                                                                                                 | 7         |
| 2.2.1            | Overview .....                                                                                                                          | 7         |
| 2.2.2            | Media Cells of the Afferent Arteriole.....                                                                                              | 9         |
| 2.2.3            | Morphological Prerequisites for Vasoconstriction<br>in the Renin-Positive and Renin-Negative Portions<br>of the Afferent Arteriole..... | 14        |
| 2.2.4            | Additional Aspects of the Functional Morphology of the<br>Proximal and Distal Portions of the Afferent Arteriole .....                  | 15        |
| 2.3              | Efferent Arteriole.....                                                                                                                 | 17        |
| 2.4              | Goormaghtigh Cell Field .....                                                                                                           | 20        |
| 2.5              | Macula Densa .....                                                                                                                      | 25        |
| 2.6              | Areas of Close Proximity Between Components<br>of the Juxtaglomerular Apparatus.....                                                    | 30        |
| 2.7              | Gap Junction Coupling Between Cells<br>of the Juxtaglomerular Apparatus.....                                                            | 33        |
| 2.8              | Tight Junction Barriers in the Region<br>of the Juxtaglomerular Apparatus.....                                                          | 41        |
| <b>Chapter 3</b> | <b>Elements with Structural and/or Functional Relationships<br/>to the Juxtaglomerular Apparatus.....</b>                               | <b>45</b> |
| 3.1              | Tubulovascular Proximities Outside<br>the JGA as Parts of the Tubulovascular<br>Complex of the Nephron .....                            | 45        |
| 3.2              | Glomerulus .....                                                                                                                        | 47        |
| 3.2.1            | Overview .....                                                                                                                          | 47        |
| 3.2.2            | Mesangial Cells in the Glomerular Stalk and<br>the Centriobular Region of the Glomerulus .....                                          | 47        |
| 3.2.3            | Peripolar Cells.....                                                                                                                    | 50        |
| 3.3              | Morphological Basis of Fluid Balance in the Interstitium<br>of the Juxtaglomerular Apparatus.....                                       | 52        |
| 3.4              | Cortical Interstitium and Lymph Vessels .....                                                                                           | 59        |
| 3.5              | Innervation of the Juxtaglomerular Apparatus.....                                                                                       | 61        |

|                  |                                                                                                                                  |            |
|------------------|----------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>Chapter 4</b> | <b>Intrarenal Distribution of the Different Components of the Renin-Angiotensin System .....</b>                                 | <b>69</b>  |
| 4.1              | Renin.....                                                                                                                       | 69         |
| 4.1.1            | Intrarenal Distribution of Renin.....                                                                                            | 69         |
| 4.1.2            | Factors Influencing the Localization of Granulated Cells in the Renal Arterial Tree.....                                         | 80         |
| 4.1.3            | Renin-Positive Cells of Different Origin?.....                                                                                   | 84         |
| 4.1.4            | Quantitative Evaluation of Histochemical and Immunohistochemical Experiments in Relation to the Renin Status of the Kidney ..... | 87         |
| 4.2              | Angiotensins .....                                                                                                               | 89         |
| 4.3              | Angiotensin-Converting Enzyme.....                                                                                               | 94         |
| 4.4              | Angiotensinogen .....                                                                                                            | 97         |
| 4.5              | Angiotensinases.....                                                                                                             | 99         |
| 4.6              | Nonrenin Angiotensin-Forming Enzymes .....                                                                                       | 100        |
| <br>             |                                                                                                                                  |            |
| <b>Chapter 5</b> | <b>Synthesis and Traffic of Renin in Epithelioid Cells .....</b>                                                                 | <b>103</b> |
| 5.1              | Granulopoiesis in Epithelioid Cells and Packaging of the Secretory Product.....                                                  | 103        |
| 5.2              | Renin Synthesis and Activation .....                                                                                             | 109        |
| 5.3              | Epithelioid Cell Secretory Granules Viewed as Lysosomes .....                                                                    | 113        |
| 5.3.1            | Lysosomal Enzymes as Constituents of Renin Granules.....                                                                         | 113        |
