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FOREWORD

It is well known that the understanding and treatment of many human diseases has been enhanced by the study of laboratory animals in the past, and that the use of laboratory animals continues to be of major importance in medical research.

The current and growing use of animals in research has made it imperative that the benefits, conditions and limitations of such use be widely understood. To aid in increasing and disseminating information and understanding of this important aspect of research, the National Heart and Lung Institute (NHLI) sponsored a National Conference on Research Animals in Medicine.

I believe the Conference itself contributed a better understanding, among the 1000 participants, of many techniques and results of the use of animals and of some general features of animal models, and I hope that this book will be useful in bringing this information to the attention of an even wider audience.

I shall not attempt to summarize any of the

technical findings or identify any that appear to be of major significance. One area that I do want to mention, however may seem to be "non-technical"—that dealing with animal care and welfare. I think it is very important to keep in mind the necessity of adequate care and humane treatment, not only because of legal requirements, but equally because of two other considerations: scientific validity and ethical concern.

The Conference and this text are one example of the continuing effort of NHLI to improve medical care and to disseminate information to the scientific community and to the public.

A handwritten signature in cursive script that reads "Theodore Cooper". The signature is written in dark ink and has a fluid, elegant style with long, sweeping strokes.

Theodore Cooper, M.D.
Director, National Heart and Lung Institute
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PREFACE

“Man, unlike any other thing, organic or inorganic in the universe, grows beyond his work, walks up the stairs of his concepts, emerges ahead of his accomplishments.”

John Steinbeck, *The Grapes of Wrath*

In medicine, animal research is a critical path to accomplishment that permits us to grow beyond our current limitations and leads us to greater heights of knowledge and understanding of human health and disease.

Biological research is entering a new era in support of clinical medicine through greatly improved instrumentation and participation from the physical sciences. Along with this increased capacity for performance, there is an increased potential for well-defined and controlled animal experiments that focus on clinical problems. Critical emphasis must be placed on animal experiments, and these must involve the proper use and care of the laboratory animal. Advances in treatment and prevention of human disease are deeply rooted in animal research, which has provided a rich background of knowledge and insight. The developments of drugs and devices, as well as in techniques of application, are inseparably tied to *in vivo* studies. The results of these efforts are clearly reflected in those now living normal lives despite past devastating illness.

This book provides an additional step toward a better understanding of the role of animal research in medicine. It describes over 100 scientific investigations, the work of over 250 individual scientists in a variety of fields and includes the highly informative discussion engendered by the presentation of these investigations to the more than 1000 participants at the National Conference on Research Animals and Medicine, sponsored by the National Heart and Lung Institute in Washington, D.C. January 28–30, 1972.

The principal objectives are to: (1) review animal models simulating various cardiac, pulmonary, and systemic diseases; (2) identify

pertinent physiological and biological data concerning the use of large animal species (e.g., dog, calf, sheep, minipig and primate) in medical research; (3) identify test-animal requirements for cardiopulmonary research and development, such as the testing and evaluation of circulatory or respiratory assist devices and techniques; (4) review current surgical techniques in animals (especially cardiovascular surgery and organ transplantation), including pre-operative care and preparation, techniques of anesthesia, and immediate and chronic post-operative care; (5) review some aspects of the pharmacology of anesthetics, cardiac drugs, and other agents in mammals (particularly ruminants and carnivores) as well as the genetic and biologic effects of irradiation on large animals; (6) identify preventive and management techniques for coping with common disease problems of research animals; (7) review equipment and techniques for monitoring respiratory and cardiac functions, circulatory dynamics, and other physiological alterations in animals, and to compare the data thus obtained with clinical data; and (8) provide a brief overview of guidelines and welfare requirements for care of research animals.

