

Animal Models in Cardiovascular Research

David R. Gross

Animal Models in Cardiovascular Research

Third Edition



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David R. Gross
Professor Emeritus
University of Illinois
Urbana Champaign
College of Veterinary Medicine
Department of Veterinary Biosciences
2001 S. Lincoln Ave.
Urbana IL 61802
USA

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*To Drs. Theodore S. Gross and Jeffrey
M. Gross who continue the family obsession
for the acquisition and dissemination of new
knowledge.*

Preface

This new edition of *Animal Models in Cardiovascular Research* describes historical and recent advances in our understanding of the cardiovascular system from studies conducted in a variety of animal models. Since the last edition, we have witnessed an explosion in the use of both congenic and transgenic animals. The use of specific knock-in and knock-out transgenic models has resulted in an avalanche of genetic, molecular, and protein-based information that, potentially, could result in an amazing new array of treatment and management options. However, the results of these studies also introduce a sometime bewildering array of redundant, overlapping, and competing molecular pathways involved in both physiological and pathological responses.

This third edition is designed to provide a better basis for understanding and using animal models in the current climate of background knowledge and information. It is significantly different than the previous two editions. Chapter 1 is updated from the previous editions addressing general principles of animal selection. It also provides expanded tables of normal physiological values for easy reference. Chapter 2 covers preoperative care, preanesthesia, and chemical restraint, and includes a significantly expanded section on pain recognition and analgesia particularly in rodents. Chapter 3 provides a summary of normal cardiovascular parameters obtained from intact, awake animals. The data have been rearranged in outline rather than the previous tabular form hopefully resulting in easier reference.

Chapter 4 addresses the techniques, problems, and pitfalls of measuring cardiac function in animals. There is an emphasis on the proper use of these measurements to develop new treatment and management strategies as well as using them to study mechanisms of disease. Chapter 5 emphasizes the techniques, problems, and pitfalls involved in the measurement of arterial function and ventricular/arterial coupling dynamics. Again the emphasis is on the use of these parameters to develop new treatment and management strategies and for studying the mechanisms of disease. Chapter 6 is an all new chapter dealing specifically with the problems and pitfalls inherent in using isolated heart preparations. The need for this chapter became apparent because so much information was published using obviously non-physiologic preparations. The use of both pumping and nonpumping preparations is described along with techniques necessary for using hearts from larger species where oxygen-carrying capacity of the perfusate is critical. The importance of hypoxia and anoxia in the interpretation of results is discussed.

Chapter 7 focuses on the cardiovascular effects of the postoperative analgesic drugs commonly used today and how to avoid potential problems resulting from these effects when reporting experimental data. These data are also presented in outline form rather than the tabular format used in the two previous editions. Chapter 8 addresses the use of naturally occurring animal models of valvular and infectious cardiovascular disease. The information presented has been updated and expanded from the second edition. Chapter 9 examines iatrogenic models of ischemic heart disease.

Chapter 10 is new. It provides a review of iatrogenic, transgenic, and naturally occurring animal models of cardiomyopathy and heart failure. Chapter 11 includes new, updated, and revised information reviewing iatrogenic and transgenic models of hypertension. Chapter 12 contains new and updated information on iatrogenic and transgenic models of atherosclerotic disease.

Chapter 13 is completely a new material dealing with animal models for the study of neurohumeral and central nervous system control of the cardiovascular system. Chapter 14 is also new. It provides examples of cardiovascular studies involving the use of specific transgenic models that are not normally associated with the cardiovascular system, such as estrogen receptor knockouts, to study cardiovascular function.

Urbana, IL

David R. Gross

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Rosalie Gross has supported, encouraged, loved and endured since April of 1960. Our journey together continues.

Special thanks are owed to Professor Gary A. Iwamoto. Chapter 13 benefited significantly from his critical review and insightful suggestions.

