Strategies For Translational Research

Frederick A. Moore MD

February 28, 2012

Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team

PICS – the New Predominant Phenotype of MOF

Strategies For Translational Research

Trauma Research: Historic Perspective

Participating in Multidisciplinary Translational Research

Creating a Multidisciplinary Translational Research Team

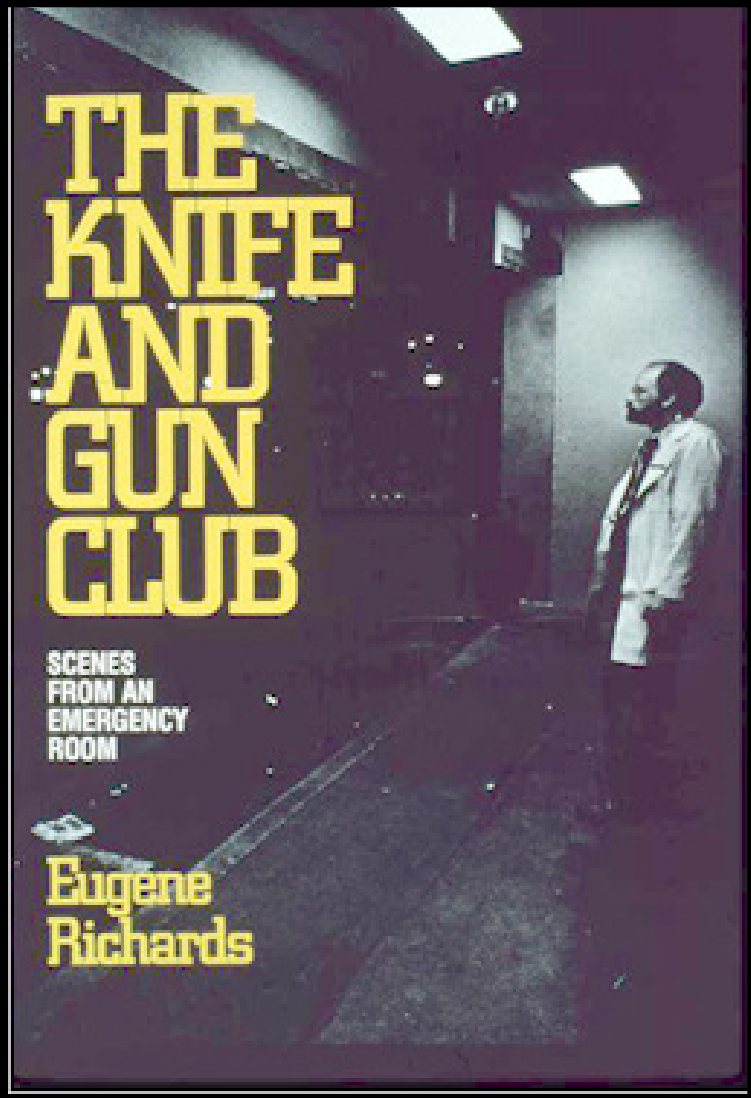
PICS – the New Predominant Phenotype of MOF

Focus on the Process not the Science

TRAUMA RESEARCH
Historic Perspective

Denver General (DG)

Inner City Hospital



TRAUMA RESEARCH
Chief of Surgery

Denver General (DG)

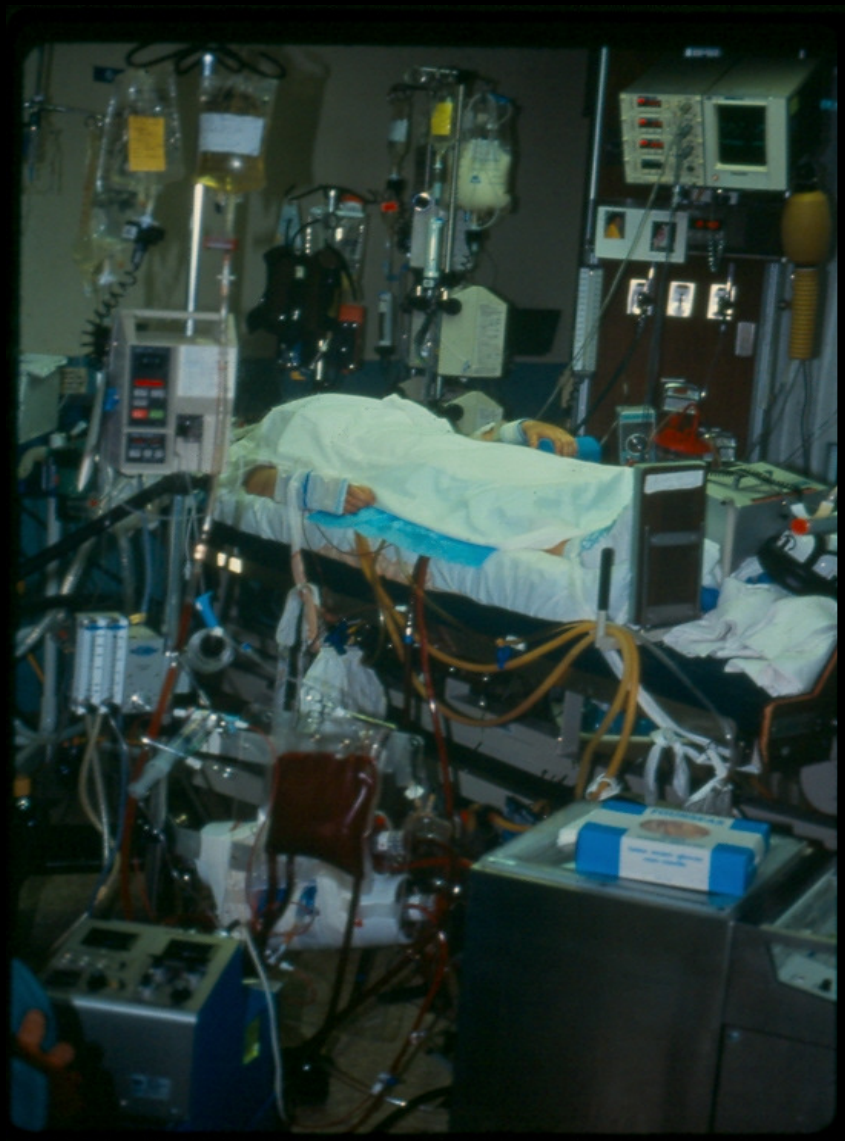
Ben Eiseman

TRAUMA SURGERY
Created Engaging Environment

Brother John

Great operations

TRAUMA SURGERY
Created Engaging Environment



ECMO at DG

Great operations

Surgical critical care

TRAUMA SURGERY
Created Engaging Environment

Nutritional Support Team

Great operations

Surgical critical care

Excellent research

TRAUMA SURGERY
Same Thing Happened Through Out USA

San Francisco General: William Blaisdell
Cook County Chicago: Robert Freeark
Shock Trauma Baltimore: R. Adams Cowley
Parkland Dallas: G.Tom Shires
Detroit Receiving: Charlie Lucas & Anne Leaderwood
Grady Memorial Atlanta: Harlan Stone
Buffalo General: John Border
King County New York: Gerald Shaftan
Charity New Orleans: F. Carter Nance

TRAUMA SURGERY

Same Thing Happened Through Out USA

San Francisco General: William Blaisdell
Cook County Chicago: Robert Freeark
Shock Trauma Baltimore: R. Adams Cowley
Parkland Dallas: G.Tom Shires
Detroit Receiving: Charlie Lucas & Anne Leaderwood
Grady Memorial Atlanta: Harlan Stone
Buffalo General: John Border
King County New York: Gerald Shaftan
Charity New Orleans: F. Carter Nance

Research was a Core Value of Trauma Surgery

 # 1: "Create the Culture"

Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

MULTIPLE ORGAN FAILURE

B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., *and* L. Norton, M.D., F.A.C.S.,
Denver, Colorado

Surg Gyn Obstet 1977

#2: Pick a Topic

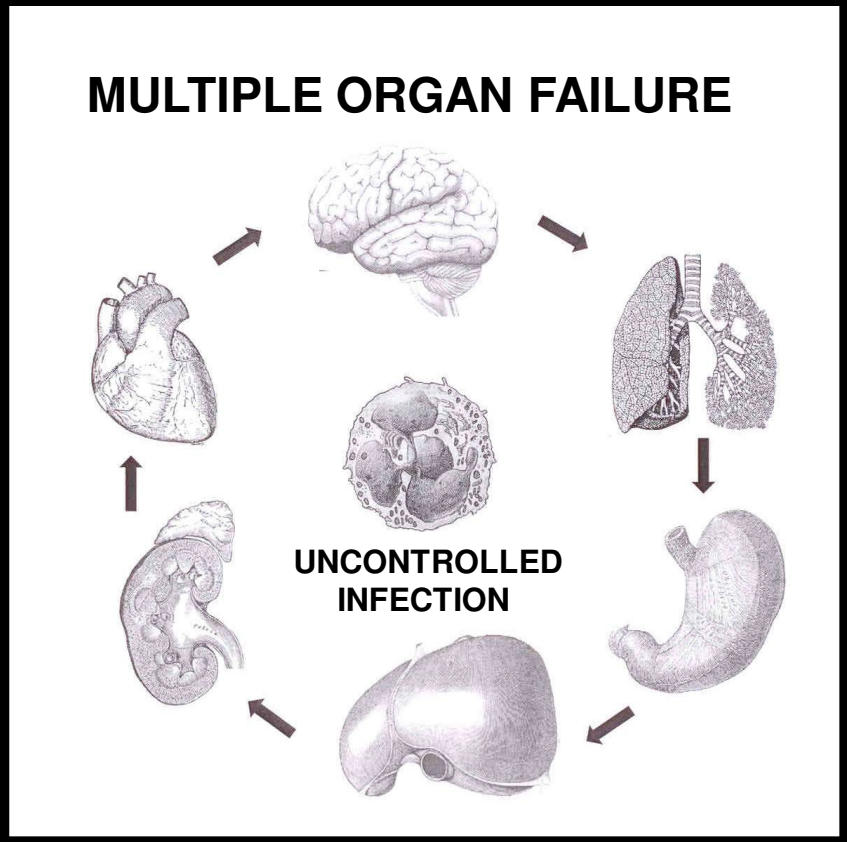
Ben Eiseman

MULTIPLE ORGAN FAILURE

B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., *and* L. Norton, M.D., F.A.C.S.,
Denver, Colorado

Surg Gyn Obstet 1977

Important & Confusing Problem

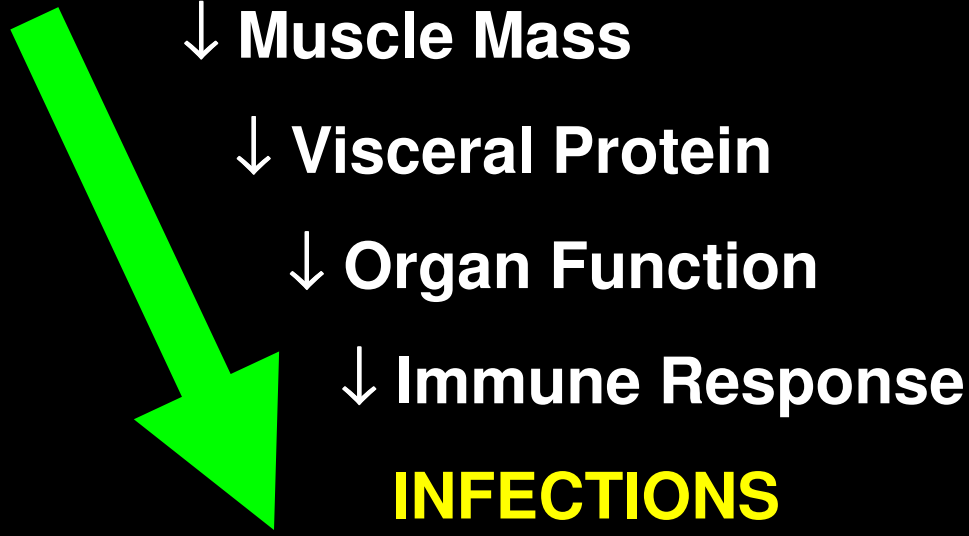


Became DG's Research Focus

Ben Eiseman

INJURY STRESS RESPONSE INDUCES

ACUTE PROTEIN MALNUTRITION



↓ Muscle Mass

↓ Visceral Protein

↓ Organ Function

↓ Immune Response

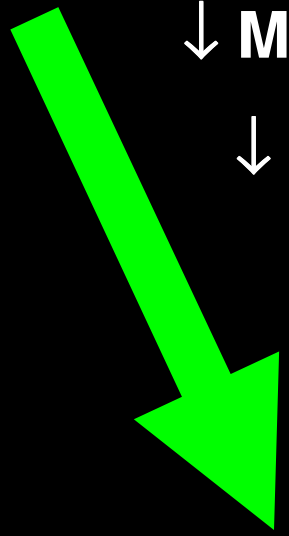
INFECTIONS

MULTIPLE ORGAN FAILURE

Hypothesis

ACUTE PROTEIN MALNUTRITION

Early Nutritional Support



↓ Muscle Mass

↓ Visceral Protein

↓ Organ Function

↓ Immune Response

INFECTIONS

MULTIPLE ORGAN FAILURE

Benefits of Immediate Jejunostomy Feeding after Major Abdominal Trauma—A Prospective, Randomized Study

ERNEST E. MOORE, M.D., AND TODD N. JONES, B.S.N.

J Trauma 1986

Early TEN vs. Delayed TPN

Decreased Infections

TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

Early TEN vs. Early TPN

Decreased Infections

TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

Early TEN vs. Early TPN

Decreased Infections

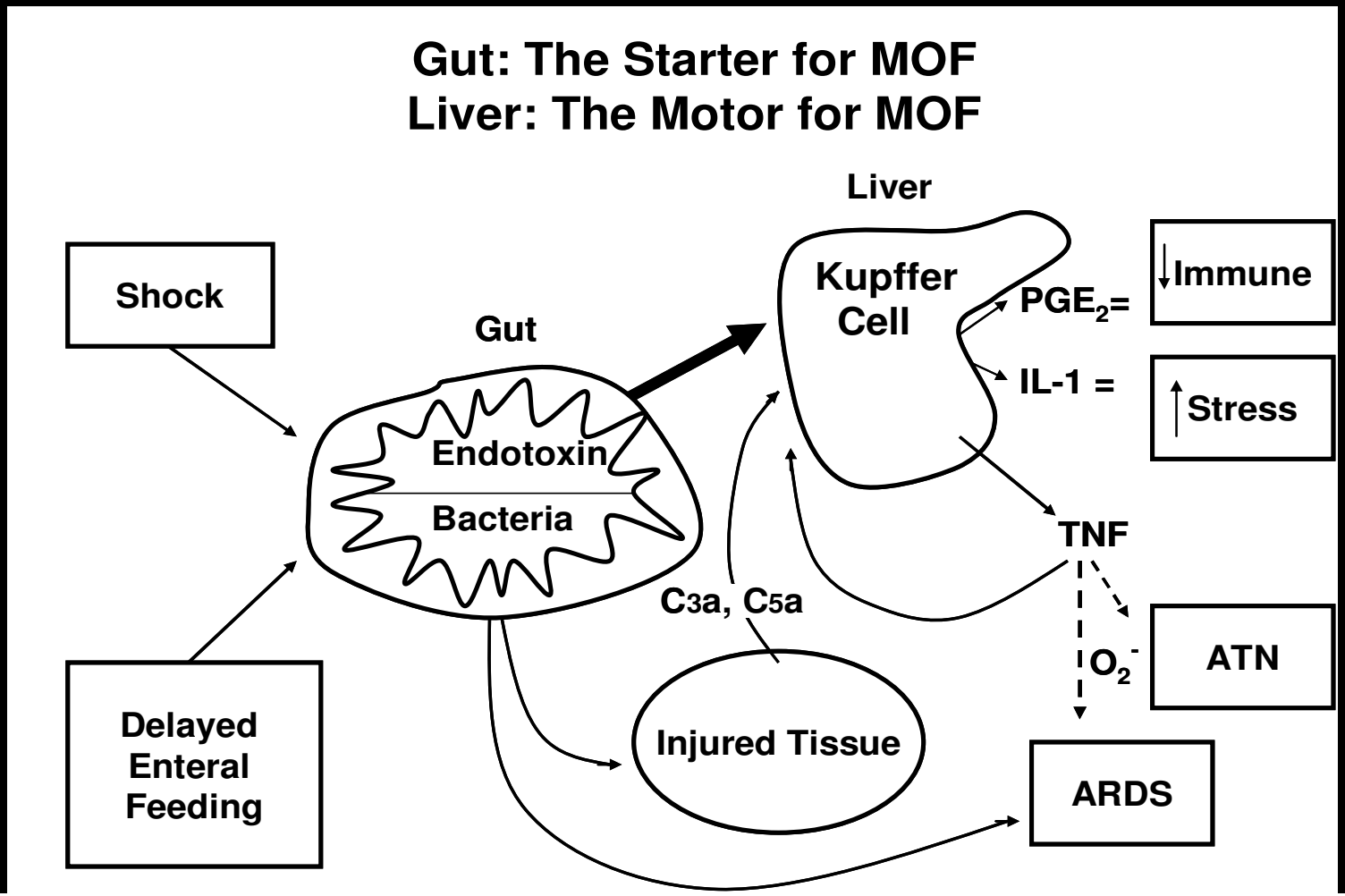
Is TEN good or is TPN bad ?

TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

3: Draw a cartoon

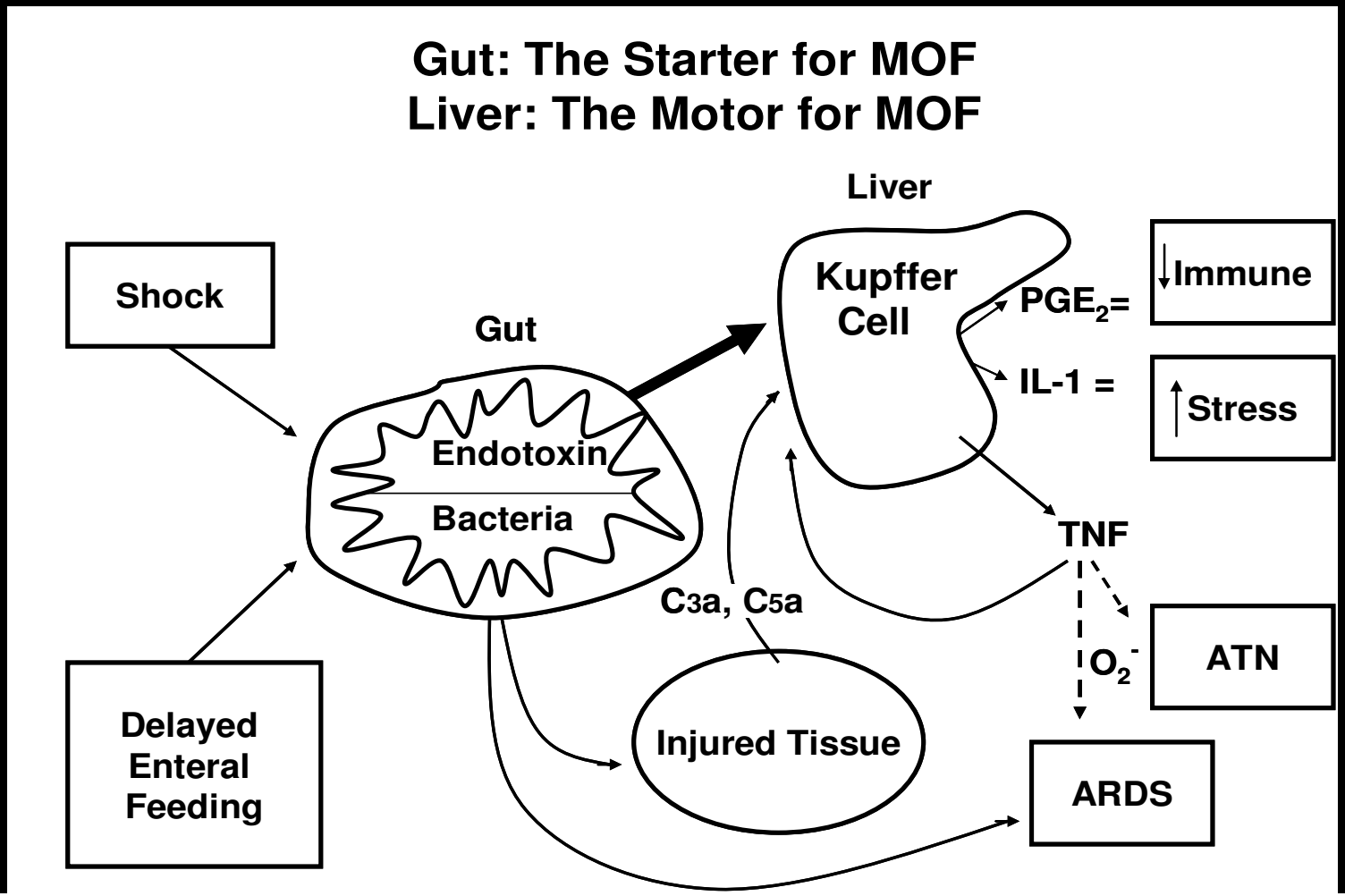


TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

"Win-win" hypothesis:

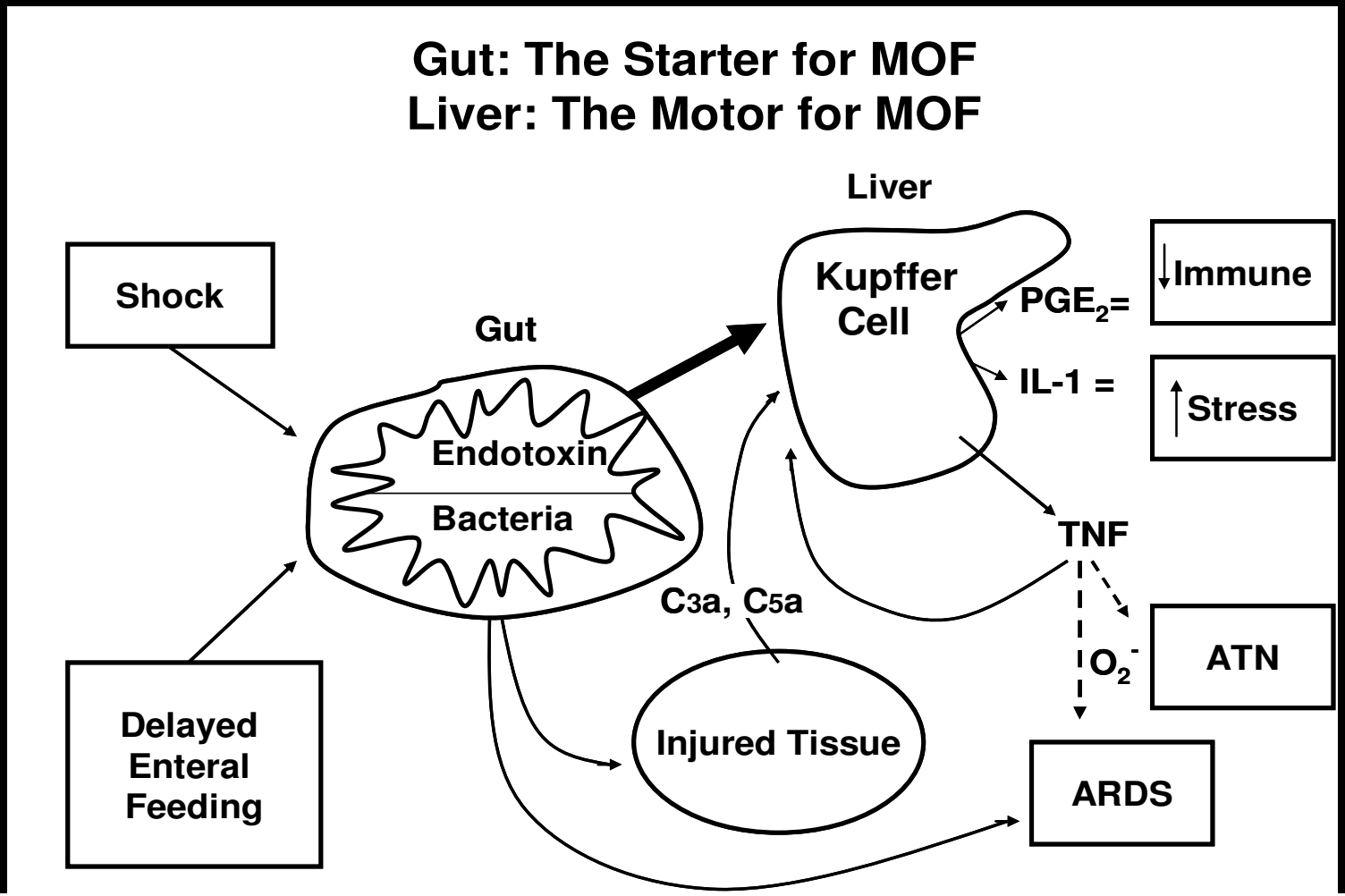


TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

"Win-win" hypothesis: bacterial translocation via portal vein

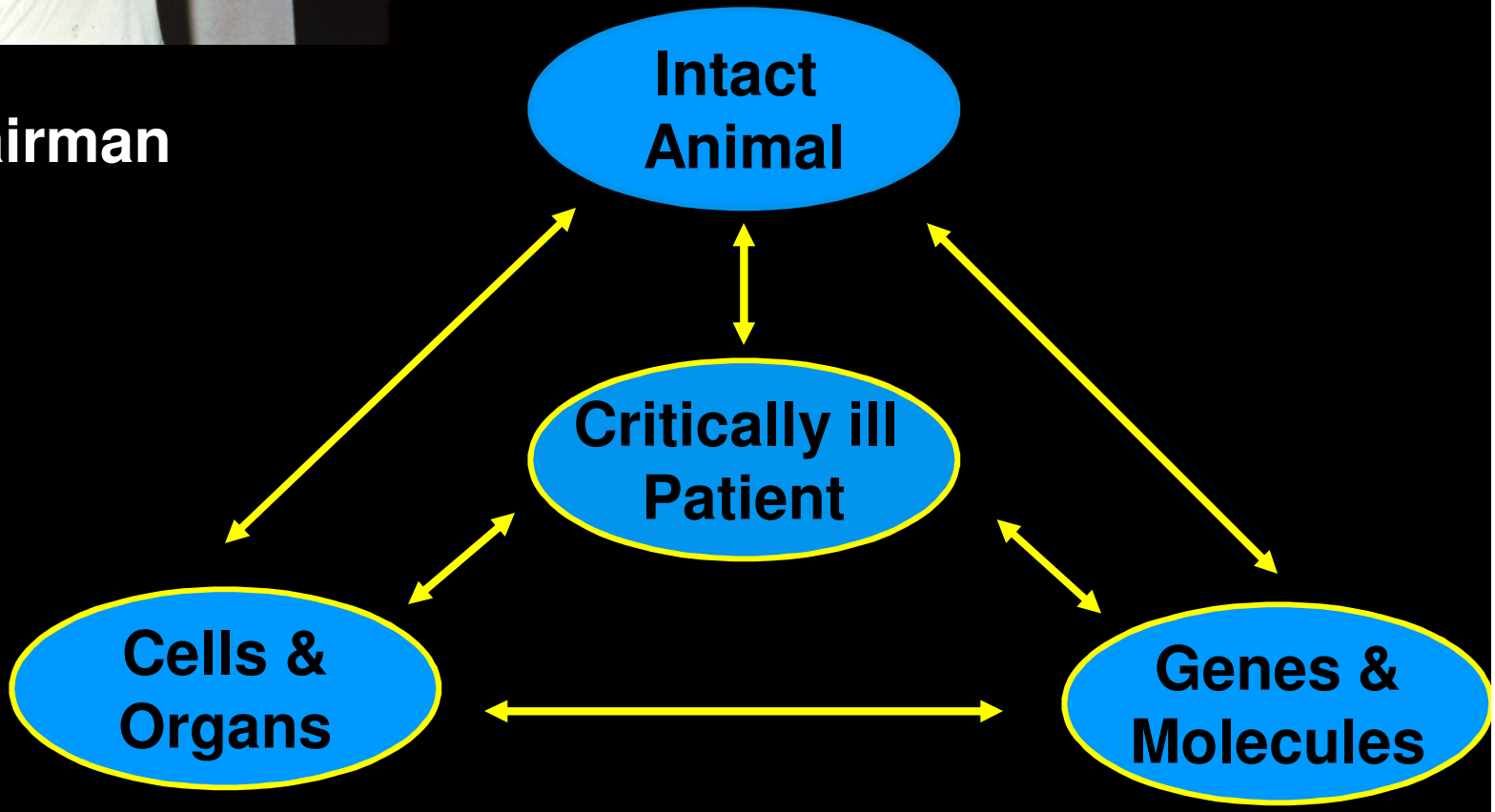


Alden Harken

New Chairman

4: Be a Cheer Leader

TRAUMA RESEARCH CENTER
UNIVERSITY OF COLORADO

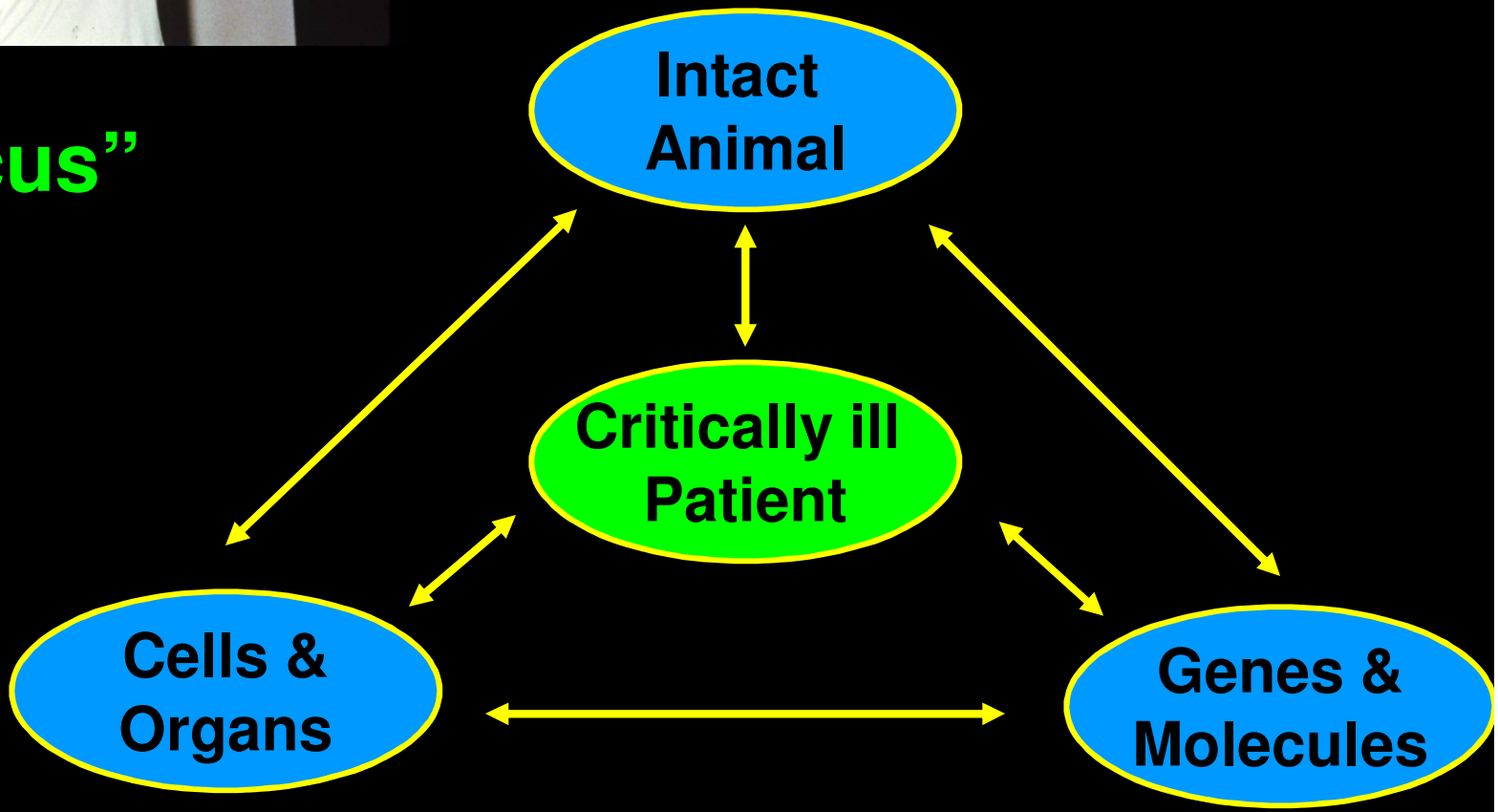


Alden Harken

TRAUMA RESEARCH CENTER

DG SICU - CLINICAL CORE

"Focus"



Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D.,
OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.,

J Trauma 1991

20 High Risk Torso Trauma Patients

Clinical Relevance

Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF

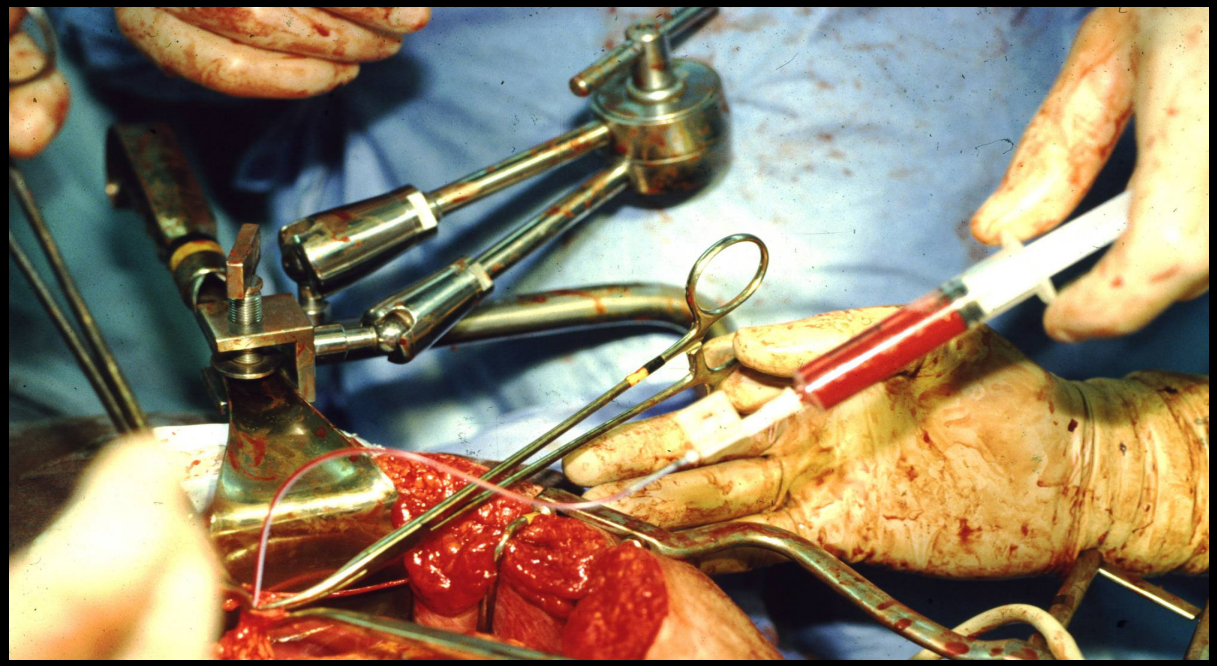
Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D.,
OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.,