Scientific material addressed to these objectives is presented in 14 chapters. The first provides an overview of the role of animal research in clinical medicine; chapters II and III describe animal models of cardiac and pulmonary diseases, respectively, and chapter IV the use of animal models in surgery and transplantation. The next five chapters (V–X) describe contributions of fundamental disciplines (hematology, hemodynamics, physiology, pharmacology, anatomy and pathology, and nuclear medicine and genetics) to animal research. Animal diseases and animal resources are discussed in chapters XI and XII, respectively; monitoring techniques in chapter XIII. The final chapter is addressed to physical and ethical problems of animal care. Each chapter is more or less a

single entity with numerous ties to other chapters based on the discipline point of view being pursued. Several key aspects of the text are highlighted in the following paragraphs to permit scope and content to be brought into quick focus.

Animal models of acute myocardial infarction and cardiogenic shock have been valuable in the study of hemodynamics, myocardial metabolism and treatment of acute conditions by drugs or cardiac devices. However, these acute models do not provide opportunities to study the natural course of coronary atherosclerosis and its complications. The development of chronic models which will extend use of models to the study of the natural course of disease in various animal species and non-human primates is of prime importance. Various types of cardiac models using both closed and open chest techniques are discussed.

The development and evaluation of models of lung diseases, which is in an early phase, offers a significant opportunity for better definition and understanding of both normal and diseased lung performance. At this stage, particular emphasis has been placed on correlating clinical and physiologic aberrations with pulmonary morphology. Some of the pulmonary model studies have included attention to pulmonary hypertension, hypoxic-induced bovine pulmonary hypertension, pulmonary vascular disease (including medial hypoplasia of the pulmonary artery), acute respiratory insufficiency through induced fluid overload, alteration and study of the pulmonary micro-circulation and physiologic preparations utilizing perfused isolated lung. These studies as well as others may give insight into respiratory disease and function; and lead to better characterization and improved treatment and prevention techniques for man.

In the area of surgery and transplantation significant strides have been made in techniques involving anesthesia, ventilation, anti-arrhythmic regimes, implantation and post-operative techniques for many animal species. The information covered points up both the similarities and unique characteristics of various animal species; e.g., dog, cat, pig, sheep, and non-human primates.

In animal research, the individual—and

sometimes unique—features of each species must be taken into consideration. Four kinds of hemostatic mechanisms operate in animal species; blood coagulation, vaso-constriction, platelet agglutination, and the cross-linking reaction which occurs by means of the enzyme called plasmatransglutaminase. It should be noted that certain animals have only one of these mechanisms, and in case the mechanism fails, survival is not assured by any other compensatory mechanism. In many species, all four mechanisms operate and, although one may function abnormally, hemostasis may still be achieved. All four mechanisms function in man, hence, man has some degree of freedom regarding hemostasis. However, this increased freedom is associated with a greater probability of complications from thrombosis, a factor in finding suitable blood-compatible materials. It should also be noted that the study of blood groups in animals, despite their complexity, has yielded practical as well as theoretical results of immense value to the field. Further, animal colonies with both normal and abnormal blood systems provide significant opportunities to study and explore thrombosis and hemostasis.

The increased attention to prosthetic devices and biomedical instrumentation for monitoring has led to significant progress in defining and better understanding animal hemodynamics and extrapolating it to man. The information discussed deals with cardiovascular function in ponies, chimpanzees, horses, calves, and dogs. Although some of these species have not been studied as extensively as the dog, their specific physiological, pathological, genetic, and other characteristics make them appropriate for specific types of research models.

The role of laboratory animals in pharmacological studies with potential application to man has had a long history, and has raised many questions. In brief, when utilizing laboratory animals and extrapolating the data collected to man, one must have reasonable assurance that the drugs are handled and utilized in the species under study as they would be in man; otherwise, serious questions may arise concerning the applicability of the animal studies. For example, where there are marked differences in the techniques of handling the drugs in one or in several

species, the efficacy of the drugs come under question. Any differences in technique or handling procedures must be compensated for by the development of relevant toxicity data, if these drugs are considered for use in man. The discussion identifies limitations and advantages in utilizing numerous animal species in pharmacological investigations and the difficulty in extrapolating animal results to man. Particular attention is directed to the differences in metabolic rates among animal species. Recognition of these variations will strengthen the data base in animal investigation when testing new pharmacological agents intended for use in man.