Introduction

Animal rights activist organizations lobbied for and obtained significantly more restrictive regulations from governments worldwide since the last edition of this text. The agenda of most animal rights groups is to stop our use of animals. If biomedical science is to advance, we must understand the complexities and interrelationships of the various physiological control mechanisms that regulate living whole animal systems. It is more essential than ever that we persevere.

“Old guard” physiologists, pharmacologists, and toxicologists, familiar with whole animal homeostatic control mechanisms, believe some “new breed” scientists working at the molecular level are so focused in their particular area of expertise they have little appreciation for the potential effects of the iatrogenic changes they induce on the whole animal. Frequently lost in the landslide of new information is an understanding of how any particular gene, molecule, and/or protein fits into our broad understanding of the basic physiology of the animal species and how that relates to the human species. A few scientists even seem unaware that most, if not all, physiological systems have multiple and redundant control mechanisms that adjust any particular organ or system behavior to the homeostatic requirements of the whole animal.

Physiological systems may have several stimulatory and inhibitory controls that operate at some constant level of activity. The same physiological response is therefore possible by increasing stimulation or decreasing inhibition or vice versa. At the molecular and cellular level, the more information we obtain the more apparent it becomes that multiple pathways are present to achieve the same response. When cells, or organ systems, are perturbed by interrupting, knocking out, or upregulating a specific molecular or genetic pathway, redundant pathway(s) are, appropriately, up- or downregulated in response to maintain homeostasis.

A significant number of the animal models described in this text have been derived using either congenic or transgenic techniques. It is therefore appropriate to provide an abbreviated description of how these animals are produced.

Congenic strains of animals are developed by mating two inbred strains and then backcrossing the descendants for at least five and up to ten or more generations with one of the original strains. At each step, selections are made for the specific phenotype or genotype of interest. This allows the phenotype or genotype to pass from the donor strain onto an otherwise uniform recipient strain. The congenic

strain can then be compared to the pure recipient strain to determine phenotypical or genetic differences. Producing large numbers of eggs via superovulation in females and then using microsatellite or nucleotide polymorphism markers to track the genes of interest can speed up specific congenic strain development.

Transgenic animals are generally created using one of two different protocols. The first uses recombinant DNA methodology to insert (knock in) or remove (knock out) a specific gene or protein from the genome. The DNA used usually includes a structural gene, as well as other sequences, that enables it to be incorporated into the DNA of the host and to be expressed by the particular cells of interest. The most common method of producing a transgenic animal model involves harvesting embryonic stem cells from the inner cell mass of blastocysts. When these cells are grown in culture, they retain their ability to produce all the cells of the mature animal. The cultured cells are then exposed to the DNA of interest and those cells that successfully incorporate the DNA are identified and separated. These isolated cells are then injected into the inner cell mass of blastocysts. The resulting embryos are transplanted into a pseudopregnant dam. It is uncommon, at least in mice, for more than a third of the embryos thus transplanted to develop into healthy offspring. The next step is to test all the offspring to identify those with the desired gene. Usually, no more than 10–20% will have that gene and they will be heterozygous for it. The next step is to mate two heterozygous mice and screen their offspring for the one in four that will be homozygous for the transgene of interest. Mating homozygous animals produces the transgenic strain.

A second method of producing transgenic animals involves the same preparation of the DNA of interest and then harvesting freshly fertilized eggs before the sperm head has become a pronucleus. The male pronucleus is injected with the DNA of interest, and when the pronuclei have fused to form diploid zygote nuclei, the zygote is allowed to divide by mitosis to form a two-cell embryo. The two-cell embryo is then implanted in the pseudopregnant foster mother and the same steps used in the embryonic stem cell method are followed.