J Trauma 1991

20 High Risk Torso Trauma Patients

Portal Vein Catheters & Sampled Blood X 5 days



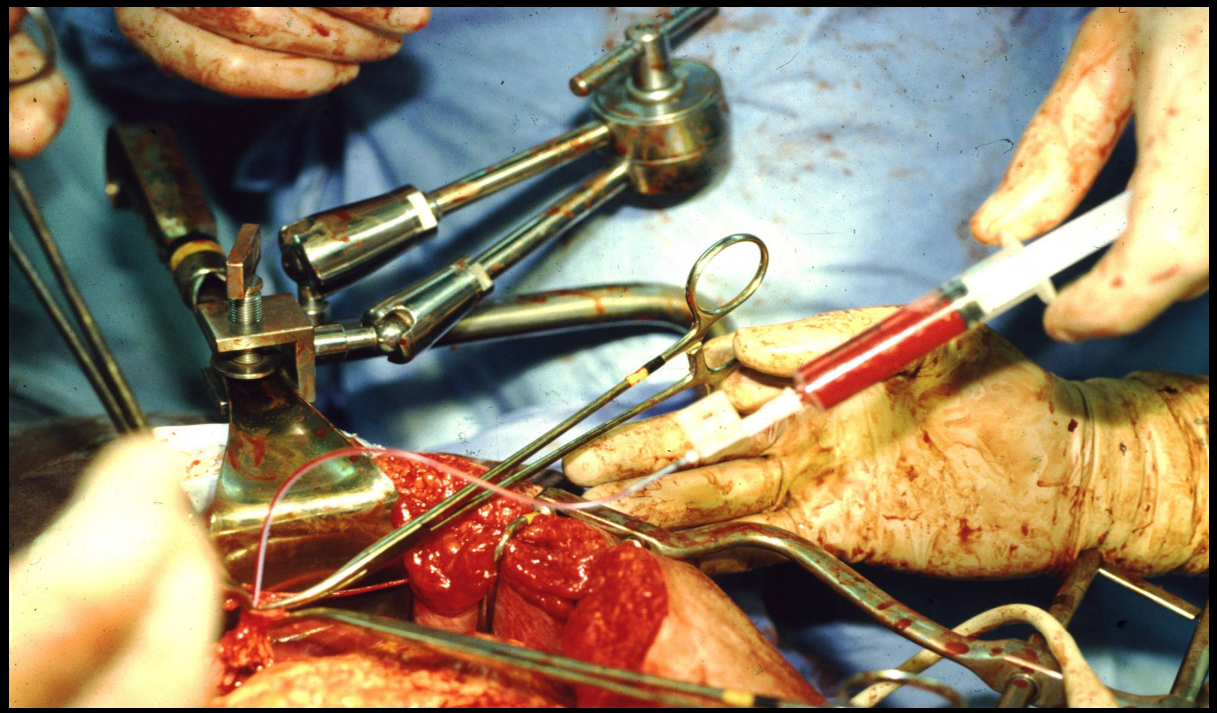
Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF

Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D.,
OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.,

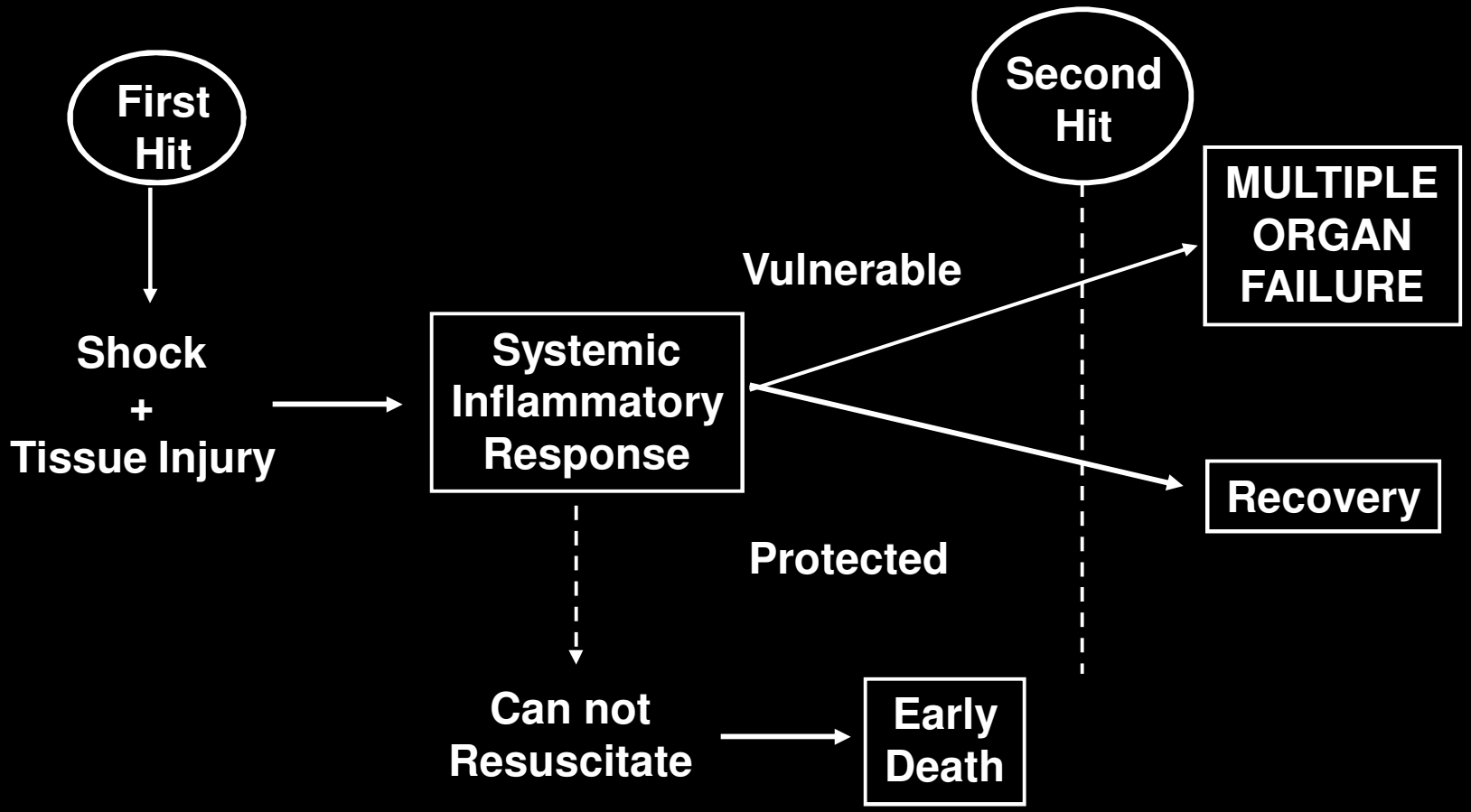
J Trauma 1991

20 High Risk Torso Trauma Patients
Portal Vein Catheters & Sampled Blood X 5 days

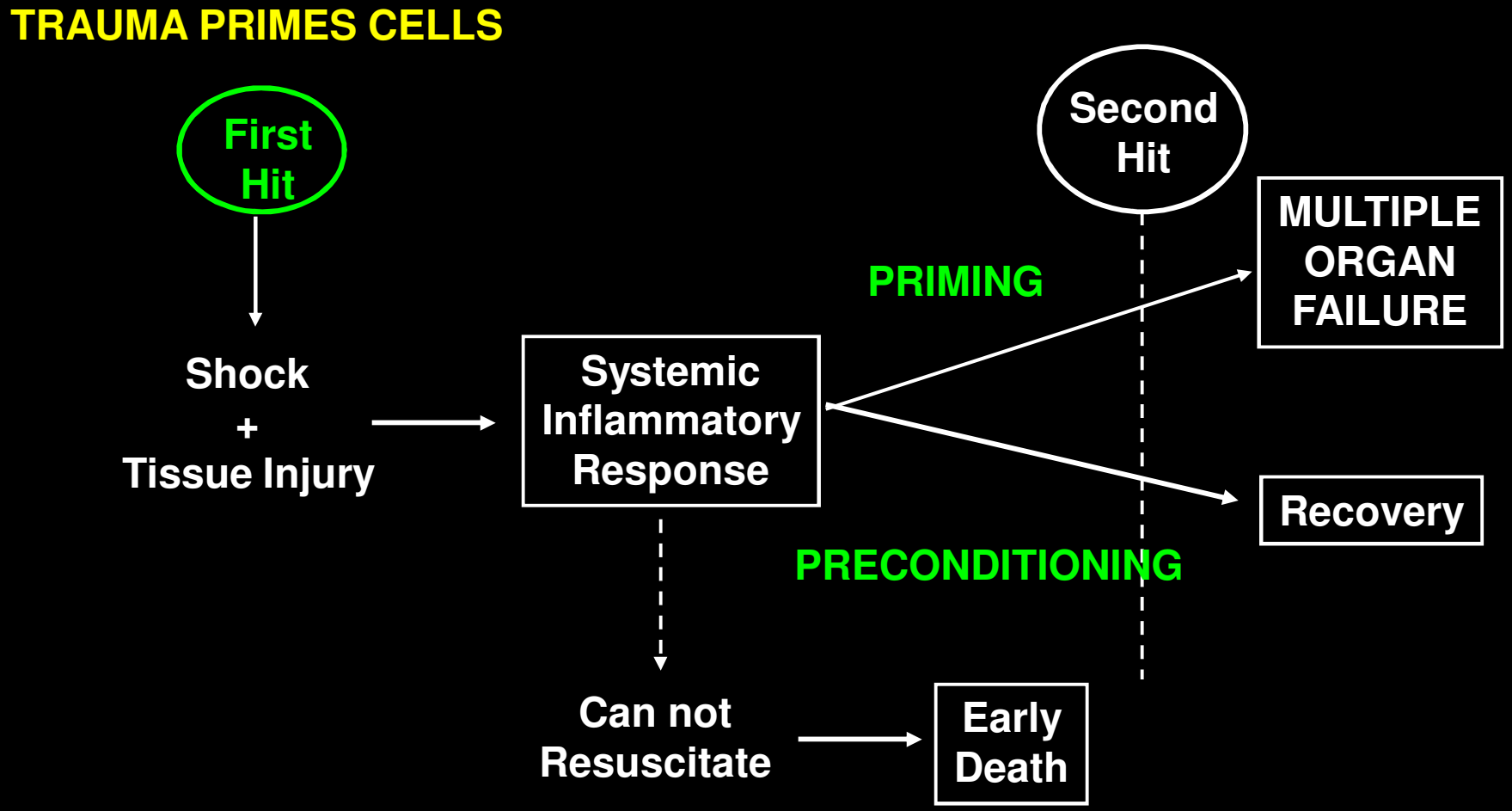


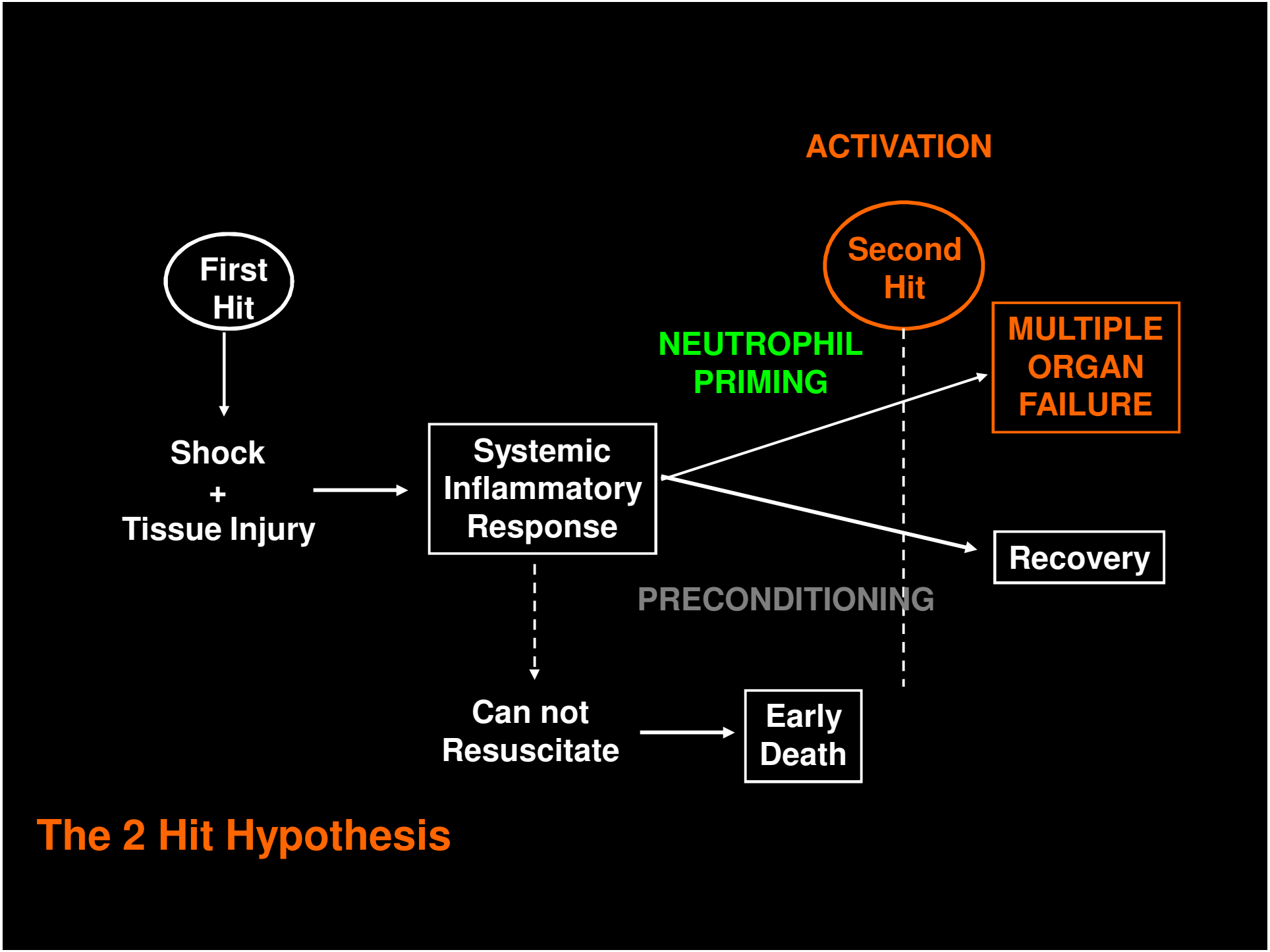
Found no endotoxin or bacteria in portal vein

Back to the Drawing Board



Cartoon for P-50 Trauma Center Grant





The 2 Hit Hypothesis

Lung Injury Is a Reversible Neutrophil-Mediated Event Following Gut Ischemia

Renato S. Poggetti, MD; Frederick A. Moore, MD; Ernest E. Moore, MD;
Denis D. Bensard, MD; Benjamin O. Anderson, MD; Anirban Banerjee, PhD

Arch Surg 1992

Renato Poggetti

 # 5: Create clinically relevant lab model

Shock Induced Gut Ischemia Reperfusion

1st Research Fellow - Brazilian Trauma Surgeon

THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

Ernest E. Moore, MD, Frederick A. Moore, MD, Reginald J. Franciose, MD, Fernando J. Kim, MD, Walter L. Biffl, MD, and Anirban Banerjee, PhD

J Trauma 1994

45 Min SMA Occlusion

Activates Gut PLA_2

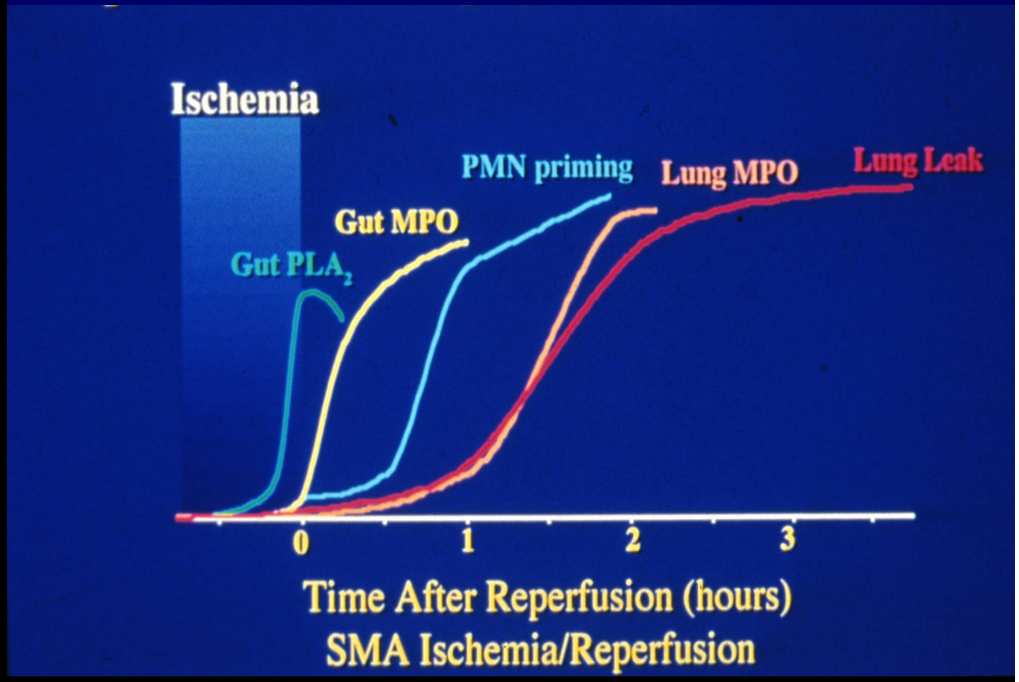
Sequesters PMN's in Gut

Primes Circulating PMN's

Sequesters PMN's in Lung

Causes Lung Injury

Pathophysiologic Sequence



THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

Ernest E. Moore, MD, Frederick A. Moore, MD, Reginald J. Franciose, MD, Fernando J. Kim, MD, Walter L. Biffl, MD, and Anirban Banerjee, PhD

J Trauma 1994

45 Min SMA Occlusion

Activates Gut PLA_2

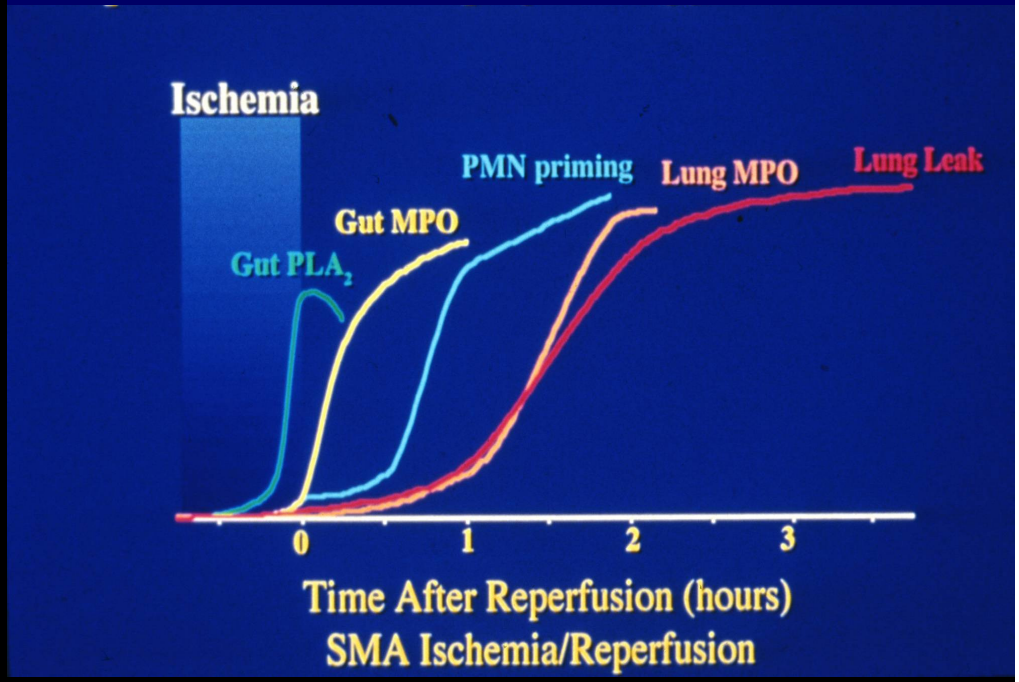
Sequesters PMN's in Gut

Primes Circulating PMN's

Sequesters PMN's in Lung

Causes Lung Injury

Pathophysiologic Sequence



POSTINJURY NEUTROPHIL PRIMING AND ACTIVATION STATES: THERAPEUTIC CHALLENGES

Botha AJ, Moore FA, Moore EE, Fontes B, Banerjee A, and Peterson VM:

Shock **1993**

Abrie Botha

UK General Surgeon

Pete Peterson

Pediatric Hematologist

Postinjury neutrophil priming and activation: An early vulnerable window

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Fernando J. Kim, MD, Anirban Banerjee, PhD, *and* Verlyn M. Peterson, MD,
Denver, Colo.

