

VOLUME 10

Editors

Sherwood M. Reichard

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H. Richard Adams

ADVANCES IN SHOCK RESEARCH

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ADVANCES IN SHOCK RESEARCH

VOLUME 10

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**ADVANCES
IN SHOCK
RESEARCH**

VOLUME 10

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Contents of Volume 9

Part 1 of the Proceedings of the Fifth Annual Conference on Shock

KEYNOTE ADDRESS

Shock Research and Therapy in the 1980s / *Arthur E. Baue*

METABOLIC ACTIVITIES IN SHOCK

Metabolism of Prolonged Shock / *Anna M. Daniel, Melarie E. Taylor, Bomi Kapadia, and Lloyd D. MacLean*

Nonsuppressible Insulinlike Activity (NSILA) and the Glucose Dyshomeostasis of Agonal Sepsis / *Rico E. Viray and James P. Filkins*

Effects of Gabexate Mesilate on the Reactions of Lipid Metabolism in Endotoxic Shock / *F.W. Schmahl, R.W. Wabnitz, G. Rox, K. Drysch, G. Richardt, and E. Poetter*

Protons and Glucose Metabolism in Shock / *P.W. Hochachka*

NUTRITIONAL THERAPY

Nutrients and Ventilation / *J. Askanazi, C. Weissman, P.A. LaSala, and P.M. Charlesworth*

Isotopic Approaches to the Estimation of Protein Requirements in Burn Patients / *Robert R. Wolfe, Richard D. Goodenough, and Marta H. Wolfe*

PATHOPHYSIOLOGIC RESPONSES IN SEPTIC SHOCK

The Pathophysiology of Septic Shock: Responses to Different Doses of Live *Escherichia Coli* Injection in Rats / *Junji Tanaka, Toshihide Sato, Raymond T. Jones, Benjamin F. Trump, and R Adams Cowley*

The Pathophysiology of Septic Shock: Comparison of Systemic Hemodynamical Responses in the Rat Following a Sonicated, Heat-Killed, and Live *E. coli* Injection / *T. Sato, J. Tanaka, J.R. Cottrell, R.A. Cowley, and B.F. Trump*

Effect of Age and Splenectomy in Murine Endotoxemia / *R.G. Karanfilian, C.R. Spillert, G.W. Machiedo, B.F. Rush Jr., and E.J. Lazaro*

Contractile Function of Heart Muscle Isolated From Endotoxin-Shocked Guinea Pigs and Rats / *Janet L. Parker*

The Role of Vasopressin in the Maintenance of Cardiovascular Function During Early Endotoxin Shock / *Daniel J. Brackett, Carl F. Schaefer, and Michael F. Wilson*

Peripheral Vascular Adrenergic Depression During Hypotension Induced by *E. coli* Endotoxin / *Robert F. Bond*

HYPOVOLEMIA

Renal Hemodynamic Alterations Following Administration of Thiopental, Diazepam, or Ketamine to Conscious Hypovolemic Dogs / *Lawrence L. Priano*

Cerebral, Coronary, and Renal Blood Flows During Hemorrhagic Hypotension in Anesthetized Miniature Swine / *M. Harold Laughlin*

Crystalloid Versus Colloid for Fluid Resuscitation of Hypovolemic Patients / *Robert F. Tranbaugh and Frank R. Lewis*

HYPOTHERMIA

Effect of Hypothermia on Survival Time and ECG in Rats With Acute Blood Loss / *Junji Tanaka, Toshihide Sato, Irene K. Berezsky, Raymond T. Jones, Benjamin F. Trump, and R Adams Cowley*

xii / Contents of Volume 9

Development of a Primate Model of Exposure Hypothermia / *Larry C. Casey, Harry K. Ballantyne, J. Raymond Fletcher, Bart Chernow, and C. Raymond Lake*

IMMUNE MECHANISMS IN SHOCK

Influence of Septic Peritonitis on Circulating Fibronection, Immunoglobulin, and Complement: Relationship to Reticuloendothelial Phagocytic Function / *Michael H. McCafferty and Thomas M. Saba*