Contents

| | | |
|----------|--|----|
| 1 | General Principles of Animal Selection and Normal Physiological Values | 1 |
| | Special Requirement Considerations..... | 2 |
| | Normal Physiological Data | 3 |
| 2 | Preanesthesia, Anesthesia, Chemical Restraint, and the Recognition and Treatment of Pain and Distress | 17 |
| | General Principles of Pain Recognition in Animals..... | 17 |
| | The Use of Anti-Cholinergic Drugs for Preanesthesia..... | 21 |
| | General Comments on Preanesthetic Agents | 22 |
| | Preanesthesia and Anesthesia in Rats and Mice..... | 22 |
| | Chemical Restraint (Sedation) in Rats and Mice | 23 |
| | Pain and Distress Recognition in Rats and Mice | 23 |
| | Treatment of Pain in Rats and Mice | 26 |
| | Local Anesthetic Agents..... | 26 |
| | Nonsteroidal Anti-Inflammatory Drugs | 26 |
| | Narcotics..... | 26 |
| | Preanesthesia and Anesthesia in Rabbits..... | 28 |
| | Chemical Restraint (Sedation) in Rabbits | 29 |
| | Pain Recognition in Rabbits | 29 |
| | Treatment of Pain in Rabbits..... | 29 |
| | Local Anesthetics | 29 |
| | Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) | 30 |
| | Narcotics..... | 30 |
| | Alpha-Agonists | 30 |
| | Preanesthesia and Anesthesia in Dogs | 30 |
| | Chemical Restraint (Sedation) in Dogs..... | 32 |
| | Pain Recognition in Dogs..... | 33 |
| | Treatment of Pain in Dogs..... | 34 |
| | Local Anesthetics | 34 |
| | NSAIDs | 34 |
| | Narcotics..... | 34 |
| | Alpha-Agonists..... | 35 |

- Preanesthesia and Anesthesia in Cats..... 35
- Chemical Restraint (Sedation) in Cats 36
- Pain Recognition in Cats 37
- Treatment of Pain in Cats 37
 - Local Anesthetics 37
 - NSAIDs 37
 - Narcotics..... 37
 - Alpha-Agonists..... 38
- Preanesthesia and Anesthesia in Guinea Pigs 38
- Chemical Restraint (Sedation) in Guinea Pigs 38
- Pain Recognition in Guinea Pigs..... 38
- Treatment of Pain in Guinea Pigs..... 39
 - Local Anesthetic Agents..... 39
 - NSAIDs 39
 - Narcotics..... 39
 - Alpha-Agonists..... 39
- Preanesthesia and Anesthesia in Pigs..... 39
- Chemical Restraint (Sedation) in Pigs 41
- Pain Recognition in Pigs 41
- Treatment of Pain in Pigs 41
 - Local Anesthetic Agents..... 41
 - NSAIDs 42
 - Narcotics..... 42
 - Alpha-Agonists..... 42
- Preanesthesia and Anesthesia in Calves, Sheep,
and Goats..... 42
- Chemical Restraint (Sedation) in Small Ruminants..... 43
- Recognition of Pain in Small Ruminants 43
- Treatment of Pain in Small Ruminants 44
 - Local Anesthetic Agents..... 44
 - NSAIDs 44
 - Narcotics..... 44
 - Alpha-Agonists..... 44
- Preanesthesia and Anesthesia in Rhesus Monkeys 45
- Chemical Restraint (Sedation) in Rhesus Monkeys 45
- Pain Recognition in Rhesus Monkeys 45
- Treatment of Pain in Rhesus Monkeys..... 46
 - Local Anesthetics 46
 - NSAIDs 46
 - Narcotics..... 46
- Conclusions 47