Surgery 1995

Focused observational studies done DG SICU patients

Early Neutrophil Sequestration after Injury: A Pathogenic Mechanism for Multiple Organ Failure

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Angela Sauaia, MD, Anirban Banerjee, PhD, and Verlyn M. Peterson, MD

J Trauma 1995

Proof of Concept

Sequential systemic platelet-activating factor and interleukin 8 primes neutrophils in patients with trauma at risk of multiple organ failure.

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Chistopher C Silliman, MD and Verlyn M. Peterson, MD

Br J Surg 1996

Postinjury neutrophil priming and activation: An early vulnerable window

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Fernando J. Kim, MD, Anirban Banerjee, PhD, *and* Verlyn M. Peterson, MD,
Denver, Colo.

Surgery 1995

Focused observational studies done DG SICU patients

Early Neutrophil Sequestration after Injury: A Pathogenic Mechanism for Multiple Organ Failure

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Angela Sauaia, MD, Anirban Banerjee, PhD, and Verlyn M. Peterson, MD

J Trauma 1995

Proof of Concept

Sequential systemic platelet-activating factor and interleukin 8 primes neutrophils in patients with trauma at risk of multiple organ failure.

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Chistopher C Silliman, MD and Verlyn M. Peterson, MD

Br J Surg 1996

Early Predictors of Postinjury Multiple Organ Failure

Angela Sauaia, MD; Frederick A. Moore, MD; Ernest E. Moore, MD; James B. Haenel, RRT; Robert A. Read, MD; Dennis C. Lezotte, PhD

Arch Surg 1992

Angela Sauaia

6: Develop a Clinical Database

Brazilian Internist

Early Predictors of Postinjury Multiple Organ Failure

Angela Sauaia, MD; Frederick A. Moore, MD; Ernest E. Moore, MD; James B. Haenel, RRT; Robert A. Read, MD; Dennis C. Lezotte, PhD

Arch Surg 1992

Angela Sauaia

ACUTE PREDICTION MODELS

Host Factors

Age > 55 years

Tissue Injury

ISS > 25

Shock Indices

Blood Transfusion > 6 units

ED Base Deficit > 8mEq/L

Lactate > 2.5 mmol/L after 12 hrs

Multiple Organ Failure Can Be Predicted as Early as 12 Hours after Injury

Angela Sauaia, MD, PhD, Frederick A. Moore, MD, Ernest E. Moore, MD, Jill M. Norris, PhD, Dennis C. Lezotte, PhD And Richard F. Hamman. MD DrPH

J Trauma 1998

Angela Sauaia

ACUTE PREDICTION MODELS

Host Factors

Age > 55 years

Validated

Tissue Injury

ISS > 25

Shock Indices

Blood Transfusion > 6 units

ED Base Deficit > 8mEq/L

Lactate > 2.5 mmol/L after 12 hrs

Multiple Organ Failure Can Be Predicted as Early as 12 Hours after Injury

Angela Sauaia, MD, PhD, Frederick A. Moore, MD, Ernest E. Moore, MD, Jill M. Norris, PhD, Dennis C. Lezotte, PhD
And Richard F. Hamman, MD DrPH

J Trauma 1998

Angela Sauaia

"Win, Win" Collaboration

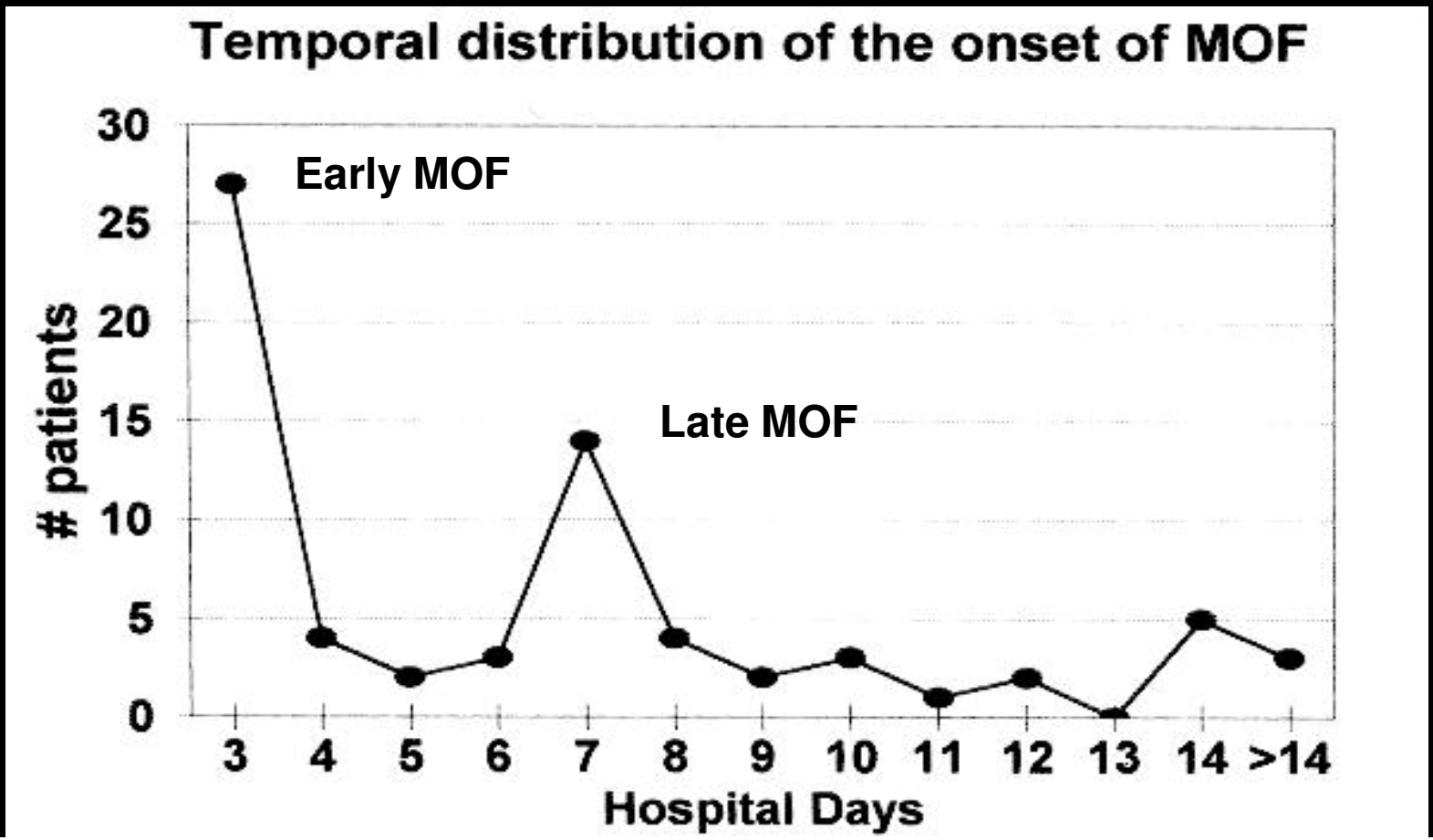
Denver MOF Database

Postinjury Multiple Organ Failure: A Bimodal Phenomenon

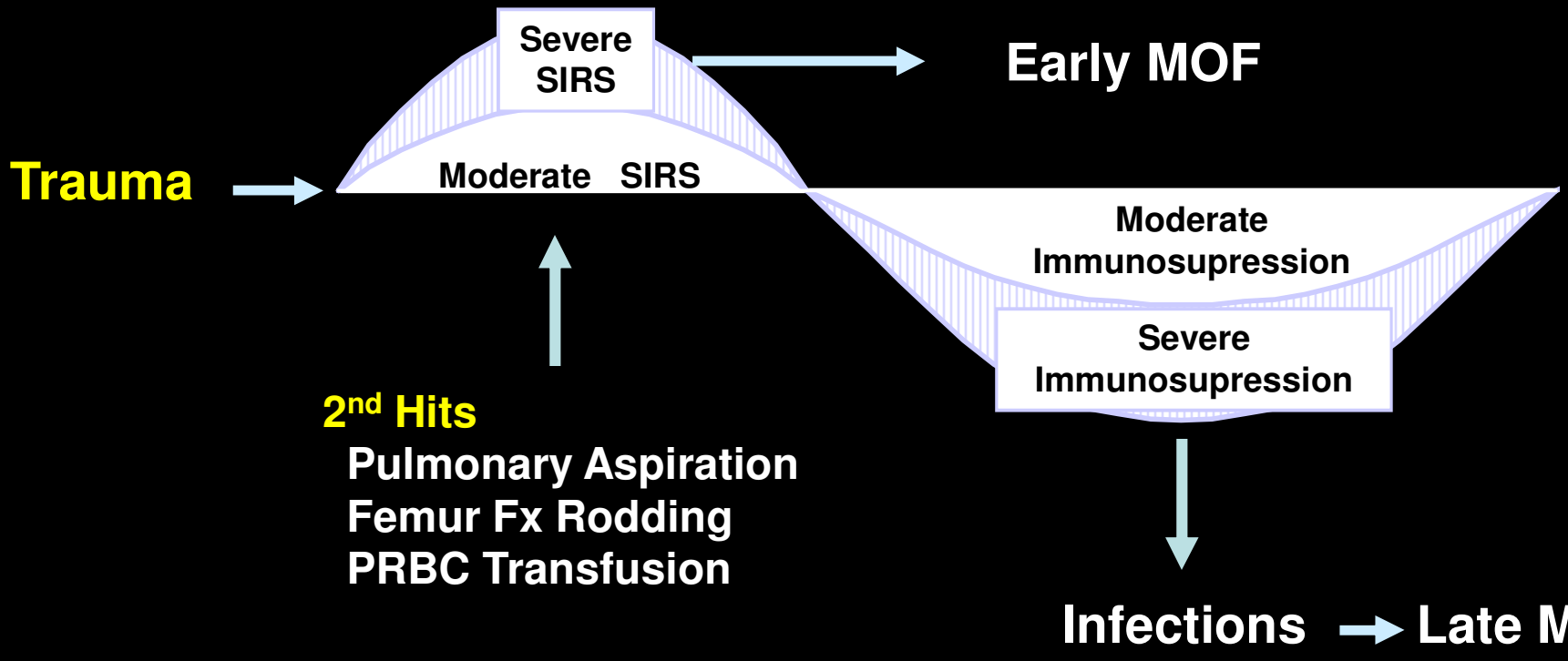
Frederick A. Moore, MD, Angela Sauaia, MD, Ernest E. Moore, MD, James B. Heanel, RRT, Jon M. Burch, MD and Dennis C. Lezotte, PhD

J Trauma 1996

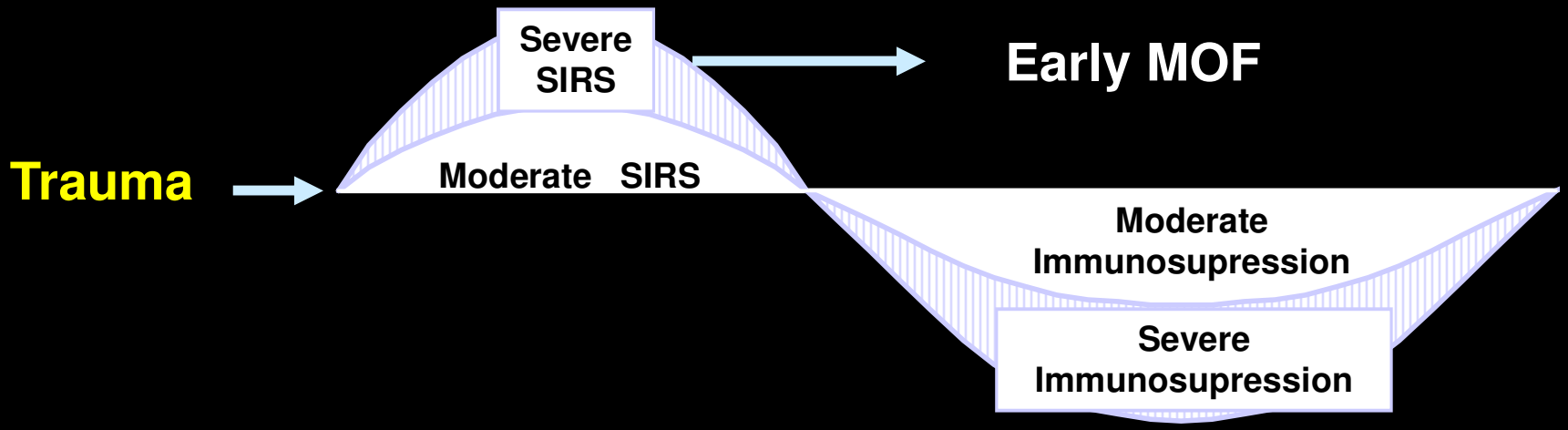
Denver MOF Database



POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE



POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

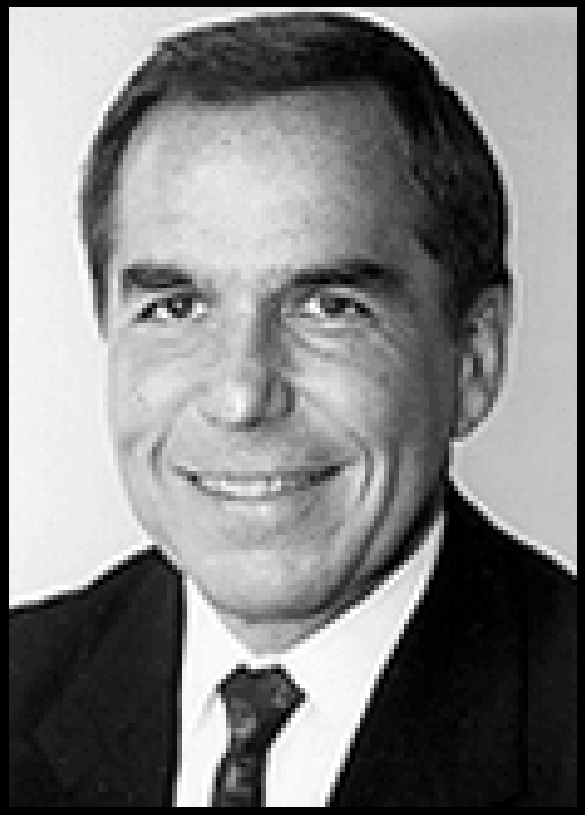


Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS)