The classic disciplines of anatomy and pathology continue to provide valuable information, new approaches, and fresh insights into a number of diseases and important problems associated with various disease. Genetic and biological effects of radiation on large animals, and how such models have served to provide data relevant to man, are reviewed. In assessing these effects of radiation, it is of overriding importance that the quality of radiation, its dose rate, and dose to the susceptible tissue be carefully defined. Moreover, these data must be viewed in the light of other available information about the effects of radiation in man and animal.

One cannot overemphasize the importance of animal diseases in animals used in medical research. Their effects can mask or modify the course of other diseases being studied. Those concerned with laboratory animal medicine fully realize the import of specific animal diseases and their possible perturbing effect upon the principal studies being conducted in the animal. Research studies involving unhealthy animals not only have limited or no value, but can waste both time and resources. The discussions include consideration of animal diseases that are useful in medical research as well as those which are detrimental when the animals are used in research and in the formulation of specific types of animal models.

In discussions of animal resources, the principal attention is directed to coping with such basic problems in the use of animals as their highly variable and unknown genetic background, age, temperament, and disease status.

To some extent, it was felt that these problems, as well as others, could be overcome through the use of animals from more standardized colonies in which baseline data pertaining to anatomy, physiology, hematology, biochemistry, etc. for specific sex, age, and other groups would be available. Some investigators have been reluctant to use the non-human primate because of unavailability of properly conditioned animals, inadequate knowledge of the primate, of methods for their maintenance and handling, of appropriate equipment and of trained animal technicians. Obviously, these problems have made it difficult for small colonies to be maintained by single investigators for their own study purposes. However, some of these problems are now being overcome through the primate research centers and institutional primate resources that contribute to research economy and conservation of animals. Further, it should be noted that there exists a primate information center which can provide normative data and bibliographic services on primates and their use in research.

Modern instrumentation and techniques of application are making possible great strides in the acquisition of information on anesthetized and unanesthetized animals under acute and chronic conditions. The topics discussed range from engineering details of instrumentation through new knowledge of cardiovascular, respiratory and other diseases derived by use of new instrumentation. An important element to note is that greater emphasis is being applied to the importance of making measurements of physiological variables in the unanesthetized animal with all normal control mechanisms intact. This is in contrast with the more traditional work on the anesthetized animal or excised tissue preparations in the past. It is apparent that the development and application of atraumatic instrumentation will have a significant, conceivably revolutionary, impact on disease diagnosis, monitoring and treatment.

Of vital importance to the field of animal research are effective guidelines and legislation to assure the proper treatment and welfare of research animals. And, equally important, is the interpretation, communication, and understanding of the various facets of these require-

ments. The discussion is directed to the regulations required by law, the recommendations included in the NIH Guidelines, implementation of these guidelines, and the practical considerations in achieving improved laboratory investigations. It is apparent from the discussions and information presented by both the research investigator and those interested in animal welfare that enormous strides have been made in

bringing into balance the various approaches and philosophies concerning animal research.

I hope that the conference on research animals in medicine and this text will stimulate new, imaginative, and creative efforts in this field, and foster contacts and interactions between those who search for knowledge and those who must use the results in the treatment and prevention of disease.

A handwritten signature in cursive script, reading "Lowell T. Harmison". The signature is written in dark ink and is positioned above the printed name and title.