- 3 Normal Cardiac Function Parameters..... 55**

| | |
|---|-----------|
| 4 Measuring Cardiac Function | 65 |
| The Pressure–Volume Relationship..... | 67 |
| Another Measure of Ventricular Elasticity | 68 |
| Measurement of Electrical Activity | 68 |
| Measurement of Pressure | 69 |
| Echocardiography..... | 70 |
| History | 70 |
| Physics of Echo Technology..... | 72 |
| Doppler Flow Velocity and Tissue Doppler Imaging..... | 74 |
| History | 74 |
| Physics of Doppler Technology..... | 75 |
| Tissue Doppler Imaging | 76 |
| Examples of Ultrasound Data Reported Using | |
| <20-MHz Transducers..... | 77 |
| Examples of Ultrasound Data Reported Using 20-MHz | |
| (or Greater) Transducers..... | 78 |
| Summary of Information Needed to Ascertain | |
| the Reliability of Ultrasound Data..... | 80 |
| Techniques for Measuring Ventricular Volumes | 80 |
| Radiographic..... | 80 |
| Echocardiography and Tissue Doppler Imaging | 81 |
| Sonomicrometry | 81 |
| Radionuclide Ventriculography..... | 81 |
| Magnetic Resonance Imaging and Computer-Assisted | |
| Tomography Scan..... | 82 |
| Conductance-Derived Volume Measurements | 82 |
| Other Measures of Myocardial Physical Properties..... | 84 |
| Myocardial Resistivity..... | 85 |
| Tissue Characterization | 85 |
| Measuring Diastolic Dysfunction..... | 86 |
| | |
| 5 Measuring Vascular Function and Ventricular/ | |
| Arterial Coupling Dynamics | 93 |
| History..... | 93 |
| Quantification of Arterial Compliance | 94 |
| Force-Displacement Measurements | 95 |
| Pulse Wave Velocity | 97 |
| Modeling Techniques for Estimating Vascular Mechanical Behavior | 99 |
| Ventricular/Vascular Coupling | 101 |
| Ventricular/Vascular Coupling Determined Using | |
| the Input Impedance | 101 |
| Ventricular/Vascular Coupling Determined Using | |
| the Ratio of Ventricular End-Systolic Pressure | |
| and Stroke Volume (P_{es}/SV) Designated E_a | 102 |

Diastolic Ventricular/Vascular Coupling 104

MRI Imaging for Detection of Ventricular/Vascular Coupling 104

Tissue Doppler Imaging and Elasticity Imaging 104

6 Isolated Heart Preparations, Problems, and Pitfalls 109

Development of the Isolated Heart Preparation 109

Retrograde Perfusion Preparations (The Langendorff Preparation)..... 112

Choosing between the Pressure-Regulated or Flow-Regulated
Langendorff-Type Preparation 114