| 5.3.2            | Autophagic Phenomena in Renin Granules.....                                                                                      | 117        |
| 5.3.3            | Renin Granules and Lysosomotropic Substances.....                                                                                | 119        |
| 5.3.4            | Exogenous Tracers and Renin Granules.....                                                                                        | 122        |
| 5.3.5            | Conclusions and Outlook .....                                                                                                    | 125        |
| <br>             |                                                                                                                                  |            |
| <b>Chapter 6</b> | <b>Morphology of Renin Release from Epithelioid Cells.....</b>                                                                   | <b>127</b> |
| <br>             |                                                                                                                                  |            |
| <b>Chapter 7</b> | <b>Physiology, Pathophysiology, and Biochemistry of Renin Secretion.....</b>                                                     | <b>137</b> |
| 7.1              | Experimental Models.....                                                                                                         | 137        |
| 7.1.1            | Studies in the Intact Organism.....                                                                                              | 137        |
| 7.1.2            | The Kidney In Situ.....                                                                                                          | 138        |
| 7.1.3            | The Isolated Perfused Kidney.....                                                                                                | 138        |
| 7.1.4            | Kidney Slices.....                                                                                                               | 139        |
| 7.1.5            | Isolated Glomeruli .....                                                                                                         | 140        |
| 7.1.6            | Isolated Cells.....                                                                                                              | 140        |
| 7.2              | Renal Baroreceptor Mechanism .....                                                                                               | 141        |
| 7.3              | Tubular Signals, Renin Secretion, and Vascular Reactions - The Macula Densa Hypothesis .....                                     | 144        |
| 7.3.1            | Acute Tubulovascular Interactions.....                                                                                           | 145        |
| 7.3.2            | Location of the Tubular Sensor.....                                                                                              | 147        |
| 7.3.3            | The Macula Densa Signal.....                                                                                                     | 147        |
| 7.3.4            | Concluding Remarks .....                                                                                                         | 150        |
| 7.4              | Renal Nerves and Renin Secretion.....                                                                                            | 151        |

|                  |                                                                                               |            |
|------------------|-----------------------------------------------------------------------------------------------|------------|
| 7.5              | Hormonal Signals Influencing Renin Secretion .....                                            | 154        |
| 7.5.1            | Dopamine .....                                                                                | 154        |
| 7.5.2            | Prostaglandins and Related Products .....                                                     | 155        |
| 7.5.3            | Kallikrein and Kinins .....                                                                   | 157        |
| 7.5.4            | Histamine .....                                                                               | 159        |
| 7.5.5            | Platelet-Activating Factor .....                                                              | 160        |
| 7.5.6            | Vasoactive Intestinal Polypeptide .....                                                       | 160        |
| 7.5.7            | Acetylcholine .....                                                                           | 161        |
| 7.5.8            | Atrial Natriuretic Factor .....                                                               | 162        |
| 7.5.9            | Angiotensin .....                                                                             | 166        |
| 7.5.10           | Antidiuretic Hormone .....                                                                    | 169        |
| 7.5.11           | Neuropeptide Y .....                                                                          | 170        |
| 7.5.12           | Other Hormonal Agents .....                                                                   | 171        |
| 7.5.13           | Synopsis of Hormonal Signals .....                                                            | 172        |
| 7.6              | Intracellular Control of Renin Release .....                                                  | 173        |
| 7.6.1            | Introductory Remarks .....                                                                    | 173        |
| 7.6.2            | Role of Adenosine 3',5'-Cyclic Monophosphate .....                                            | 173        |
| 7.6.3            | Role of Guanosine 3',5'-Cyclic Monophosphate .....                                            | 175        |