Role of Lymphocytes in the Ovine Response to Endotoxin / *D.L. Traber, J. Jenkins, K. Rice, L. Sziebert, T. Adams Jr., N. Henriksen, L.D. Traber, and P.D. Thomson*

Serum Complement Levels in Canine Endotoxin Shock: Relation to Survival and to Corticosteroid Therapy / *Clayton H. Shatney and Richard C. Lillehei*

Effect of a New Synthetic Complement Inhibitor on Hepatic Glycolytic Intermediates in Septic Rats / *Toshiaki Ebata, Robert E. Kuttner, Frank O. Apantaku, and William Schumer*

Preface

Pharmacologic approaches to problem-solving in circulation research were addressed during the 5th Annual Conference on Shock held by the Shock Society at Smugglers' Notch, Vermont, June 9–11, 1982. Two separate symposia and several independent research papers dealing directly or indirectly with drug-related topics were presented, and the manuscripts derived from these presentations comprise Volume 10 of *Advances in Shock Research*.

The first symposium was entitled "Pharmacologic Problems in Shock" and five separate papers considered positive and negative aspects about several drug groups important to cardiovascular research in general with emphasis on shock research in particular. The introductory presentation in this collection assumed the "devil's advocate" position, relative to the employment of drugs as experimental tools, and pointed out how interpretations of drug-based data can be inadvertently oversimplified if subsidiary biologic actions of tested compounds escape attention. Subsequent talks in this symposium considered pros and cons about drugs that inhibit synthesis of prostanoid metabolites of arachidonate; free-radical formation in shock and free-radical scavenging agents; and the use and misuse of inotropic drugs employed in the therapeutic management of cardiogenic shock. The drug group known originally as "calcium antagonists" but now more appropriately named as "calcium channel blockers" or "calcium entry blockers" was also addressed and this presentation provided a preview of how this "new" group of important compounds may be applied to shock research.

The second symposium focused entirely on "The Role of Endogenous Opiates in Shock," a subject that has arisen only within the past few years. This area of research entails a new concept that endogenous opiates contribute to cardiovascular dysfunction in shock. Opiate receptor antagonists have been used to test the hypothesis and the data presented indicate that agents such as naloxone not only improve cardiovascular function but also improve longterm survival. The symposium consists of six papers that considered opiate mechanisms involved in hemorrhagic and endotoxic shock and spinal trauma in a broad spectrum of animal models; an evaluation of areas of the central nervous system involved in the mechanism; opiate-endocrine interactions; peripheral effects of opiate antagonists in shock; and putative clinical applications of the experimental findings. The symposium is the first to be devoted to the subject.

A group of independent research papers reemphasized the ongoing interest in opioid agonists and antagonists, and brought new insight about possible species differences in the effects of opioid antagonists in stress situations. Similarly,

several presentations provided more data to the growing volume of information about non-steroidal anti-inflammatory drugs used in attempts to modify synthesis of the prostaglandin cascade. Other papers continued the search for a resolution of benefit-risk ratios associated with the use of adrenal corticosteroids in low-flow and shock states.

The content of this volume is significant from at least three points of view. First, a critical evaluation of the use of pharmacological agents in shock research is an exercise that should be practiced frequently by those engaged in such research. Secondly, the subject of opiate mechanisms in shock is presented in a manner to explain the rationale of the concept. Lastly, the information presented on the formation of free-radicals in shock introduces the concept that the enzyme, superoxide dismutase, could have a role in shock therapy. Further significant work in this last area will surely be forthcoming.

The editors wish to thank Nancy M. Bailey for her editorial and secretarial assistance in the preparation of this volume.