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TABLE OF CONTENTS

	<i>Page</i>
FOREWORD	iii
PREFACE	v
REVIEW BOARD	ix
ACKNOWLEDGEMENT	x
TABLE OF CONTENT	xi
CHAPTER I—INTRODUCTION	
The Role of Animal Research in Clinical Medicine <i>Robert Van Citters</i>	3
CHAPTER II—CARDIAC MODELS	
Animal Models of Atherosclerosis <i>Thomas B. Clarkson</i>	11
Animal Research in Shock <i>R. M. Hardaway, III</i>	21
Observations on Experimental Myocardial Infarctions in Dogs <i>Jacob I. Hirsch, Fritz Streuli and Fred Gorstein</i>	29
Animal Models of Myocardial Infarction: Current Limitations and Future Promise <i>W. B. Hood, Jr. and J. C. Norman</i>	41
Turkey Round Heart Disease: A Model Cardiomyopathy <i>E. F. Jankus, N. A. Staley and G. R. Noren</i>	53
Studies of a Cardiogenic Shock Model <i>P. Kezdi, S. N. Misra, R. K. Kordenat, and T. J. Smith</i>	61
Biventricular Mechanical Bypass; Physiological Studies During Induced Ventricular Failure <i>C. Grant LaFarge and W. F. Bernhard</i>	75
Model of Advanced Coronary Atherosclerosis, Myocardial Infarction and Sudden Death with Lethal Arrhythmias in Swine <i>K. T. Lee, J. Jarmolych, D. N. Kim and W. M. Lee</i>	93
Experimental Myocardial Infarction in Nonhuman Primates <i>M. R. Malinow, J. D. Hill, M. Lees, W. P. McNulty and A. J. Ochsner, III</i>	105
Canine Coronary Insufficiency Models for Evaluating Systems for Circulatory Support <i>J. Rosensweig and S. Chatterjee</i>	119
Pulmonary Artery Constriction in the Cat: A Model for Ventricular Hypertrophy and Congestive Heart Failure <i>J. F. Spann, Jr. and G. M. Lemole</i>	141
Experimental Myocardial Infarction by Closed Chest Technique <i>E. L. Stanley, P. Kezdi and R. K. Kordenat</i>	157
Left Ventricular Failure and Cardiogenic Shock Following Acute Myocardial Infarction: A Correlation of Clinical and Experimental Observations <i>K. T. Weber, R. A. Ratshin, C. E. Rackley and R. O. Russell, Jr.</i>	169
Proteases and Chemical Mediators in Acute Coronary Occlusion in the Dog <i>H. J. Wilkens, R. Steger and N. Back</i>	179

CHAPTER III—PULMONARY MODELS

Pulmonary Hypertension in Young Macaca Arctoides Monkeys: A Sequela to Monocrotaline Intoxication	
<i>J. R. Allen, J. M. Jenny and C. F. Chesney</i>	187
Hypoxic-Induced Bovine Pulmonary Hypertension	
<i>A. F. Alexander, C. S. Card, R. S. Jaenke, J. L. Hicks and D. H. Will</i>	193
A Model for Closed Thoracic Observation of the Pulmonary Microcirculation in Shock	
<i>W. A. Cook, P. B. Speiller, H. Sherman and S. K. Klausner</i>	201
A Pulmonary Xenograft Model for Microcirculatory Observation	
<i>W. A. Cook, P. B. Speiller, S. K. Slausner, S. B. P. Sinha, Y. Kikkawa and F. J. Veith</i>	209
Acute Bovine Pulmonary Emphysema: Evaluation of Tryptophan Induction	
<i>R. A. Kainer, C. S. Card and G. P. Epling</i>	217
Chronic Obstructive Lung Disease in Horses	
<i>J. R. Gillespie and W. S. Tyler</i>	223
Pathophysiologic Assessment of a Canine Model of Induced Acute Respiratory Insufficiency	
<i>Robert H. Liss and John C. Norman</i>	229
Medial Hyperplasia of the Pulmonary Arteries of Cats	
<i>T. W. Swerczek</i>	237
Alveolar, Bronchiolar and Pulmonary Vascular Responses of Isolated Rat and Guinea Pig Lungs	
<i>Frederick Sperling, William L. Marcus and A-A. O. Coker</i>	243
The Effect of Hypoxia on the Pulmonary Microcirculation	
<i>W. W. Wagner, L. P. Latham and D. R. Halsey</i>	253
Cinemicroscopy of the Pulmonary Microcirculation in Shock	
<i>Watts R. Webb, Stennis D. Wax, K. Kusajima, Frederick B. Parker, T. M. Kamiyama and T. Murakami</i>	261
Models of Cardiopulmonary Function in Calves	
<i>J. A. Will, G. E. Bisgard, A. V. Ruiz and R. F. Grover</i>	267