Roger C. Bone, MD

Ann Intern Med 1996

Roger Bone

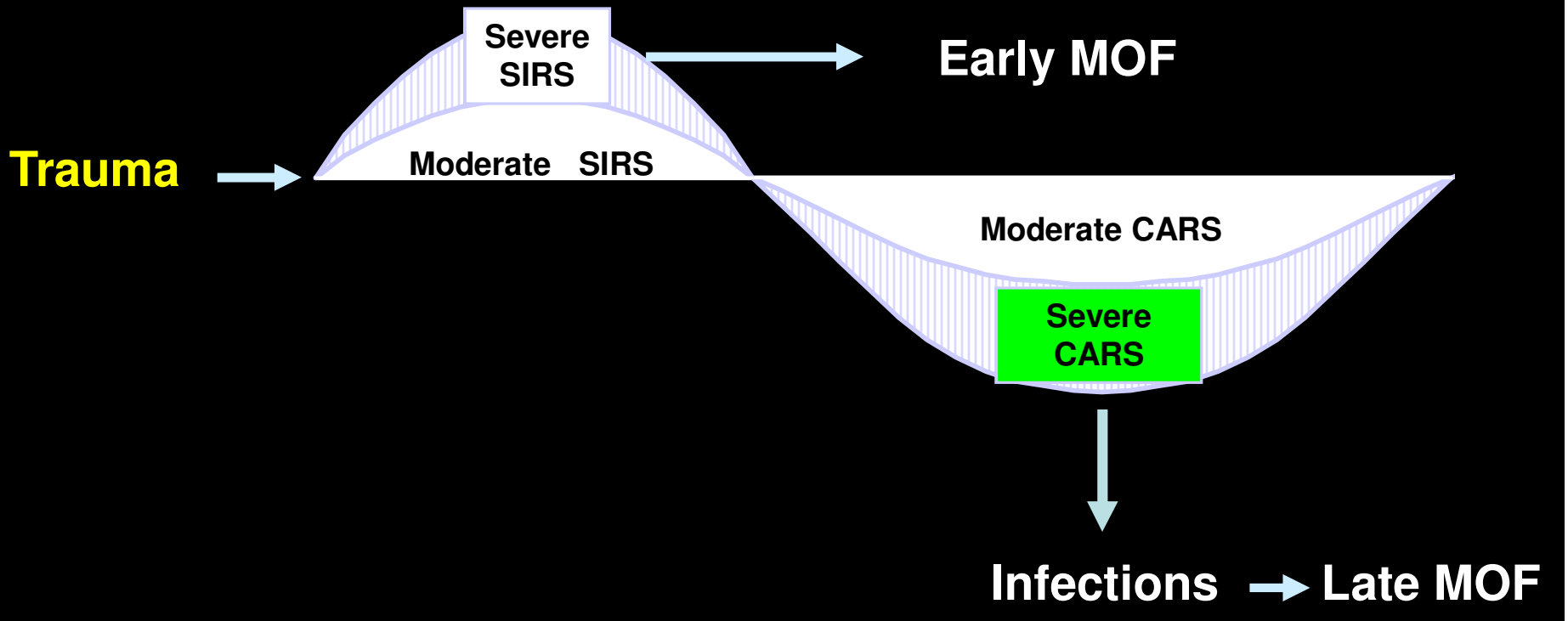


Adaptive Immune Response
Lymphocytes

CARS

COMPENSATORY ANTI-INFLAMMATORY RESPONSE SYNDROME

POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE



Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team

Hermann Hospital

UT Houston Medical School

Medical Director of Trauma 1996 to 2006

NIGMS Sponsored P-50 Trauma Center Grant (TRC)

Gut Inflammation and Ileus

Norm Weisbrodt

Physiologist

Frank Moody

Surgeon

Decreased ileal muscle contractility and increased NOS II expression induced by lipopolysaccharide

LPS

NORMAN W. WEISBRODT, THOMAS A. PRESSLEY, YONG-FANG LI, MALGORZATA J. ZEMBOWICZ, SANDRA C. HIGHAM, ARTUR ZEMBOWICZ, ROBERT F. LODATO, AND FRANK G. MOODY

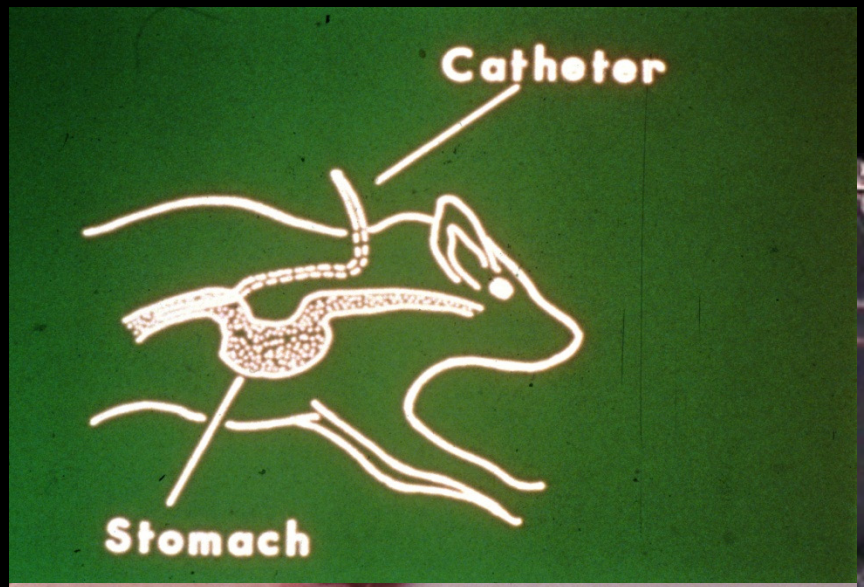
Focus: Sepsis Induced Ileus

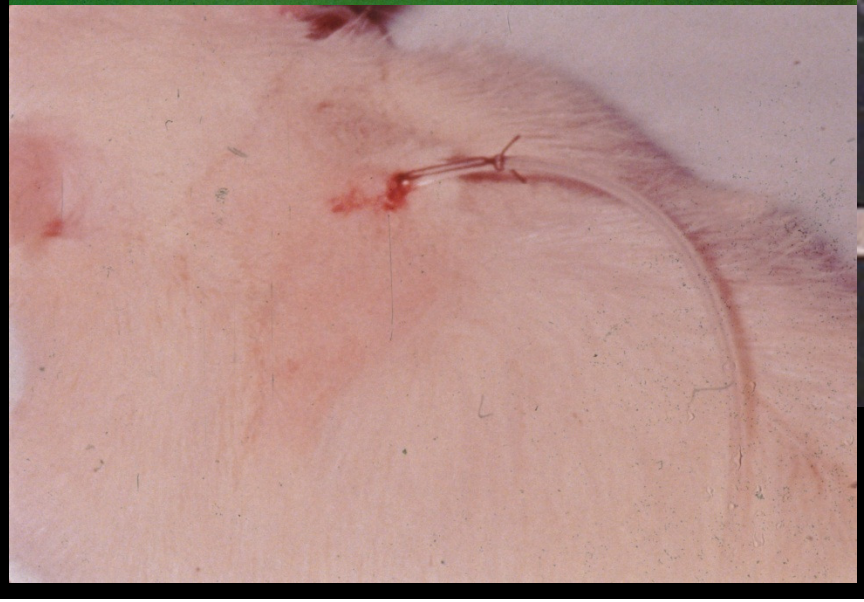
Am J Physiology 1996

Physiologist

Surgeon

Preparation for Intestinal Transit Studies



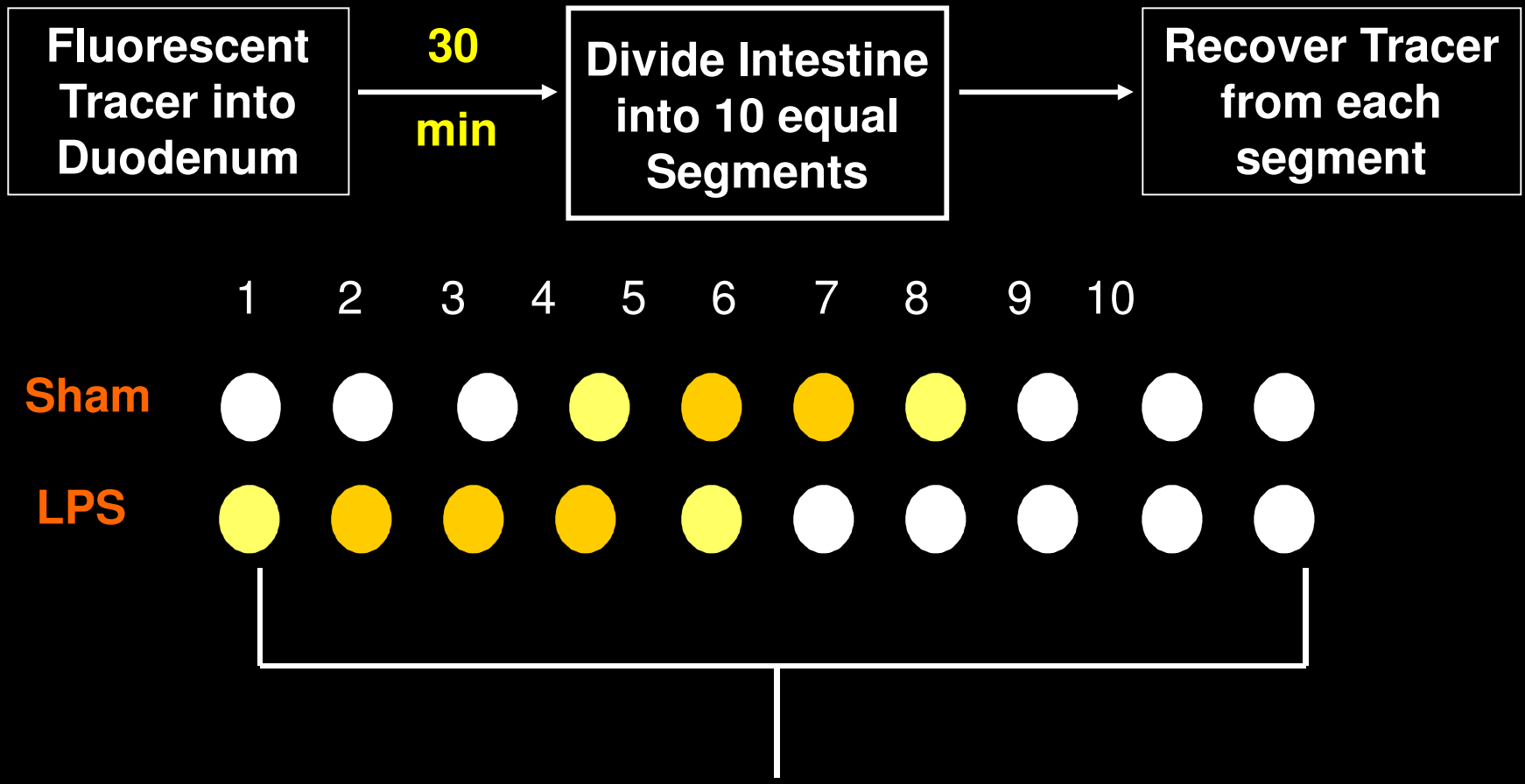


Unanesthetized & Unrestrained

SMALL INTESTINAL TRANSIT

Administer LPS or Sham

Wait at least 5 hours



Inducible Nitric Oxide Synthase Mediates Gut Ischemia/Reperfusion-Induced Ileus Only after Severe Insults[1]

Heitham T. Hassoun, M.D.,* Norman W. Weisbrodt, Ph.D.,† David W. Mercer, M.D.,* Rosemary A. Kozar, M.D., Ph.D.,* Frank G. Moody, M.D.,* and Frederick A. Moore, M.D.*,[2]

Heitham Hassoun

“Diamond in the Rough”

1st UT Research Fellow

Inducible Nitric Oxide Synthase Mediates Gut Ischemia/Reperfusion-Induced Ileus Only after Severe Insults[1]

Heitham T. Hassoun, M.D.,* Norman W. Weisbrodt, Ph.D.,† David W. Mercer, M.D.,*
Rosemary A. Kozar, M.D., Ph.D.,* Frank G. Moody, M.D.,* and Frederick A. Moore, M.D.*,[2]

Heitham Hassoun

Role of iNOS in gut I/R induced ileus

Denver SMAO rodent model

Measured intestinal transit

Characterized gut inflammation

Different iNOS blockers

1st UT Research Fellow

POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,*
Norman W. Weisbrodt,‡ and Frederick A. Moore*

Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

7: Write Review Articles & Propose New Paradigms

Our " Story of Life "

Research Focus: Role of the gut in MOF

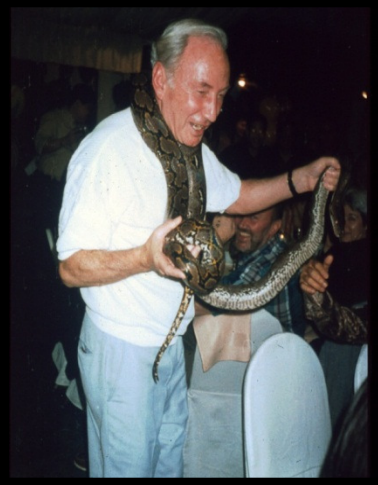
POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,*
Norman W. Weisbrodt,‡ and Frederick A. Moore*

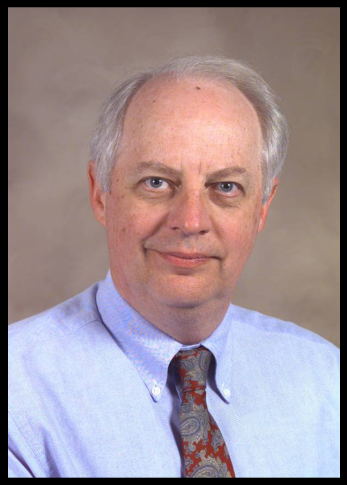
*Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

Bruce Kone
Chair of Medicine

David Mercer
Chief LBJ



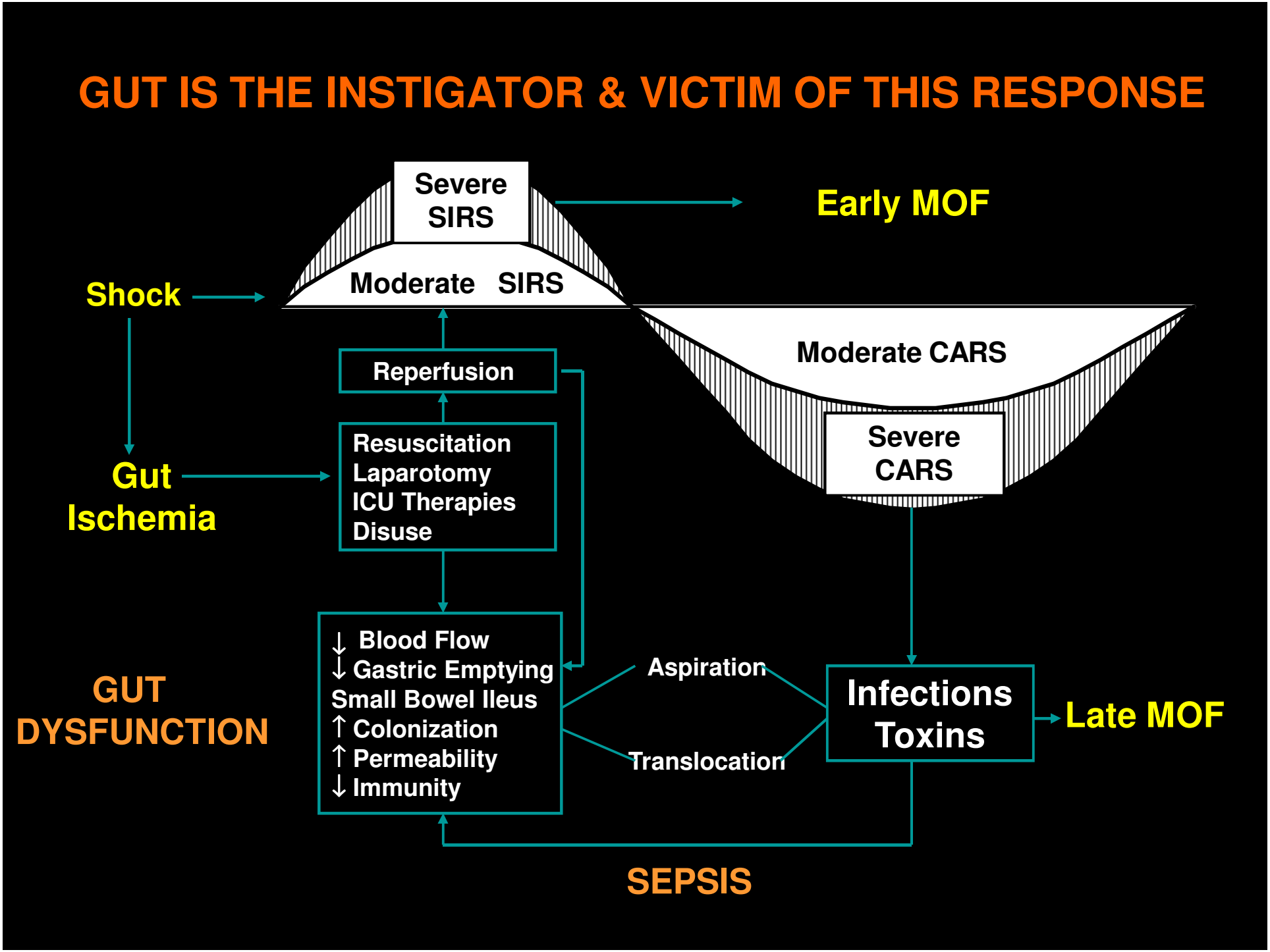
Frank Moody
PI of P 50 grant



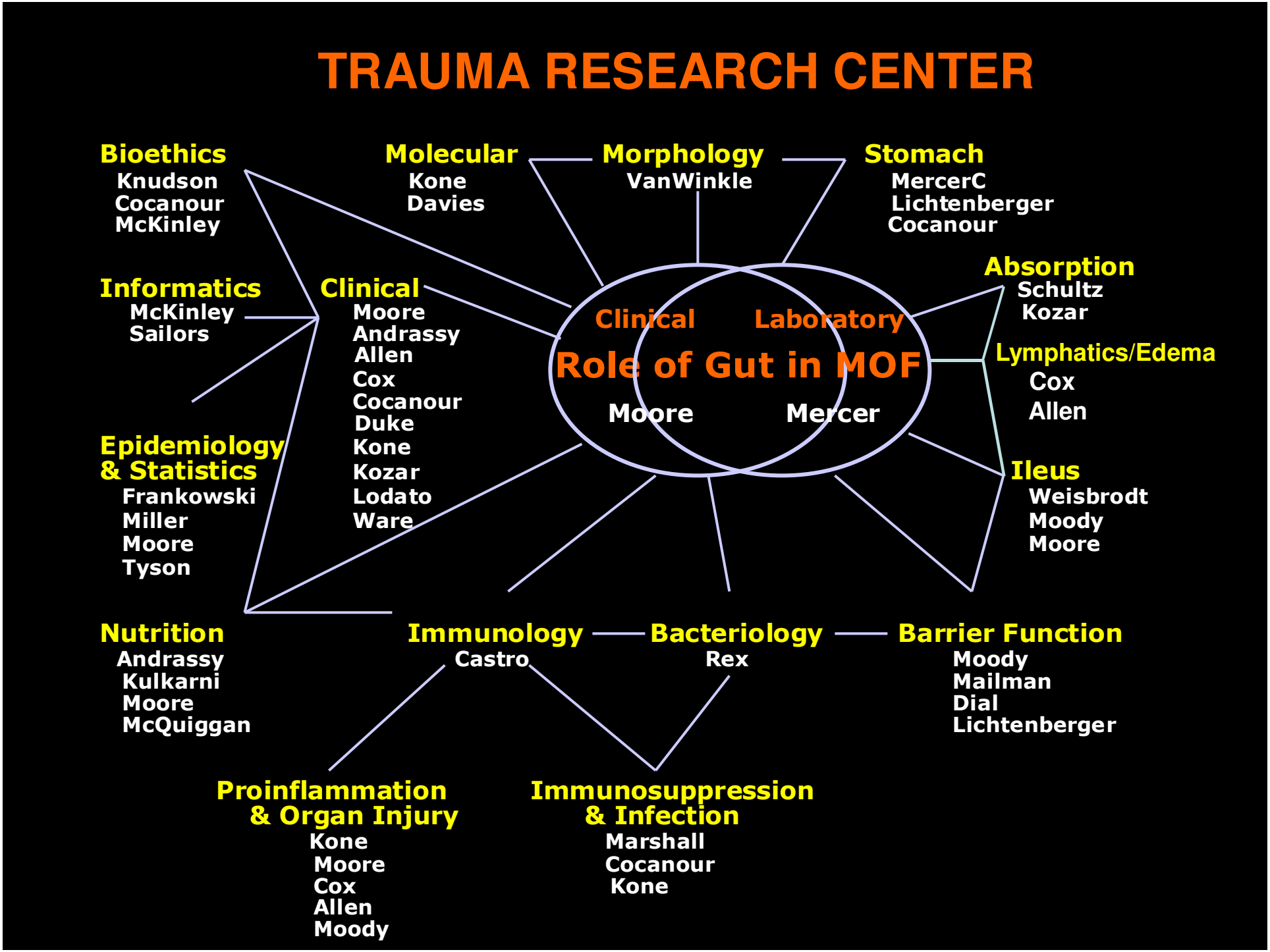
Norm Weisbrodt
Chair of Physiology

8: Align Institutional "Super Stars"

GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE



TRAUMA RESEARCH CENTER



Heitham Hassoun

Rosemary Kozar

Poster Kids

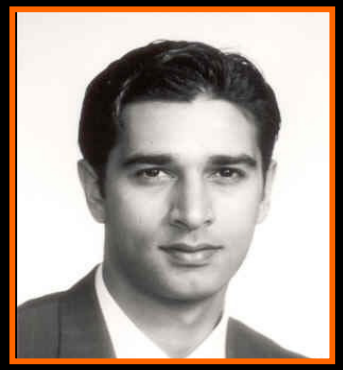
NIGMS T-32 Research Training Grant

Formal Training for Translational Research

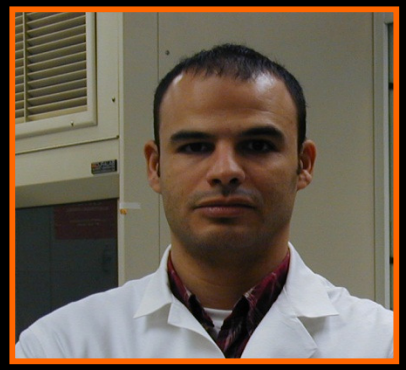
Bioethics
Statistics
Epidemiology
Clinical Trial Design
Outcomes Research

9: Train the next Generation to be Translational Scientists

Heitham Hassoun



Bashir Attuwaybi



Ken Helmer

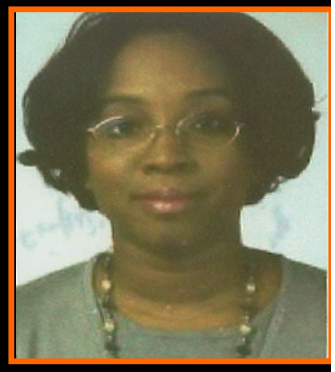
Sonlee West

Ernest Gonzalez

NIGMS T-32 Research Fellows

TRC Catalyst

Stacey Moore



Sasha Adams

Ben Delano

Ravi Radhakrishnan

James Suliburk

NIGMS K-08 Grants

Chuck Cox **Rosemary Kozar** **Emily Robinson**

Previous UT Surgery Residents

NIGMS K-08 Grants

Chuck Cox

Rosemary Kozar

Emily Robinson

NIH Lab Training at Other Institutions

NIGMS K-08 Grants

Chuck Cox **Rosemary Kozar** **Emily Robinson**

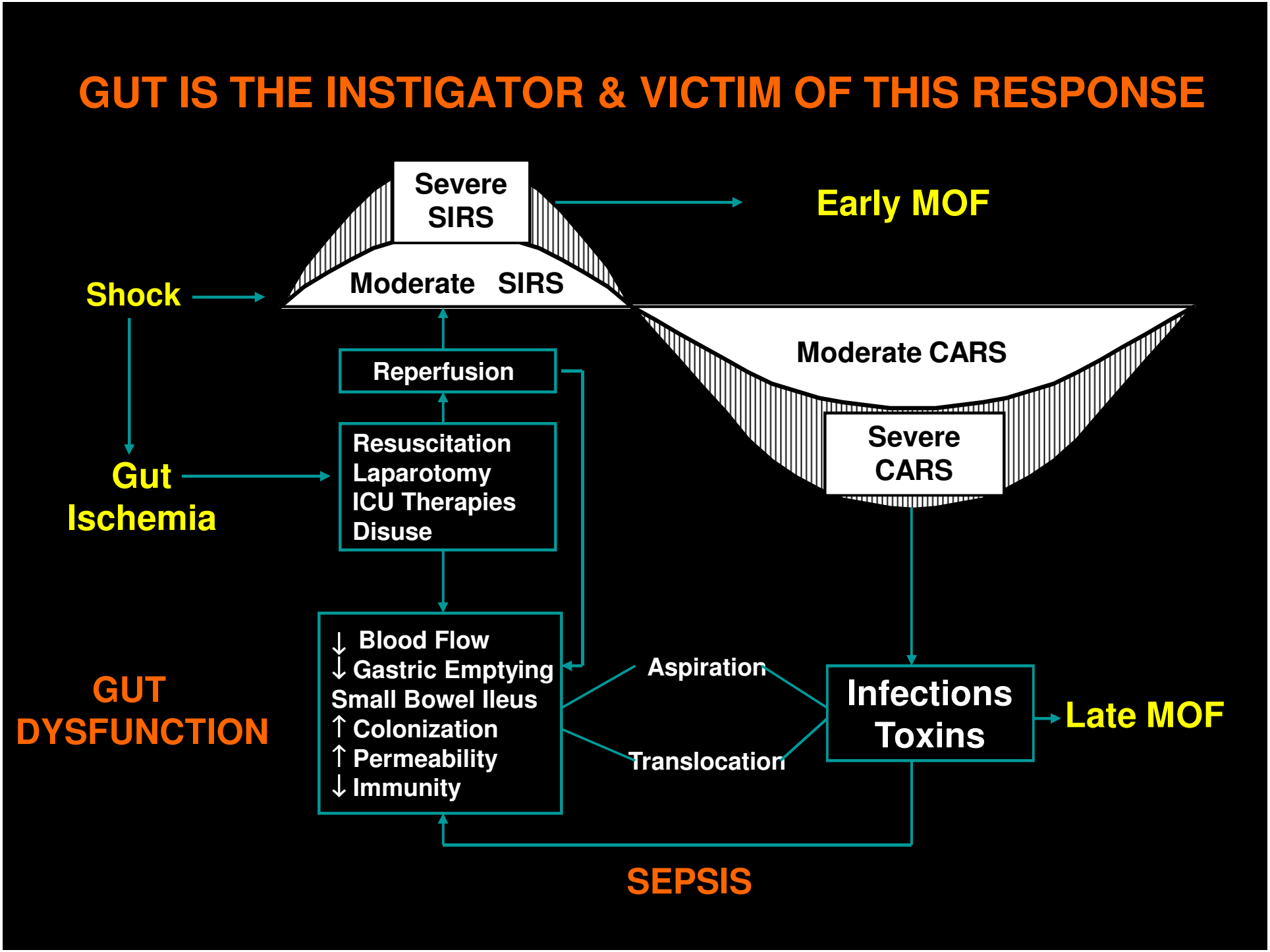
Assistant Professors worked on the TRC Projects

Rosemary Kozar

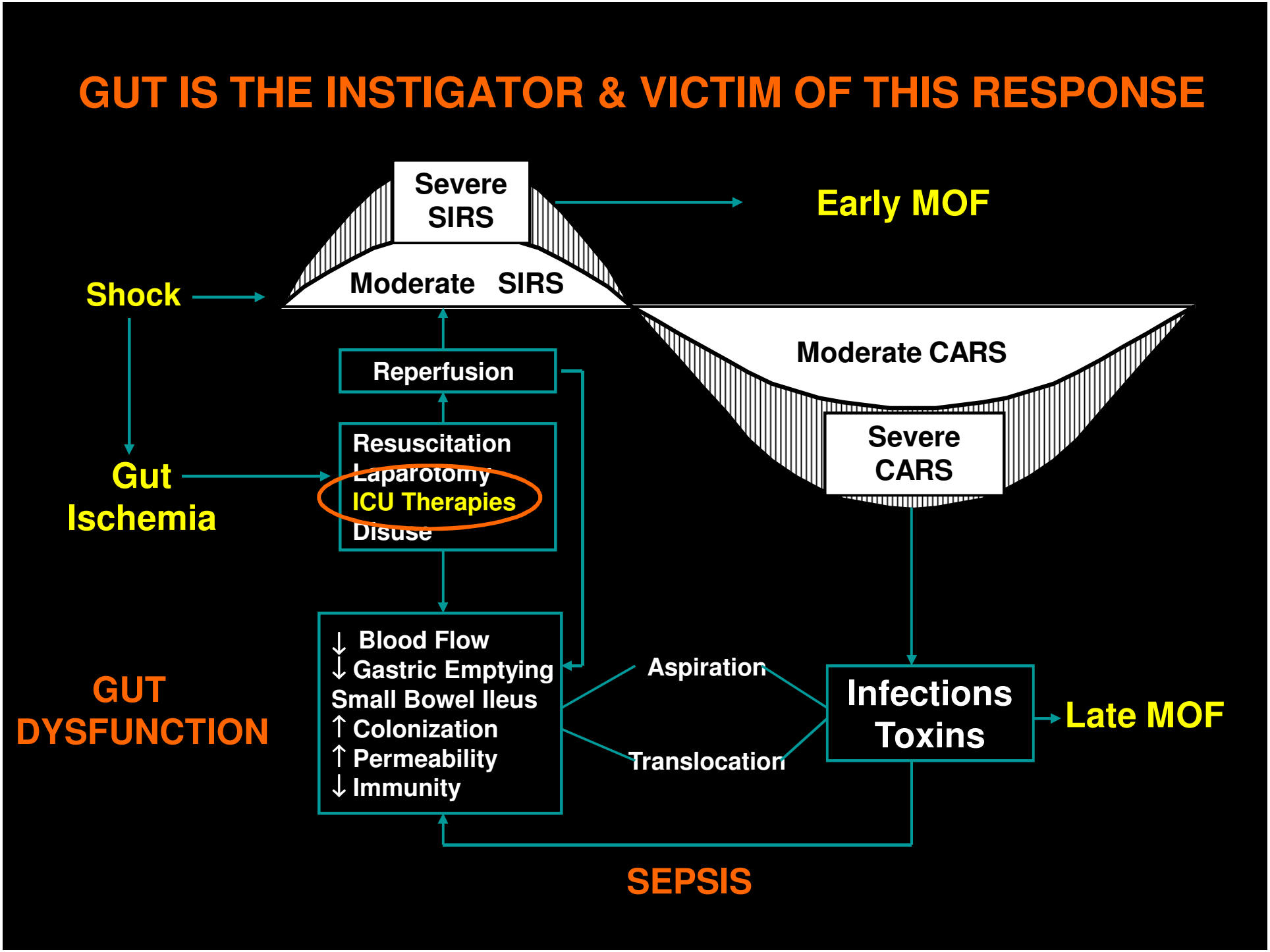
Critical Care Fellow 1999

UT-Houston Surgery Resident
PhD Baylor College of Medicine
Trauma Surgeon Hahnemann University Philadelphia,

GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE



GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE



ICU THERAPIES

Early Enteral Nutrition

Sedation & Analgesia

Stress Gastritis Prophylaxis

Enteral Feeding Following Major Torso Trauma: From Theory to Practice

New Horizons 1999

Margaret M. McQuiggan, MS, RD, CSM; Robert G. Marvin, MD; Bruce A. McKinley, PhD, FCCM; Frederick A. Moore, MD, FCCM

Maggie McQuiggan

ICU Dietician

ENTERAL FEEDING PROTOCOL

Background & Rationale

Patient & Formula Selection

Enteral Access

Formula Advancement

Managing GI Intolerance

Nurse Driven

Monitoring Effectiveness

Postinjury Enteral Tolerance Is Reliably Achieved by a Standardized Protocol[1]

J Surg Res 2002

Rosemary A. Kozar, M.D., Ph.D.*,[2] Margaret M. McQuiggan, M.S., R.D., C.S.M.,‖ Ernest E. Moore, M.D.,†
Kenneth A. Kudsk, M.D.,‡ Gregory J. Jurkovich, M.D.,§ and Frederick A. Moore, M.D.*

Phase I – 17 Shock Resuscitation Patients

Tolerance	Early	Late
Good	82 %	65 %
Moderate	0	6 %
Poor	18 %	17 %
Abandon EN	0	12 %

Postinjury Enteral Tolerance Is Reliably Achieved by a Standardized Protocol[1]

J Surg Res 2002

Rosemary A. Kozar, M.D., Ph.D.*,[2] Margaret M. McQuiggan, M.S., R.D., C.S.M.,‖ Ernest E. Moore, M.D.,†
Kenneth A. Kudsk, M.D.,‡ Gregory J. Jurkovich, M.D.,§ and Frederick A. Moore, M.D.*

Phase I – 17 Shock Resuscitation Patients

Tolerance	Early	Late
Good	82 %	65 %
Moderate	0	6 %
Poor	18 %	17 %
Abandon EN	0	12 %

Phase II - 49 Major Trauma Patients at 4 Level I Centers

Tolerance	Early	Late
Good	84 %	80 %
Moderate	16 %	16 %
Poor	0	4 %
Abandon EN	0	0

Nonocclusive Bowel Necrosis Occurring in Critically Ill Trauma Patients Receiving Enteral Nutrition Manifests No Reliable Clinical Signs for Early Detection

Robert G. Marvin, MD, Bruce A. McKinley, PhD, Margaret McQuiggan, RD, Christine S. Cocanour, MD, Frederick A. Moore, MD, *Houston, Texas*