The Isolated, Working, In Situ Heart-Lung Preparation 114

The Isolated Working Left Heart Preparation 114

The Langendorff-Type Perfused Working Left Heart Preparation..... 115

The Biventricular Isolated Working Heart Preparation 117

The Biventricular, Retrograde-Perfused,
Working Heart Preparation..... 119

Perfusion Solutions 120

Support Animals 122

Washed Red Blood Cell Addition to the Perfusate 122

Problems and Pitfalls 123

 Exclusion Criteria 123

 Problems Common to Crystalloid Perfusion 124

 Contamination 124

 Temperature 125

 Metabolic “Poisoning” 125

 Pacing vs. Spontaneously Beating Preparations..... 125

 Frequency Response Testing of Ventricular Pressure
 Recording Systems 126

Heterotopic Transplants..... 126

**7 Cardiovascular Effects of Anesthetics, Sedatives,
Postoperative Analgesic Agents, and Other Pharmaceuticals 131**

Barbiturates 131

Propofol 132

α-Chloralose 133

Urethane 134

α-Chloralose + Urethane 134

Steroid Anesthetic Agents 134

Inhalation Anesthetic Agents 135

 General 135

 Halothane 136

 Isoflurane 137

 Desflurane 138

 Sevoflurane 139

 Ether 140

 Nitrous Oxide 140

| | |
|---|-----|
| Trichloroethylene..... | 140 |
| The Opioids | 141 |
| Morphine | 141 |
| Meperidine (Demerol)..... | 144 |
| Methadone | 144 |
| Levomethadone..... | 145 |
| Pentazocine..... | 145 |
| Fentanyl | 145 |
| Butorphanol | 147 |
| Buprenorphine | 147 |
| Oxymorphone | 148 |
| Naloxone..... | 148 |
| Other Synthetic Opioids | 149 |
| Dissociative Anesthetic Agents..... | 150 |
| Ketamine..... | 150 |
| Tiletamine..... | 151 |
| Imidazole and Other Hypnotic, Amnesiac, Anxiolytic, or Antipsychotic Compounds..... | 152 |
| Etomidate..... | 152 |
| Metomidate..... | 153 |
| Benzodiazepines | 153 |
| Rilmenidine | 155 |
| α -2 Adrenergic Receptor Agonists..... | 156 |
| Medetomidine and Dexmedetomidine..... | 156 |
| Clonidine | 157 |
| β -2-Adrenergic Receptor Agonists | 157 |
| Clenbuterol | 157 |
| KUR-1246 | 158 |
| Fenoterol..... | 158 |
| Rauwolfia Derivatives | 158 |
| Reserpine | 158 |
| Phenothiazine Derivatives | 160 |
| Chlorpromazine and Promazine | 160 |
| Acetylpromazine (Acepromazine)..... | 162 |
| Other Phenothiazine Derivatives | 163 |
| Triflupromazine, Levomepromazine, Prochlorperazine (thioridazine), Cyamemazine | 163 |
| Butyrophenones..... | 164 |
| Droperidol..... | 164 |
| Haloperidol..... | 165 |
| Azaperone..... | 166 |
| Other Antipsychotic/Anxiolytic/Antidepressant (Tranquilizer) Drugs..... | 166 |
| Tricyclic Antidepressants | 167 |
| Selective Serotonin Uptake Inhibitors | 167 |

| | |
|--|-----|
| Atypical Antipsychotics | 169 |
| Sertindole..... | 169 |
| Pimozide..... | 169 |
| Clozapine..... | 169 |
| Risperidone..... | 170 |
| Amisulpride..... | 170 |
| Minaprine | 171 |
| Atypical Antipsychotics | 171 |
| Aripiprazole..... | 171 |
| Fezolamine | 171 |
| Olanzapine..... | 171 |
| Lortalamine..... | 171 |
| Xylazine..... | 172 |
| Drugs in Combination Providing Neurolept Analgesia/Anesthesia..... | 172 |
| Metomidate + Azaperone | 172 |
| Medetomidine + Butorphanol..... | 173 |
| Medetomidine + Butorphanol + Midazolam | 173 |
| Medetomidine + Buprenorphine + Ketamine..... | 173 |
| Medetomidine + Midazolam | 174 |
| Medetomidine + Hydromorphone | 174 |
| Dexmedetomidine + Butorphanol | 174 |
| Medetomidine + Ketamine | 174 |
| Medetomidine + Ketamine + Midazolam..... | 175 |
| Dexmedetomidine + Ketamine | 175 |
| Ketamine in Combination with Tranquilizers | 175 |
| Ketamine + Acepromazine | 175 |
| Ketamine + Xylazine | 176 |
| Ketamine + Xylazine + Guaifenesin | 178 |
| Ketamine + Xylazine + Buprenorphine..... | 178 |
| Ketamine + Diazepam | 178 |
| Midazolam + Butorphanol..... | 179 |
| Midazolam + Fentanyl + Fluanisone..... | 179 |
| Midazolam + Methadone + Propofol + Isoflurane + Continuous | |
| Infusion of Propofol and Fentanyl..... | 179 |
| Acepromazine + Meperidine | 179 |
| Fentanyl + Droperidol (Innovar-Vet®)..... | 180 |
| Azaperone + Metomidate | 180 |
| Acepromazine + Etorphine..... | 180 |
| Fentanyl + Morphine | 180 |
| Fentanyl + Propofol..... | 181 |
| Xylazine + Morphine..... | 181 |
| Oxymorphone + Bupivacaine | 181 |
| Tiletamine + Zolazepam (Telazol®, Zoletil®)..... | 181 |
| Local Anesthetic Agents | 182 |
| Non-steroidal Anti-inflammatory Agents..... | 183 |