CHAPTER IV—SURGERY AND TRANSPLANTATION

Implantation Surgery of Artificial Hearts	
<i>T. Akutsu, H. Takagi and H. Takano</i>	277
Experimental Cardiac Surgery in the Calf	
<i>William J. Donawick and James W. Buchanan</i>	289
Regional Denervation of the Canine Heart	
<i>W. P. Geis and M. P. Kaye</i>	295
Surgical Experience with Nonhuman Primate Animals 1963-1971	
<i>E. I. Goldsmith</i>	313
Lung Transplantation in Dogs	
<i>James D. Hardy</i>	323
Experimental Aorto-Coronary Direct Revascularization in the Dog	
<i>Gerard S. Kakos and H. Newland Oldham, Jr.</i>	347
Total Cardiovascular Bypass with Membrane Oxygenator in Calves	
<i>M. P. Kaye and J. B. Pace</i>	355
Preservation of Organs for Transplantation	
<i>Theodore I. Malinin</i>	365
Pancreas Transplantation in Dog and Man	
<i>F. K. Merkel</i>	375

Left Ventricular Assist Devices in the Calf: Anesthesia, Ventilation, Antiarrhythmic Regimen, and Implantation

Farouk A. Molokhia, Fred N. Huffman, William J. Robinson, Panayiotis J.

Asimacopoulos, Ronald B. Ponn and John C. Norman 383

The Baboon in Medical Research with Particular Reference to Kidney Transplantation

G. P. Murphy 393

Preconditioning, Implantation and Postoperative Care of the Artificial Heart Research Calf

J. L. Peters, F. M. Donovan, J. Kawai, C. S. Kwan-Gett, H. H. J. Zwart and W. J. Kolff 399

The Use of Large Animals in Experimental Cardiovascular Surgery

J. N. Ross, Jr., J. M. Fuqua, Jr., B. S. Ruark and J. H. Kennedy 417

Left Ventricular Hemodynamic and Dimensional Responses to Treadmill Exercises in Normal and Cardiac Denervated Dogs

E. B. Stinson, G. Rahmoeller, P. L. Tecklenberg, S. B. Colvin, K. W. Jones and J. E. Pierce 429

Single Lung Transplantation with Immediate Ligation of the Opposite Pulmonary Artery in the Dog: A Model for Assessing the Functional Adequacy of Transplanted Lungs

F. J. Veith, S. B. P. Sinha, S. S. Siegelman and J. W. C. Hagstrom 437

CHAPTER V—HEMATOLOGY

Blood Grouping Systems in Dogs, Cattle and Sheep

E. B. Black and J. M. Stengle 449

Factors Regulating the Production of Coagulation Activities in Perfused Organs

W. J. Dodds and L. W. Hoyer 463

Hemostasis in the Animal Kingdom

K. Laki 473

Blood Groups of Apes and Monkeys: Human and Simian Types

J. Moor-Jankowski 483

Sheep Blood Coagulation Values

M. L. Povar 489

Experimental Approaches to the Study of Vitamin K

Walter H. Seegers 493

Summary of Contribution of Hemophilic Dogs to Knowledge and Human Welfare

Kenneth M. Brinkhous 501

A Survey of Blood Groups in Several Species of Large Animals Used in Medical Research