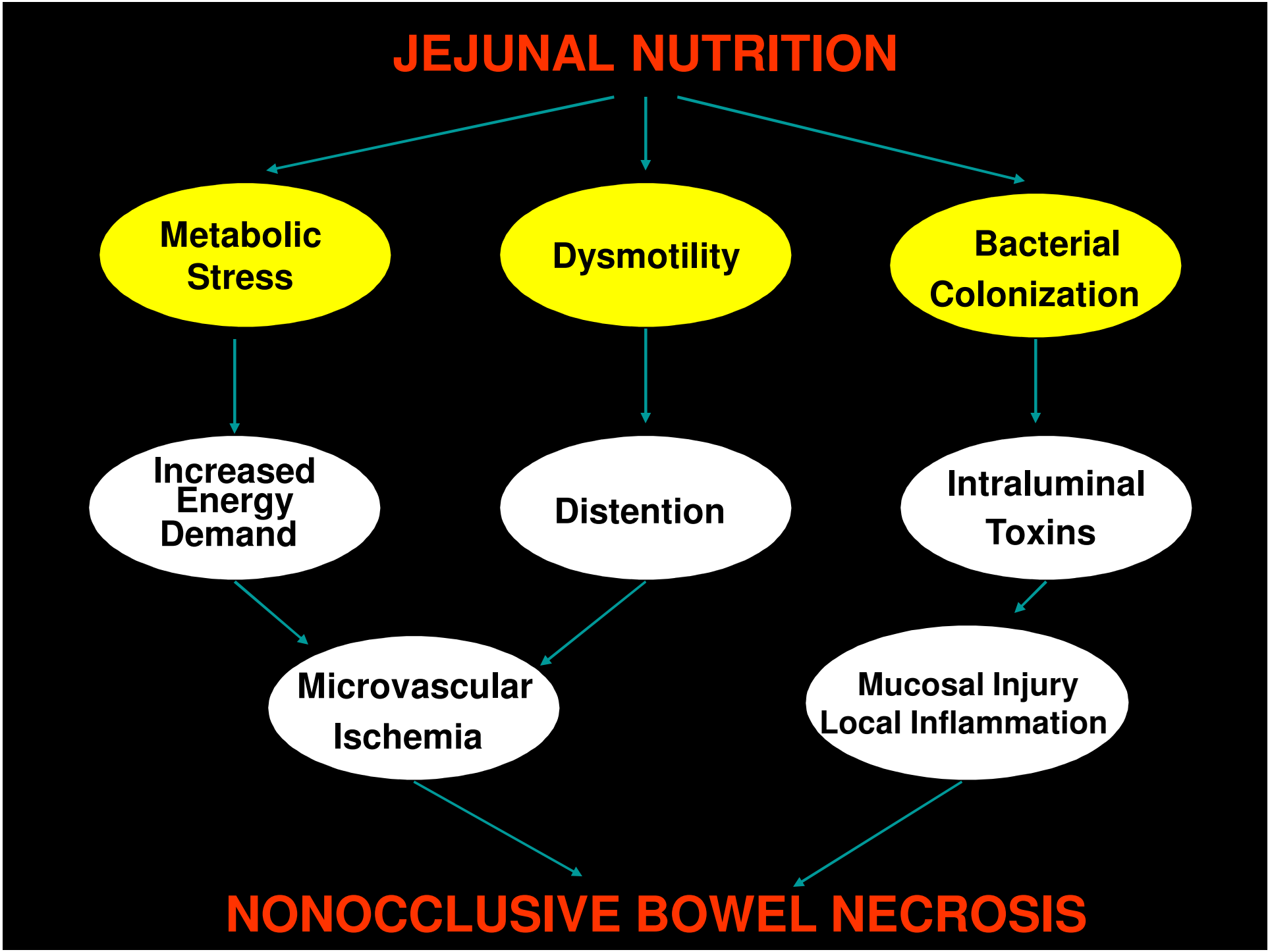
Am J Surg 1999

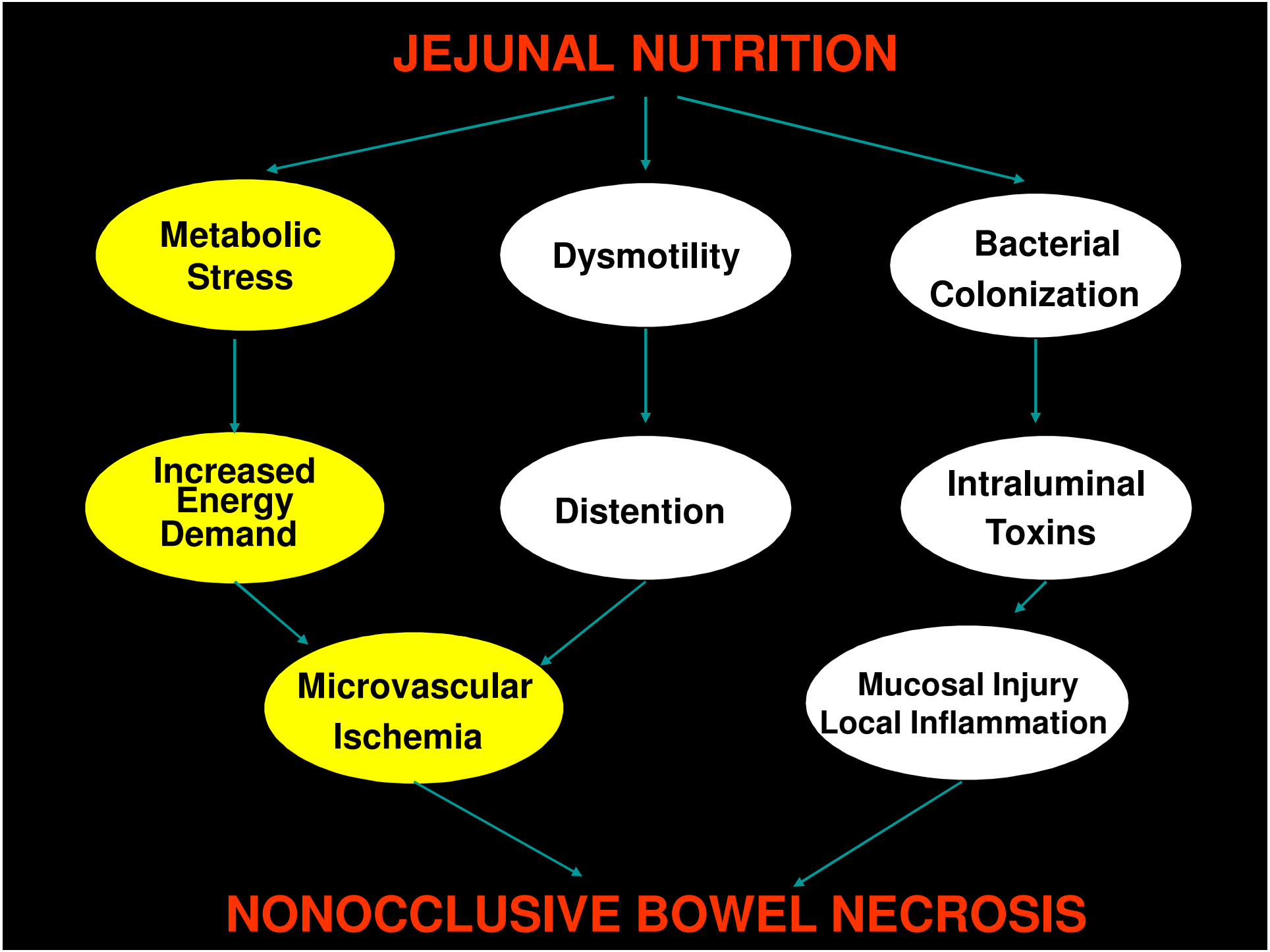
Nonocclusive Bowel Necrosis Occurring in Critically Ill Trauma Patients Receiving Enteral Nutrition Manifests No Reliable Clinical Signs for Early Detection

Robert G. Marvin, MD, Bruce A. McKinley, PhD, Margaret McQuiggan, RD, Christine S. Cocanour, MD, Frederick A. Moore, MD, *Houston, Texas*

Am J Surg 1999

Rationale for Enteral Feeding Protocol


JEJUNAL NUTRITION
Metabolic Stress
Dysmotility
Bacterial Colonization
Increased Energy Demand
Distention
Intraluminal Toxins
Microvascular Ischemia
Mucosal Injury Local Inflammation
NONOCCLUSIVE BOWEL NECROSIS


JEJUNAL NUTRITION
Metabolic Stress
Dysmotility
Bacterial Colonization
Increased Energy Demand
Distention
Intraluminal Toxins
Microvascular Ischemia
Mucosal Injury Local Inflammation
NONOCCLUSIVE BOWEL NECROSIS

8: Align Institutional "Super Stars"

Use Senior Scientists as Mentors

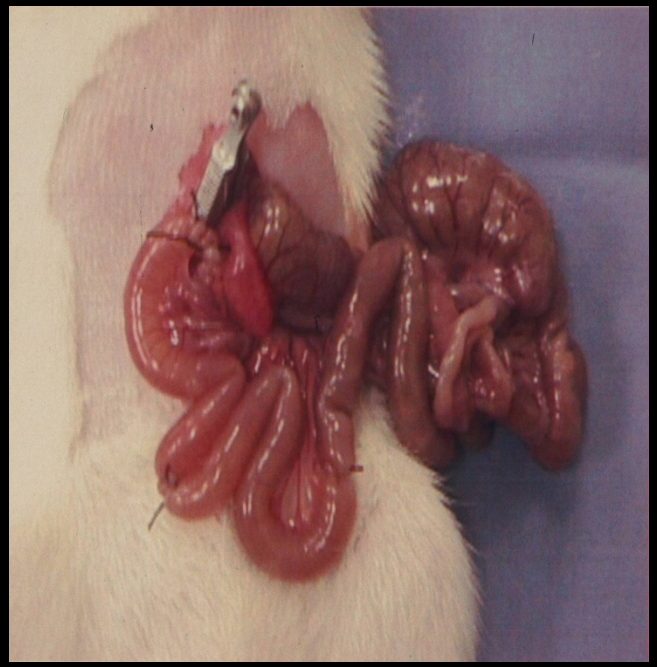
Stan Schultz

Acting Dean of Medical School

Expert on GI Epithelial Transport

Nutrient	ATP Consumed With Absorption	Can be Used by Cell to Produce ATP
Glucose	Yes	Yes Aerobic & Anaerobic
Fructose	No	Yes Aerobic & Anaerobic
Glutamine	Yes	Yes Aerobic Only
Alanine	Yes	No
Arginine	Yes	No

Create Jejunal Sacs



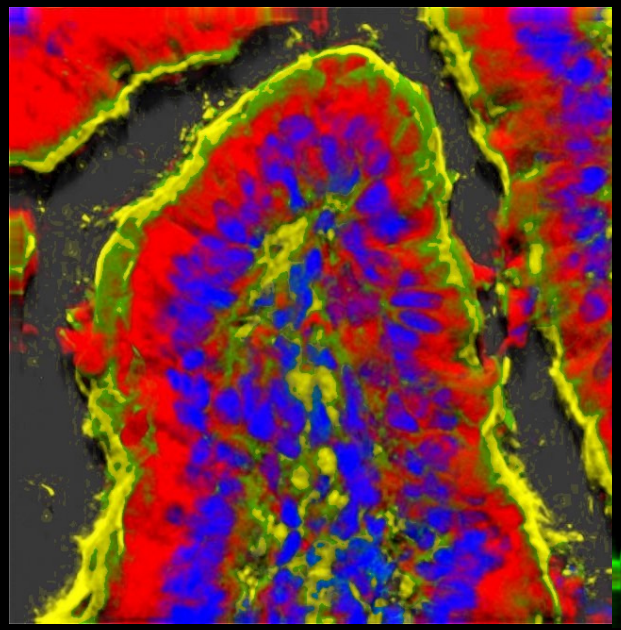
SMAO Model

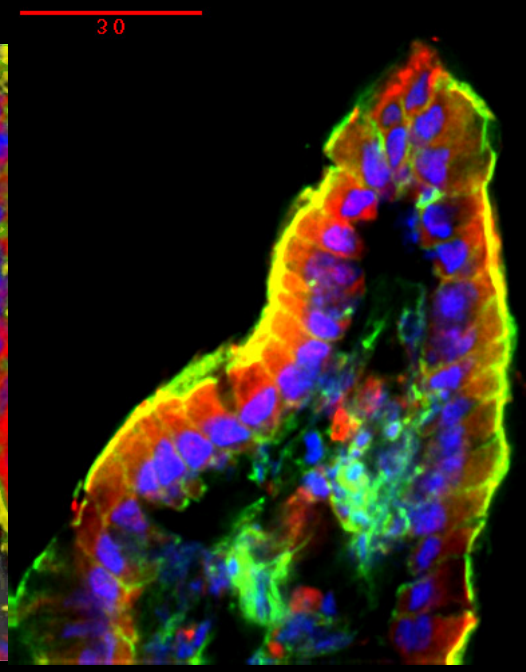
45 min ischemia
30 min reperfusion

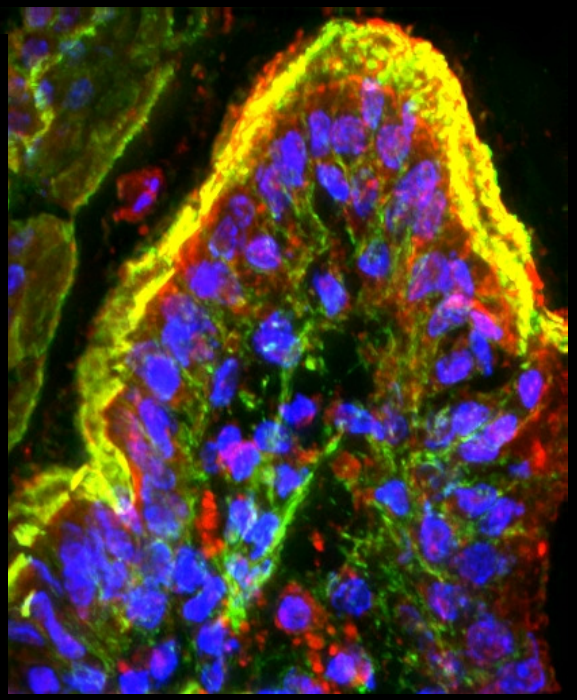
Fills Them With

1. Mannitol (Osmotic Control)
2. Glucose
3. Fructose
4. Glutamine
5. Alanine
6. Arginine

Deconvolution Microscopy

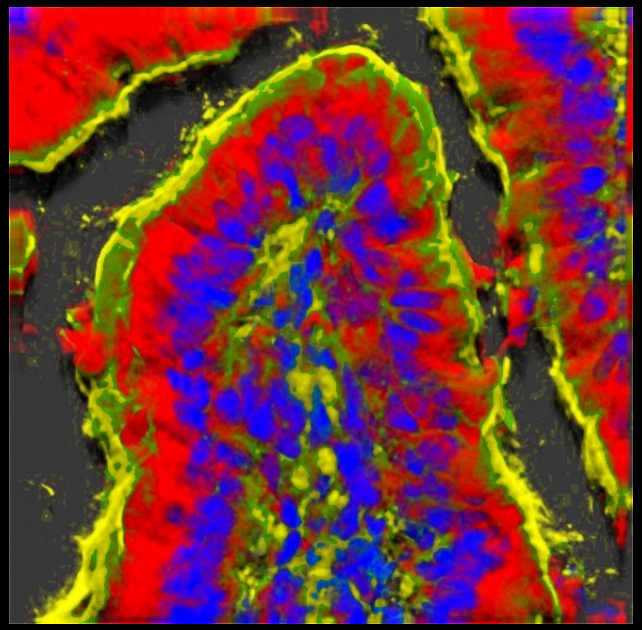


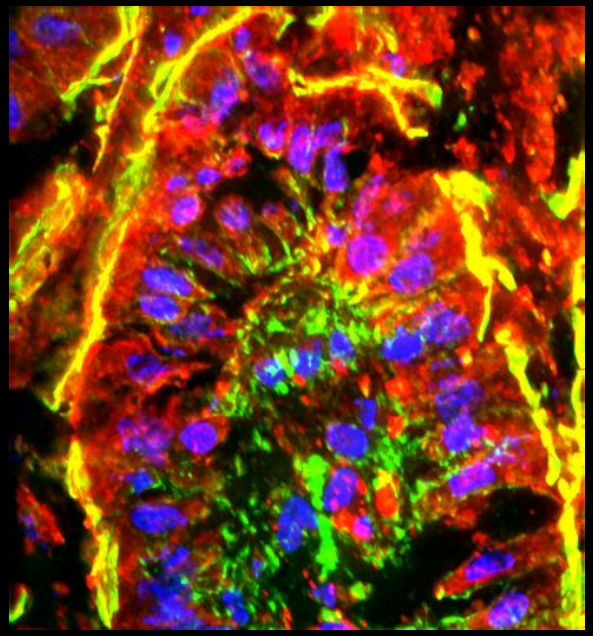


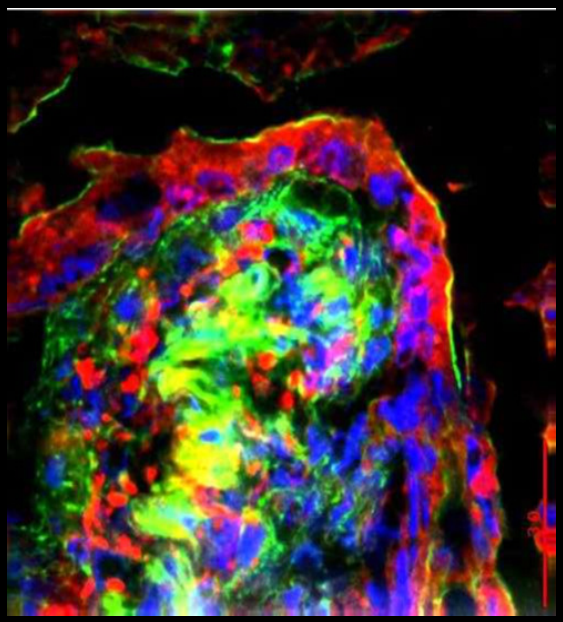


	Glucose	Fructose	Glutamine
ATP Consumer	+	–	+
ATP Producer			
Aerobic	+	+	+
Anaerobic	+	+	–

Deconvolution Microscopy







	Glucose	Alanine	Arginine
ATP Consumer	+	+	+
ATP Producer			
Aerobic	+	–	–
Anaerobic	+	–	–

The Type of Sodium-Coupled Solute Modulates Small Bowel Mucosal Injury, Transport Function, and ATP After Ischemia/Reperfusion Injury in Rats

Gastroenterology 2002

ROSEMARY A. KOZAR,* STANLEY G. SCHULTZ,† HEITHAM T. HASSOUN,* ROLAND DESOIGNIE,* NORMAN W. WEISBRODT,† MARIAN M. HABER,‖ and FREDERICK A. MOORE*

Funded K-08 Grant - 2002

Ussing Chamber

Histology

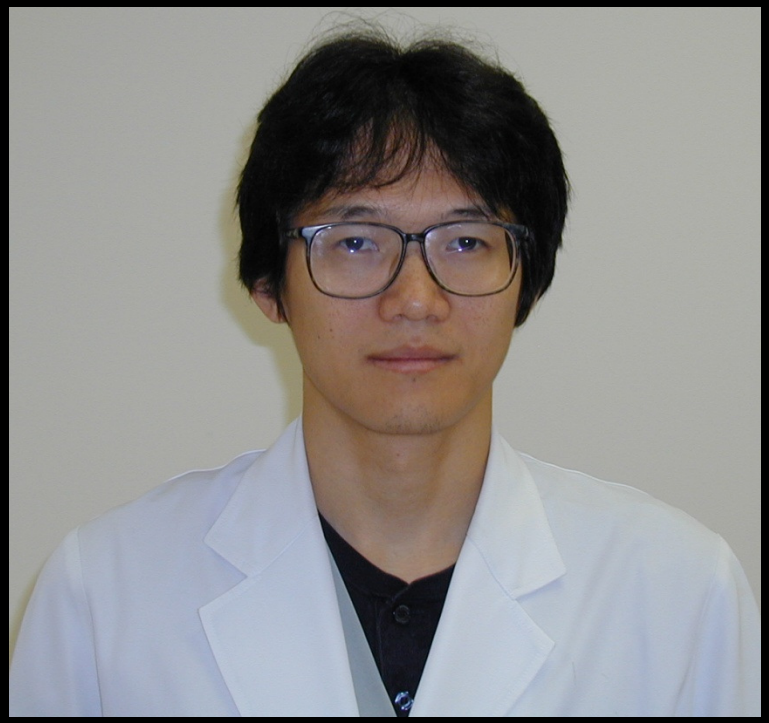
ATP Levels

The Type of Sodium-Coupled Solute Modulates Small Bowel Mucosal Injury, Transport Function, and ATP After Ischemia/Reperfusion Injury in Rats