| 7.6.4            | Role of Calcium .....                                                                         | 176        |
| 7.6.5            | Role of Calmodulin .....                                                                      | 180        |
| 7.6.6            | Role of Diacylglycerol and Protein Kinase C .....                                             | 180        |
| 7.6.7            | Interaction of Messengers .....                                                               | 181        |
| 7.6.8            | A Possible Explanation of the "Calcium Paradox"<br>of Renin Secretion .....                   | 182        |
| 7.6.9            | Summary and Conclusions .....                                                                 | 184        |
| 7.7              | Secretion of Prorenin .....                                                                   | 185        |
| 7.8              | Renin Synthesis and Secretion .....                                                           | 189        |
| <b>Chapter 8</b> | <b>Electrophysiology of Epitheloid Cells .....</b>                                            | <b>195</b> |
| <b>Chapter 9</b> | <b>Intrarenal Renin-Angiotensin System .....</b>                                              | <b>197</b> |
| 9.1              | Local Renin-Angiotensin Systems .....                                                         | 197        |
| 9.2              | Intrarenal Formation of Angiotensin II .....                                                  | 198        |
| 9.2.1            | Systemic Origin of Angiotensin I and II .....                                                 | 199        |
| 9.2.2            | Components of the Renin-Angiotensin System<br>in the Renal Interstitium and Renal Lymph ..... | 200        |
| 9.2.3            | Alternative Pathways of Angiotensin Formation .....                                           | 203        |
| 9.2.4            | Intracellular Generation of Angiotensin II .....                                              | 203        |
| 9.3              | Renal Effects of Angiotensin II .....                                                         | 204        |
| 9.3.1            | Effects on Renal Hemodynamics .....                                                           | 204        |
| 9.3.2            | Angiotensin II and the Glomerulus .....                                                       | 207        |
| 9.3.3            | Control of Sodium Excretion by Angiotensin II .....                                           | 209        |
| 9.4              | Renin-Angiotensin System in the Control of Renal<br>Hemodynamics .....                        | 210        |
| 9.5              | Summary and Conclusions .....                                                                 | 213        |

|                            |                                                                                           |            |
|----------------------------|-------------------------------------------------------------------------------------------|------------|
| <b>Chapter 10</b>          | <b>Metaplastic Transformation Between Smooth Muscle Cells and Epithelioid Cells .....</b> | <b>215</b> |
| <b>Chapter 11</b>          | <b>Long-Term Modulation of Renin Synthesis and Secretion .....</b>                        | <b>221</b> |
| 11.1                       | Relationship Between Renal Renin Content and Renin Secretion .....                        | 222        |
| 11.2                       | Uniform Reaction to Different "Stimuli" of Renin Synthesis? .....                         | 224        |
| <b>Chapter 12</b>          | <b>Interspecies Variations of the Juxtaglomerular Apparatus in Mammals .....</b>          | <b>225</b> |
| 12.1                       | Qualitative Differences .....                                                             | 225        |
| 12.2                       | Quantitative Differences .....                                                            | 226        |
| <b>Chapter 13</b>          | <b>Phylogeny and Ontogeny of the Juxtaglomerular Apparatus .....</b>                      | <b>231</b> |
| 13.1                       | Evolution of the Juxtaglomerular Apparatus in Nonmammalian Vertebrates .....              | 231        |
| 13.2                       | Ontogeny of the Juxtaglomerular Apparatus in Mammals .....                                | 235        |
| <b>Chapter 14</b>          | <b>Pathology of the Human Juxtaglomerular Apparatus .....</b>                             | <b>241</b> |
|                            | R. WALDHERR                                                                               |            |
| 14.1                       | Stimulation of the Juxtaglomerular Apparatus .....                                        | 241        |
| 14.1.1                     | Ischemic Kidney .....                                                                     | 241        |
| 14.1.2                     | Reflux Nephropathy .....                                                                  | 243        |
| 14.1.3                     | Glomerular Disorders .....                                                                | 243        |
| 14.1.4                     | Bartter's Syndrome and Related Disorders .....                                            | 245        |
| 14.1.5                     | Renin-Secreting Tumors .....                                                              | 250        |
| 14.2                       | Inhibition of the Juxtaglomerular Apparatus .....                                         | 253        |
| 14.2.1                     | Primary Hyperaldosteronism .....                                                          | 253        |
| 14.2.2                     | Miscellaneous Conditions .....                                                            | 253        |
| 14.3                       | Conclusions .....                                                                         | 254        |
| <b>References .....</b>    |                                                                                           | <b>255</b> |
| <b>Subject Index .....</b> |                                                                                           | <b>305</b> |