Neuromuscular Blocking Agents 185

Aminoglycoside, Fluoroquinolone, and Anthracycline
Antibiotics 187

**8 Naturally Occurring and Iatrogenic Animal Models
of Valvular, Infectious, and Arrhythmic
Cardiovascular Disease..... 203**

Congenital Cardiac Defects, General Information 203

Genetically Engineered Models, General Information..... 204

Naturally Occurring Models of Valvular Disease 205

Iatrogenic Models of Valvular Disease 207

Infectious Cardiovascular Disease 208

 Bartonella sp..... 208

 Borrelia sp 208

 Coxsackievirus sp..... 209

Diphtheritic Myocarditis 209

Encephalomyocarditis Virus..... 210

Autoimmune Myocarditis 210

 Infectious Complications Following Burn Injury..... 210

Arrhythmic Cardiovascular Disease..... 211

 Naturally Occurring Cardiac Arrhythmias 211

 Iatrogenic Cardiac Arrhythmias 211

9 Iatrogenic Models of Ischemic Heart Disease..... 219

Global Ischemia 219

Regional Ischemia..... 221

**10 Iatrogenic, Transgenic, and Naturally Occurring
Models of Cardiomyopathy and Heart Failure 231**

Naturally Occurring Models of Cardiomyopathy 232

 Heritable HCM in Cats 232

 DCM in Dogs 233

 Cattle with Cardiomyopathy and Woolly Hair
 Coat Syndrome..... 234

 Primates..... 235

 Whales..... 235

Iatrogenic Models of Cardiomyopathy and Heart Failure 235

 Ventricular Arrhythmia 235

 Increasing the Ventricular Workload..... 236

 Rapid Cardiac Pacing..... 236

 Pressure Overload 236

 Volume Overload 237

 Valvular Stenoses or Insufficiencies 237

| | |
|---|------------|
| Other Iatrogenic Models of Cardiomyopathy and Heart Failure | 237 |
| Anthracycline-Induced Cardiomyopathy | 237 |
| Diabetic and Lipid-Toxic Models of Cardiomyopathy | 238 |
| Chronic Myocardial Ischemia Models of Cardiomyopathy | 238 |
| Toxicosis and Mineral-Deficient Models of Cardiomyopathy | 239 |
| Autoimmune Models of Cardiomyopathy | 239 |
| Hyperthyroid and Hyper-Adrenergic Models of Cardiomyopathy | 240 |
| Chronic Hypoxia Models of Cardiomyopathy | 240 |
| Liver Cirrhosis Models of Cardiomyopathy | 240 |
| Murine Cysticercosis Model of Cardiomyopathy | 240 |
| Commercially Available Inbred-Rat Models of Cardiomyopathy and Heart Failure | 240 |
| Transgenic Models of Cardiomyopathy and Heart Failure | 241 |
| Mouse and Rat Models of Familial Hypertrophic Cardiomyopathy and HCM | 241 |
| Mouse and Rat Models of DCM | 242 |
| Overexpression Models | 245 |
| 11 Iatrogenic, Congenic, and Transgenic Models of Hypertension | 259 |
| Renovascular Hypertension | 260 |
| 2K1C and 1K1C Renovascular Hypertension in Rats | 261 |
| 2K1C and 1K1C Renovascular Hypertension Models in Mice | 263 |
| Renovascular Hypertension Models in Rabbits | 264 |
| 1K1C Renovascular Hypertension in Dogs | 265 |
| Renovascular Hypertension in Pigs | 265 |
| Genetic Models of Hypertension | 266 |
| Spontaneously Hypertensive Rat | 266 |
| Stroke-Prone SHR | 269 |
| Dahl Salt-Sensitive and Insensitive Rats | 270 |
| Other Salt-Sensitive (Salt-Induced) Models of Hypertension | 272 |
| Angiotensin-II-Induced Hypertension | 273 |
| DOCA-Induced Hypertension | 276 |
| NO-Synthesis Blockade Hypertension | 278 |
| Glucocorticoid-Induced Hypertension | 280 |
| Intrauterine Growth-Restricted Induced Hypertension | 281 |
| Other Transgenic and Congenic Models of Hypertension | 283 |
| The mRen-2 Model | 283 |
| ATR-1 Models | 283 |
| Angio-II Overexpression Models | 284 |
| G-Protein Models | 284 |
| eNOS Models | 285 |
| Endothelin Models | 285 |
| Chromogranin-A Models | 286 |
| PPAR- α Models | 286 |