Clyde J. Stormont 505

CHAPTER VI—HEMODYNAMICS

Cardiovascular Hemodynamics in Domestic Ponies

James F. Amend, Harold E. Garner, John P. Rosborough and Hebbel E. Hoff 517

Comparative Mechanical Blood Properties

P. L. Blackshear and R. J. Forstrom 525

The Effects of the Catecholamines and Glucagon on the Performance of the Equine Heart

W. C. Bowie, R. C. Purohit, P. R. Adams, K. T. Somaiah, E. W. Hawthorne and J. E. Hinds 541

An Analysis of Left Ventricular Dimensional Changes in Conscious Animals <i>L. N. Cothran, E. W. Hawthorne and H. Sandler</i>	553
A Method to Study the Regulation of Coronary Flow and of Other Cardiovascular Functions in the Unanesthetized Performing Dog <i>Walter Ehrlich, Julij G. Tosheff, Paolo Caldini, David Krausman, Francine Schrijen and Joseph V. Brady</i>	567
Rheologic Properties of Blood Vessels <i>Joseph S. Janicki, Dali J. Patel, John T. Young and Ramesh N. Vaishnav</i>	573
Requirements for Long-Term Cardiopulmonary Bypass Circulation: Hypotheses and Data From Research Animals <i>R. B. Shepard, E. I. McGowan, J. W. Scott, H. J. Baker, D. M. Bowen and K. M. Pruitt</i>	583
Hemodynamics in the Chimpanzee: Unanesthetized and Anesthetized <i>H. L. Stone and H. Sandler</i>	593

CHAPTER VII—PHYSIOLOGY

Comparative Electrocardiography <i>Robert L. Hamlin and C. Roger Smith</i>	609
Physiologic and Pharmacologic Response of Chronically Denervated Feline Hearts <i>Kenneth M. Kent, Peter J. Dempsey, Zena T. McCallum and Theodore Cooper</i>	619
"Pacing" Left Ventricular Function Curves in Conscious Dogs <i>F. Kraft-Hunter and E. W. Hawthorne</i>	625
Electrocardiogram, Myocardial Action Potential and Cardiac Excitability in Laboratory Animals <i>E. Lepeschkin</i>	647
An Animal Model of Isorhythmic Atrioventricular Dissociation <i>M. N. Levy</i>	655
Pulmonary Function Testing of Unanesthetized Beagle Dogs <i>J. L. Mauderly and J. A. Pickrell</i>	665
Changes in Left Ventricular Hemodynamics and Dimensions During Rejection of the Orthotopically Transplanted Canine Heart <i>E. B. Stinson, P. L. Tecklenberg, J. F. Hollingsworth and K. W. Jones</i>	681

CHAPTER VIII—PHARMACOLOGY

The Pharmacokinetics of Amphetamine in Domestic Animals <i>J. D. Baggot and L. E. Davis</i>	691
The Use of the Animal Model in Assessing Analgesic Potency and Dependence Liability <i>J. Cochin</i>	701
Pharmacologic Actions of Newer Beta Blocking Agents <i>Lawrence S. Cohen, George F. Vastagh and Jere H. Mitchell</i>	709
Comparative Pharmacokinetics in Domesticated Animals <i>L. E. Davis, C. A. Davis and J. D. Baggot</i>	715
The Actions of Cardioactive Drugs on Developing Myocardium <i>William F. Friedman</i>	735
Drug Studies on Isolated Animal and Human Cardiac and Vascular Tissues: Advantages and Limitations <i>Joseph V. Levy</i>	749
A Study of Cell Kinetics in the Rat Thymus After Perturbation by Dexamethasone <i>J. C. Pierce</i>	755

Application of Miniature Swine to Anesthetic Studies on the Cardiovascular System and Hepatic Inhalation Anesthetic Metabolism <i>D. C. Sawyer, E. I. Eger, II and W. V. Lumb</i>	759
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CHAPTER IX—ANATOMY AND PATHOLOGY