Sherwood M. Reichard
David G. Reynolds
H. Richard Adams

Contents

Editorial Board	vii
Contributors	ix
Contents of Volume 9	xi
Preface	
<i>Sherwood M. Reichard, David G. Reynolds, and</i>	
<i>H. Richard Adams</i>	xiii
PHARMACOLOGIC PROBLEMS IN SHOCK	
Pharmacologic Problems in Shock Research	
<i>H. Richard Adams</i>	3
Prostaglandin Synthetase Inhibitors in Endotoxin or Septic Shock—	
A Review	
<i>J. Raymond Fletcher</i>	9
Calcium Entry Blockers: Potential Applications in Shock	
<i>Michael L. Hess and Lazar J. Greenfield</i>	15
Role of Toxic Oxygen Products From Phagocytic Cells in Tissue	
Injury	
<i>Peter A. Ward</i>	27
Pharmacologic Support in Cardiogenic Shock	
<i>Robert E. Rude</i>	35
ROLE OF ENDOGENOUS OPIATES IN SHOCK	
The Role of Endogenous Opiates in Shock: Introductory Comments	
<i>John W. Holaday and David G. Reynolds</i>	53
The Role of Endogenous Opiates in the Pathophysiology of	
Hypovolemic Shock and Their Interrelationship With the	
Pituitary-Adrenal Axis	
<i>Thomas Vargish</i>	57
Naloxone in Endotoxic Shock: Experimental Models and Clinical	
Perspective	
<i>Nelson Gurll</i>	63
Studies on a Central Site of Action for Naloxone in Endotoxin	
Shock	
<i>Herbert F. Janssen</i>	73
Peripheral Effects of Opiate Antagonists in Shock	
<i>Allan M. Lefer and Mark T. Curtis</i>	83

The Role of Endogenous Opiates in Shock: Experimental and Clinical Studies In Vitro and In Vivo	
<i>Issie S. Weissglas</i>	87
Spinal Shock and Injury: Experimental Therapeutic Approaches	
<i>John W. Holaday and Alan I. Faden</i>	95
OPIATES IN SHOCK	
Effectiveness of Ethylketocyclazocine in Hemorrhagic Shock	
<i>Mark T. Curtis and Allan M. Lefer</i>	101
Interaction of Supraspinal, Serotonergic, and Opiate Systems During Hemorrhage	
<i>James A. Spath Jr. and Paul S. Blum</i>	111
Effect of Naloxone Treatment on the Cardiopulmonary Response to Endotoxin in Sheep	
<i>L. Sziebert, P.D. Thomson, J. Jenkins, K. Rice, T. Adams Jr., N. Henriksen, L.D. Traber, and D.L. Traber</i>	121
PROSTANOIDS IN SHOCK	
Arachidonic Acid Metabolism in Endotoxin Tolerance	
<i>W.C. Wise, J.A. Cook, and P.V. Halushka</i>	131
Thromboxane Synthetase Inhibitors in Septic Shock	
<i>Billie Lou Short, William M. Gardiner, Anthony N. Mishik, Peter W. Ramwell, Dick Walker, and J. Raymond Fletcher</i>	143
Effect of Lidocaine on Hepatic Prostanoid Production In Vitro Following 2,4-Dinitrophenol Administration	
<i>John T. Flynn</i>	149
Indomethacin Suppresses the Early Cardiodepressant Factor Released by Endotoxin in the Rat: Possible Involvement of a Prostacyclin-Related Material	
<i>Alain Carli, Marie-Claude Auclair, and Catherine Vernimmen</i>	161
STEROID THERAPY IN SHOCK	
The Influence of Glucocorticoids on Hepatic Glycolytic Intermediates in Fed Peritonitis Rats	
<i>Robert E. Kuttner, Toshiaki Ebata, Frank O. Apantaku, and William Schumer</i>	175
The Benefits of Corticosteroid Given After the Onset of Hypotension During Endotoxin Shock in the Conscious Rat	
<i>Carl F. Schaefer, Daniel J. Brackett, and Michael F. Wilson</i>	183
Prevention or Amelioration of Morphologic Lesions in LD ₁₀₀ E coli-shocked Baboons With Steroid/Antibiotic Therapy	
<i>L.T. Archer, S.D. Kosanke, B.K. Beller, R.B. Passey, and L.B. Hinshaw</i>	195
Index	217
Contents of Volumes 7 and 8	225

PHARMACOLOGIC PROBLEMS IN SHOCK

**(Papers in this section were presented in a Symposium at the Fifth
Annual Conference on Shock)**

Pharmacologic Problems in Shock Research

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Recent advances with receptor-selective agonists and antagonists have provided great impetus to the deployment of drugs as experimental tools in cardiovascular research. Often overlooked, however, is the important limitation that few exogenous chemicals actually exert only one biologic action. This discussion appraised several prototype drugs used in this field, and theorized how a lack of consideration of subsidiary pharmacologic actions may lead to oversimplified interpretations of drug-based data.