- Bradykinin-2 Models 286
- Estrogen Models 287
- Corin Models 287
- Vitamin D Receptor Models 287
- Glucocorticoid Receptor Models 287
- Smoothelin Models 288
- Adiponectin Models..... 288
- Aryl Hydrocarbon Models 288
- Parathyroid Hormone Type 1 Receptor Models..... 289
- Profilin Models..... 289
- Oligodeoxynucleotide Models 289
- Multiple Transgenic Models 290
- Congenetic Models 290
- Other Models of Systemic Hypertension 291
- Pulmonary Hypertension 292
 - Hypoxia-Induced Pulmonary Hypertension 292
 - Monocrotaline-Induced Pulmonary Hypertension..... 293
 - Transgenic Models of Pulmonary Hypertension 294

- 12 Naturally Occurring, Iatrogenic and Transgenic Models of Atherosclerotic Disease 307**
 - Characteristics of Plaque Rupture and Resulting Thrombosis 309
 - Implication of New “Players” in the Pathogenesis of Atherosclerotic Disease 309
 - Animal Models..... 310
 - Naturally Occurring Animal Models of Atherosclerosis 311
 - Primate Models of Atherosclerosis..... 311
 - Swine Models of Atherosclerosis 312
 - Dog and Cat Models 312
 - Rabbit Models 313
 - Transgenic Rabbit Models 314
 - Rat Models 315
 - Transgenic Rat Models 317
 - Mouse Models..... 317
 - Mice Models of Glucose Intolerance 317
 - Graft Vasculopathy..... 323
 - Hamsters 324
 - Sand Rats 324

- 13 Animal Models for the Study of Neurohumeral and Central Neural Control of the Cardiovascular System..... 331**
 - The Autonomic Nervous System in Blood Pressure
 - Homeostasis and Cardiorespiratory Reflex Responses..... 333
 - Rostal and Caudal Ventrolateral Medulla 334