A Correlative Study of the Anatomy of the Cardiovascular Systems of Animals and Man <i>Wesley D. Anderson</i>	767
Direct Visualization of the Coronary Microcirculation of the Left Atrium of the Cat <i>R. J. Bing and K. D. Hellberg</i>	807
Cardiac Effects of Hemorrhagic Shock in Dogs and Other Animals <i>D. B. Hackel, J. Chang, N. B. Ratliff and E. Mikat</i>	813
Pathological Techniques Applied to Artificial Organ Research. An Animal Model for the Detection of Surface-Induced Thrombosis and Embolism <i>B. K. Kusserow</i>	817
Spontaneous Cardiopulmonary Disease in Nonhuman Primates: Potential Models <i>W. P. McNulty</i>	829
Arteriosclerosis and Other Vascular Diseases in Zoo and Laboratory Animals <i>C. Stout and F. Bohorquez</i>	841
Alterations in DNA Synthesis and Other Metabolic Processes in Aortas of Cholesterol-Fed Swine <i>W. A. Thomas, R. A. Florentin, S. C. Nam, J. M. Reiner and K. T. Lee</i>	861

CHAPTER X—GENETIC AND BIOLOGICAL EFFECTS OF RADIATION

Radiation Studies with Swine <i>D. G. Brown</i>	875
Extracorporeal Irradiation of Blood and Lymph <i>D. D. Joel and E. P. Cronkite</i>	887
Preliminary Data on Chromosome Aberrations in Swine and Human Leukocytes with a Brief Review of Factors Affecting their Observed Frequency <i>F. P. Hungate and B. J. McClanahan</i>	899
Biological Effects of Radiation from Simulated ^{238}Pu Power Sources in Dogs <i>F. A. Kallfelz, C. L. Comar, P. H. Craig and A. P. Casarett</i>	905
Observations on Chromosomal Morphology During Simulated Intracorporeal Radiation from Nuclear-Powered Artificial Hearts <i>Farouk A. Molokhia, William J. Robinson, Fred N. Huffman and John C. Norman</i>	911
Pathologic Effects of Chronic ^{90}Sr Ingestion in Miniature Swine <i>H. A. Ragan, P. L. Hackett, B. J. McClanahan and W. J. Clarke</i>	919
A Four-Year Study of Long-Term Effects of Implanted Discrete Heat and Radiation Sources in Dogs and Primates: Preliminary Studies Leading to Implantable Nuclear-Fueled Circulatory Support Systems <i>G. W. Sandberg, Jr., F. A. Molokhia, P. R. Ponn, F. N. Huffman and J. C. Norman</i>	931
Animal Radiation Data and their Relevance to Man <i>Harry E. Walburg, Jr.</i>	939

CHAPTER XI—ANIMAL DISEASES

Experimental Viral Valvulitis <i>N. P. DePasquale and George E. Burch</i>	945
Respiratory Diseases of Dogs, Calves, and Sheep <i>R. A. Griesemer and R. L. Farrell</i>	951

Virus Infections of "Normal" Healthy Animals <i>G. D. Hsiung and N. S. Swack</i>	961
Significance of Simian Viruses <i>S. S. Kalter</i>	965
Dirofilaria Immitis: A Review of Present Knowledge <i>G. Pacheco</i>	977
Diseases Encountered During the Conditioning of Random Source Dogs and Cats <i>A. E. Palmer</i>	981
Congenital Defects of the Cardiovascular System in Dogs <i>D. F. Patterson</i>	991
Spontaneous Diseases in Germfree Animals <i>Morris Pollard</i>	1005
Resistance of Swine to Bordetella Rhinitis <i>W. P. Switzer</i>	1015