INTRODUCTION

Pharmacologic agents are used commonly in shock research as investigators attempt to identify and characterize pathogenic mechanisms involved in circulatory shock syndromes. Application of drugs as experimental probes is based on the premise that specificity of drug action provides the means to chemically modulate only selected physiologic-pathophysiologic events, leading in turn to the delineation of particular functions-dysfunctions as important components of shock. Indeed, as reported in subsequent papers in this volume, experimental use of drugs has provided new insight into organ and cellular control mechanisms operating in the pathogenic response to shock-inducing stimuli.

A potential danger to this type of pharmacologic approach is the inherent, but often overlooked, limitation that many drugs assumed to be mechanistically specific actually exert multiple biologic influences. This criticism is valid irrespective of the routine classification of drug groups according to a single pharmacologic action. If drug-based data are interpolated into new concepts too quickly, validation of the relative importance of primary vs subsidiary pharmacologic actions may be neglected and the operational value of the concept may suffer.

Perhaps the use of drugs as experimental implements should be considered a double-edged sword, leading to new insight and concepts on one edge but potentially leading to oversimplification of cause-effect relationships on the

other edge. Examples of this type of problem can be formulated from a brief overview of pharmacodynamic complexities of several drugs important to cardiovascular research.

ALPHA-ADRENERGIC BLOCKING AGENTS

Sympathoadrenal activation of alpha adrenergic mechanisms has long been implicated in the pathogenesis of shock [cf 1, 2]. This important concept was based on several lines of evidence, including observations that drugs which prevented alpha-adrenergic responses also prevented or delayed death in shock. In essence, it was concluded that alpha antagonists were beneficial because they blocked alpha receptor-mediated vasoconstriction, thereby improving microcirculation and reducing the stagnant hypoxia of shock [1, 2].

Recent discoveries in adrenergic physiology-pharmacology have shown that the net circulatory response to alpha blocking drugs cannot be explained solely by an inhibitory action at alpha receptors subserving vascular smooth muscle contraction [3-5]. Direct and indirect influences on other receptor populations, both alpha and beta, should also be considered.

Alpha-adrenergic receptors can now be differentiated into two distinct subtypes designated α_1 and α_2 [4-6]. α_1 receptors represent the more classical alpha-receptor population; they are located postjunctionally on effector cells and are blocked more potently by prazosin than yohimbine. α_2 receptors are newly discovered; they are localized prejunctionally on neuron terminals and also postjunctionally on some effector cell types, and are blocked more potently by yohimbine than prazosin. Norepinephrine and epinephrine activate both α_1 and α_2 receptors; whereas phentolamine and phenoxybenzamine block both α_1 and α_2 receptors [5, 6].

α_2 receptors of noradrenergic neurons subserve an important auto-inhibitory effect on norepinephrine release mechanisms [3]. Norepinephrine discharged from the nerve terminal can feed back and activate prejunctional α_2 receptors, resulting in a diminution of subsequent neuroeffector transmission. On the other hand, nonselective α_1 - α_2 blocking drugs inhibit alpha-mediated events in effector organs, but they also facilitate catecholamine release by freeing noradrenergic nerves from the α_2 feedback inhibition [3-7].

Thus, it seems that cardiovascular responses to nonselective α_1 - α_2 antagonists may be more faceted than originally surmised. Evidence now shows that these drugs do not simply prevent alpha-controlled events in effector organs. Because of their prejunctional α_2 blocking action, they also free or disinhibit catecholamine release mechanisms from a resident inhibitory control. This action elicits a substantial increase in circulating catecholamines [7] and perhaps even a relatively greater increment in nor-