| | |
|---|------------|
| Nucleus Tractus Solitarius | 337 |
| Hypothalamic Paraventricular Nucleus..... | 339 |
| Periaqueductal Gray | 340 |
| Anterior and Posterior Hypothalamic Areas..... | 342 |
| Median Preoptic Nucleus..... | 342 |
| Nucleus Cuneatus..... | 342 |
| Lateral Parabrachial Nucleus and the Dorsal Raphe Nucleus..... | 343 |
| Caudal Vestibular Nucleus | 343 |
| Gender Effects on Central Control of Cardiovascular Responses | 343 |
| Neurohumeral Control | 344 |
| Renin-Angiotensin System | 344 |
| Serotonin | 344 |
| Vasopressin | 345 |
| Endogenous Ouabain-Like Substance | 345 |
| Opioids..... | 345 |
| Tyrosine Hydroxylase and Phenylethanolamine | |
| N-Methyltransferase..... | 346 |
| Neuropeptide Y..... | 346 |
| Leptin | 346 |
| Dopamine-β-Hydroxylase..... | 346 |
| 11-β-Hydroxylase and Aldosterone Synthase | 347 |
| Orexin | 347 |
| Urotensin-II..... | 347 |
| Cholecystokinin | 348 |
| 14 Other Transgenic Animal Models Used | |
| in Cardiovascular Studies | 355 |
| Sex-Related Responses | 356 |
| Kinases..... | 357 |
| Oxidases and Oxygenases..... | 358 |
| Adenosine and Adrenergic Receptors..... | 359 |
| Nitric Oxide Synthase..... | 360 |
| Metabolic Syndrome..... | 361 |
| Xenotransplantation | 362 |
| Na ⁺ /Ca ²⁺ and Na ⁺ /H ⁺ Exchangers..... | 364 |
| Inflammatory Cytokines..... | 365 |
| Peroxisome Proliferator-Activated Receptor | 366 |
| Renin-Angiotensin System | 366 |
| Bradykinin-2 Receptor..... | 367 |
| Apolipoprotein-E and Low-Density Lipoprotein | |
| Knockout Models..... | 367 |
| Toll-Like Receptors..... | 368 |
| Caveolin-1 (Cav-1)..... | 368 |
| Long QT Syndrome | 369 |

Nuclear Factor Kappa-B 369

Orphan Nuclear Receptors 370

Troponin..... 370

Chromogranin A 371

Lectin-Like Oxidized Low-Density Lipoprotein Receptor..... 371

Junctin 371

Connexin 372

Phospholamban 372

Fas Ligand..... 373

Proteases, Metalloproteinases, and ATPases..... 373

Binary Calsequestrin/P2Xr-Purinergic Receptor
(CSQ/P2X4R) Transgenics 374

pro-ANP Gene Disrupted Mouse..... 375

Macrophage Colony-Stimulating Factor..... 375

Endothelin-1 375

Elastin 376

α -2-Antiplasmin..... 376

cAMP Response Element Binding Protein 376

Fatty Acid Transport Protein: CD36 376

Clotting Factor XIII 377

Apelin..... 377

T-Box Transcription Factor 377

Thrombospondin-1 and Its Receptor CD47 377

Polyomavirus Middle T Antigen..... 378

Thrombopoietin Receptor 378

Vascular Endothelial Growth Factor 378

Osteopontin 378

ATP-Binding Membrane Cassette Transporter-A1 379

The K⁺/Cl⁻ Cotransporter KCC3..... 379

Aldosterone Synthase Overexpression..... 379

Cysteine and Glycine-Rich Protein-2 (CSRP-2)..... 379

Parathyroid Hormone Type-1 Receptor
and PTH/PTH-Related Protein 380

Vitamin D Receptor 380

Thromboxane Receptor (Tp)..... 380

T and B Cells 380

Vanilloid Type-1 Receptors (TRPV-1)..... 381

Serotonin Transporter (SERT) 381

CC Chemokine Receptor-2 (CCR-2) 381

Thymosin β -4..... 381

Index..... 393

About the Author

Dr. David Gross entered private veterinary practice after earning the DVM degree from Colorado State University in 1960. In 1974 he was awarded the Ph.D. degree in physiology from the Ohio State University beginning a 36-year career in academics that culminated as professor and head of the Department of Veterinary Biosciences in the College of Veterinary Medicine, University of Illinois, Urbana-Champaign. Dr. Gross' research career encompassed 58 funded projects totaling over \$5.5 million and 91 papers published in refereed journals using a wide variety of animal models. Ironically, his three most-cited research papers received no external funding. He and his colleagues showed that feeding dietary cholesterol to rabbits induced Alzheimer's-like lesions in the brain. Their work also showed that surgery involving cardiopulmonary bypass resulted in Alzheimer's-like brain lesions in pigs. With another group of colleagues, he helped pioneer minimally invasive coronary artery bypass grafting techniques using the pig as a model.