CHAPTER XII—ANIMAL RESOURCES

Establishment, Organization, Management and Functions of an Investigative and Diagnostic Laboratory within the Department of Experimental Animal Medicine at the University of Washington <i>W. C. Dolowy and L. J. Swango</i>	1021
Special Considerations in the Use of Calves for Cardiovascular Implant Studies <i>F. T. Galysh and R. F. Wallin</i>	1033
Improved Resource Utilization Through Animal and Facilities Sharing at the Laboratory for Experimental Medicine and Surgery in Primates <i>E. I. Goldsmith, J. Moor-Jankowski and J. Davis</i>	1047
The Role of Veterinary Diagnostic Support Laboratories in a Research Animal Colony <i>A. M. Jonas</i>	1055
The Research Dog: Random Source or Colony Reared? <i>S. Potkay and J. D. Bacher</i>	1061
A Support Laboratory for a Medical School Animal Research Facility <i>Ward R. Richter</i>	1067
Progress in the Development of a Histocompatible Dog <i>J. W. Templeton, A. L. Rogers and W. S. Fletcher</i>	1073
The Primate Information Center as a Research Tool in Studies of the Heart and Lung <i>Maryeva W. Terry</i>	1081

CHAPTER XIII—MONITORING

Gamma-Ray Densitometry in the Analysis of Hemodynamic Function <i>J. D. Cohn, K. Ito and L. R. M. Del Guercio</i>	1085
The Use of a General-Purpose Time-Shared Computer in Physiology Research <i>E. Dong, G. C. M. Wiederhold</i>	1091
Biotelemetry Transmitter Design Methods <i>V. G. Ellerbruch, F. C. Fitchen and R. W. Sawrey</i>	1105
Measurement and Radiotelemetry of Cardiovascular Variables in Conscious Animals: Techniques and Applications <i>Dean Franklin, Stephen F. Vatner, Charles B. Higgins, Thomas Patrick, W. Scott Kemper and Robert L. Van Citters</i>	1119
Implant Telemetry and Stimulation <i>Wen H. Ko</i>	1135

	<i>Page</i>
Capabilities of Implantable Transducers <i>Eph Konigsberg</i>	1145
A Mathematical Model for Measuring Blood Flow by Residue Detection When Radiotracer Recirculation Interferes <i>K. B. Larson and D. L. Snyder</i>	1151
Pulsed Doppler Ultrasonic Flowmetry <i>D. Y. Loisanee, J. P. Lenriot and P. A. Peronneau</i>	1161
Implantable Ultrasonic Blood Flowmeters <i>James D. Meindl</i>	1167
Percutaneous Conduction of Electrical Signals: Interface Techniques and Tissue Reaction at Electrode Site <i>J. T. Mortimer and P. H. Peckham</i>	1187
The Use of Implantable Telemetry Systems for Animal Monitoring <i>H. Sandler, T. B. Fryer and H. L. Stone</i>	1197
The Adaptive Control of Therapeutic Procedures <i>N. P. Thompson, B. Widrow and C. Schade</i>	1207
Real-Time, Time-Sharing Computers in the Animal Laboratory <i>W. S. Topham</i>	1217
Review of Animal Instrumentation: Transducer Capability <i>W. S. Topham</i>	1229
A Multi-Station Computer System for Acquiring and Processing Animal Data <i>Eugene F. Uretz, John A. McClary and Steve Morgan</i>	1243
The Conscious Calf Preparation: Technical Aspects of Surgery, Animal Care, Im- planted Instrumentation and Monitoring for Cardiovascular Data Acquisition <i>K. T. Weber, J. S. Janicki, A. A. Walker and B. H. Dennison</i>	1259
 CHAPTER XIV—THE USE OF ANIMALS IN MEDICAL RESEARCH AND EXPERIMENTATION	
<i>Lowell T. Harmison</i>	1271
Animal Welfare Act (Public Law 91-579) and Amendments <i>D. F. Schwindaman</i>	1271
NIH Animal Care Guidelines <i>Mark Conner</i>	1274
Panel Presentations <i>Charles McPherson</i>	1277
<i>Joseph E. Pierce</i>	1277
<i>John C. Norman</i>	1280
<i>Julius Cass</i>	1282
<i>Harold Parker</i>	1283
Open Discussion	1285