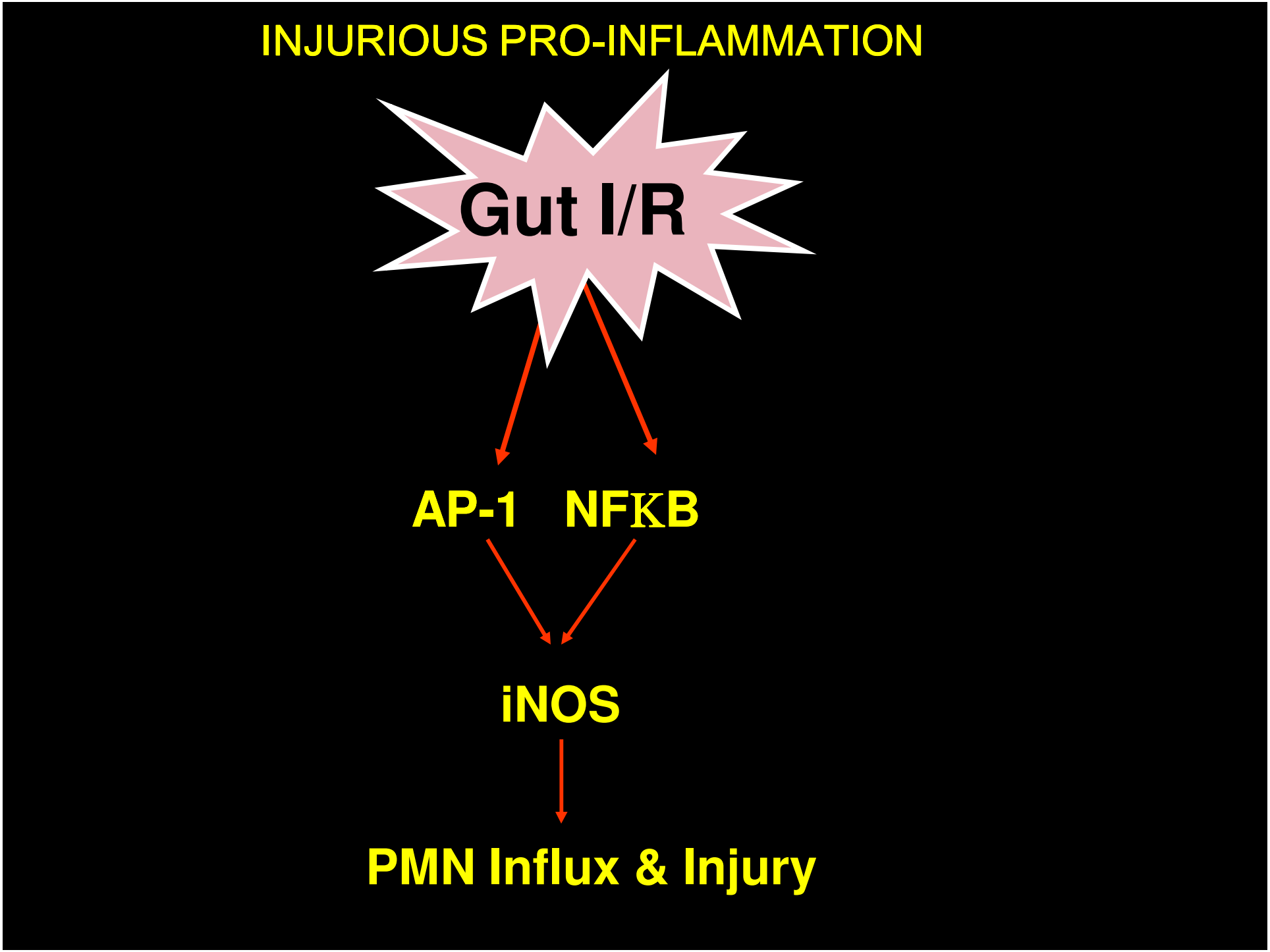
Gastroenterology 2002

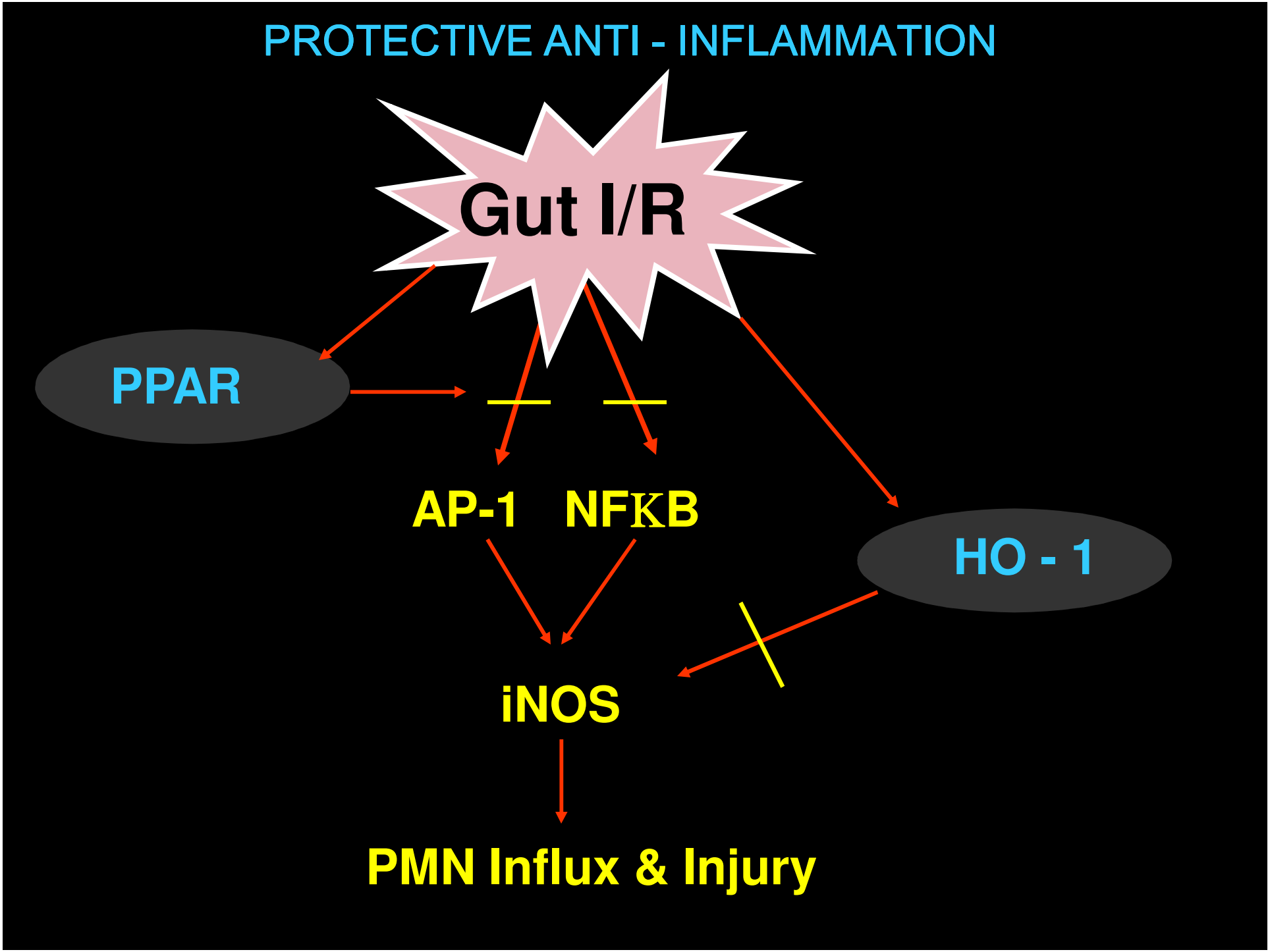
ROSEMARY A. KOZAR,* STANLEY G. SCHULTZ,† HEITHAM T. HASSOUN,* ROLAND DESOIGNIE,* NORMAN W. WEISBRODT,† MARIAN M. HABER,‖ and FREDERICK A. MOORE*

Norio Sato



Research Fellow


INJURIOUS PRO-INFLAMMATION
Gut I/R
AP-1
NFKB
iNOS
PMN Influx & Injury


PROTECTIVE ANTI - INFLAMMATION
Gut I/R
PPAR
AP-1
NFKB
HO - 1
iNOS
PMN Influx & Injury

ENTERAL FORMULA SUPPLEMENTED WITH

Glutamine

Arginine

Nucleotides

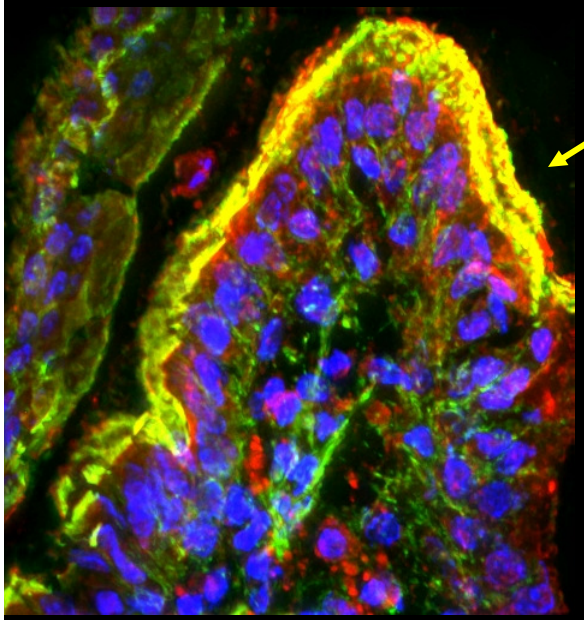
Omega-3 fatty acids

CLINICAL BENEFITS OF AN IMMUNE-ENHANCING DIET FOR EARLY POSTINJURY ENTERAL FEEDING

Frederick A. Moore, MD,[a] Ernest E. Moore, MD,[a] Kenneth A. Kudsk, MD,[b] Rex O. Brown, PharmD,[b] Robert H. Bower, MD,[c] Mark J. Koruda, MD,[d] Christopher C. Baker, MD,[d] and Adrian Barbul, MD[e]

J Trauma 1994

ENTERAL FORMULA SUPPLEMENTED WITH

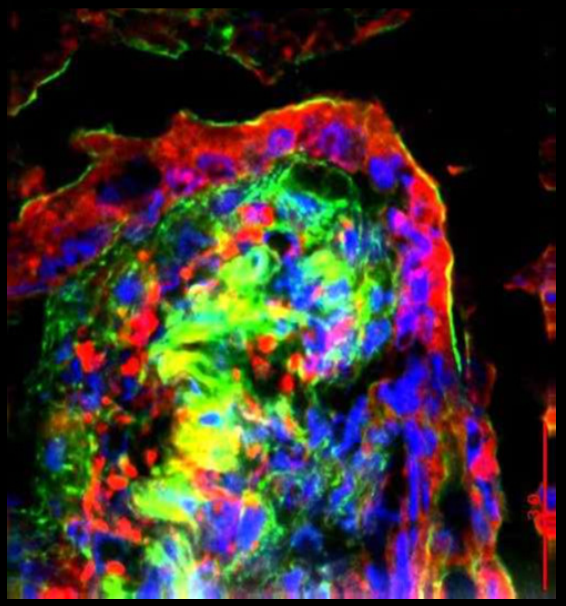


Glutamine

Arginine

Nucleotides

Omega-3 fatty acids



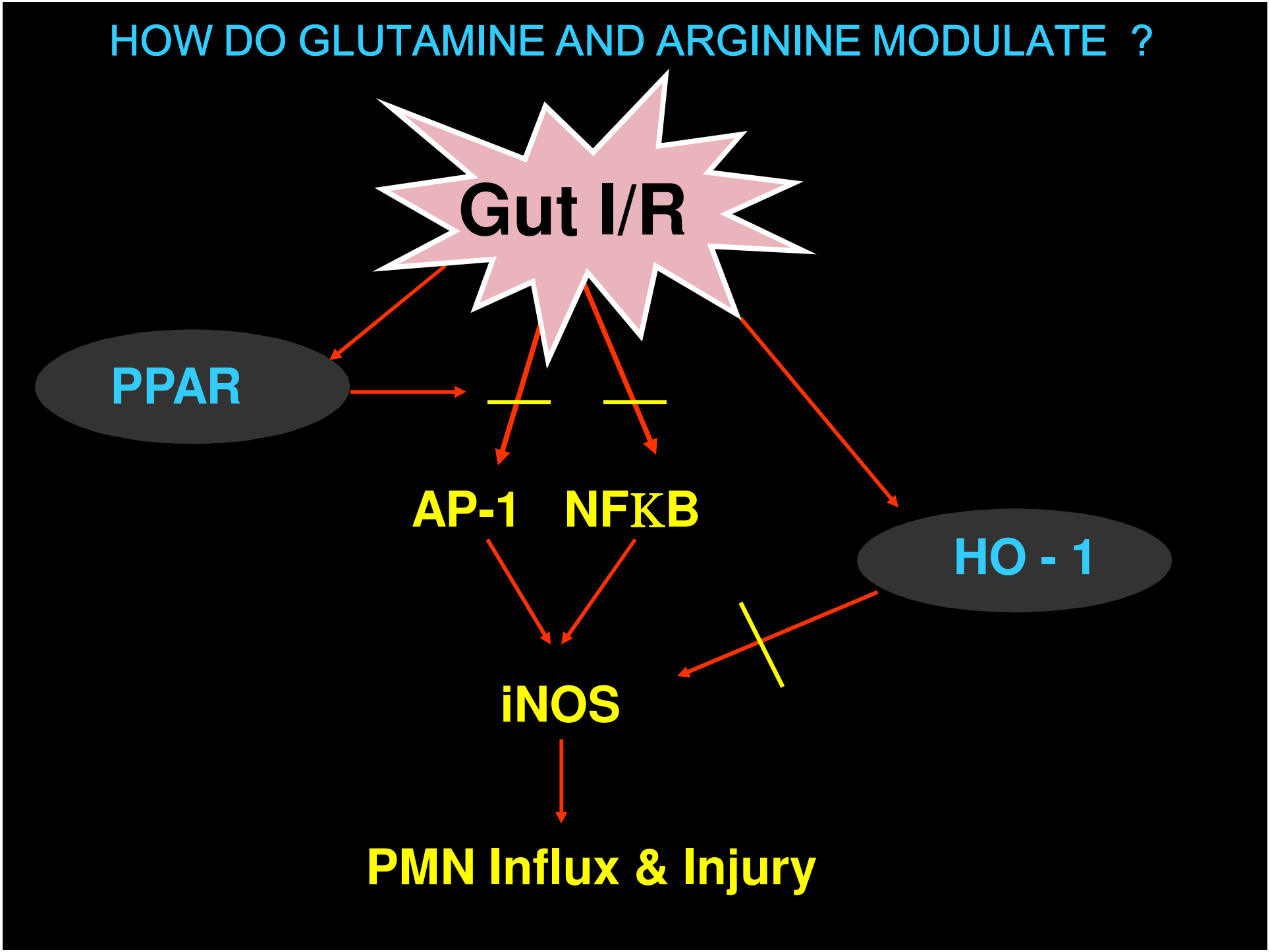
Protected

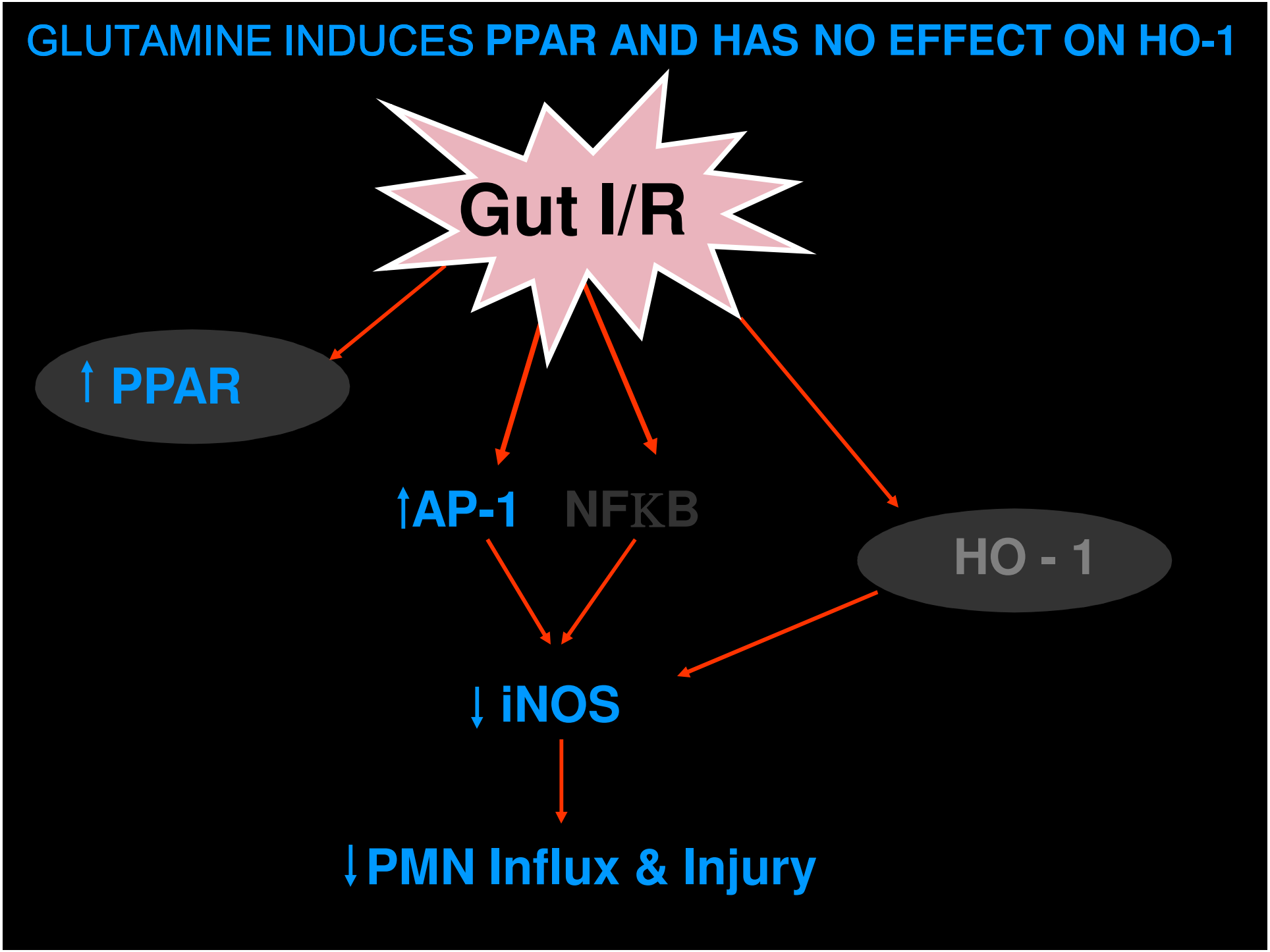
Injurious

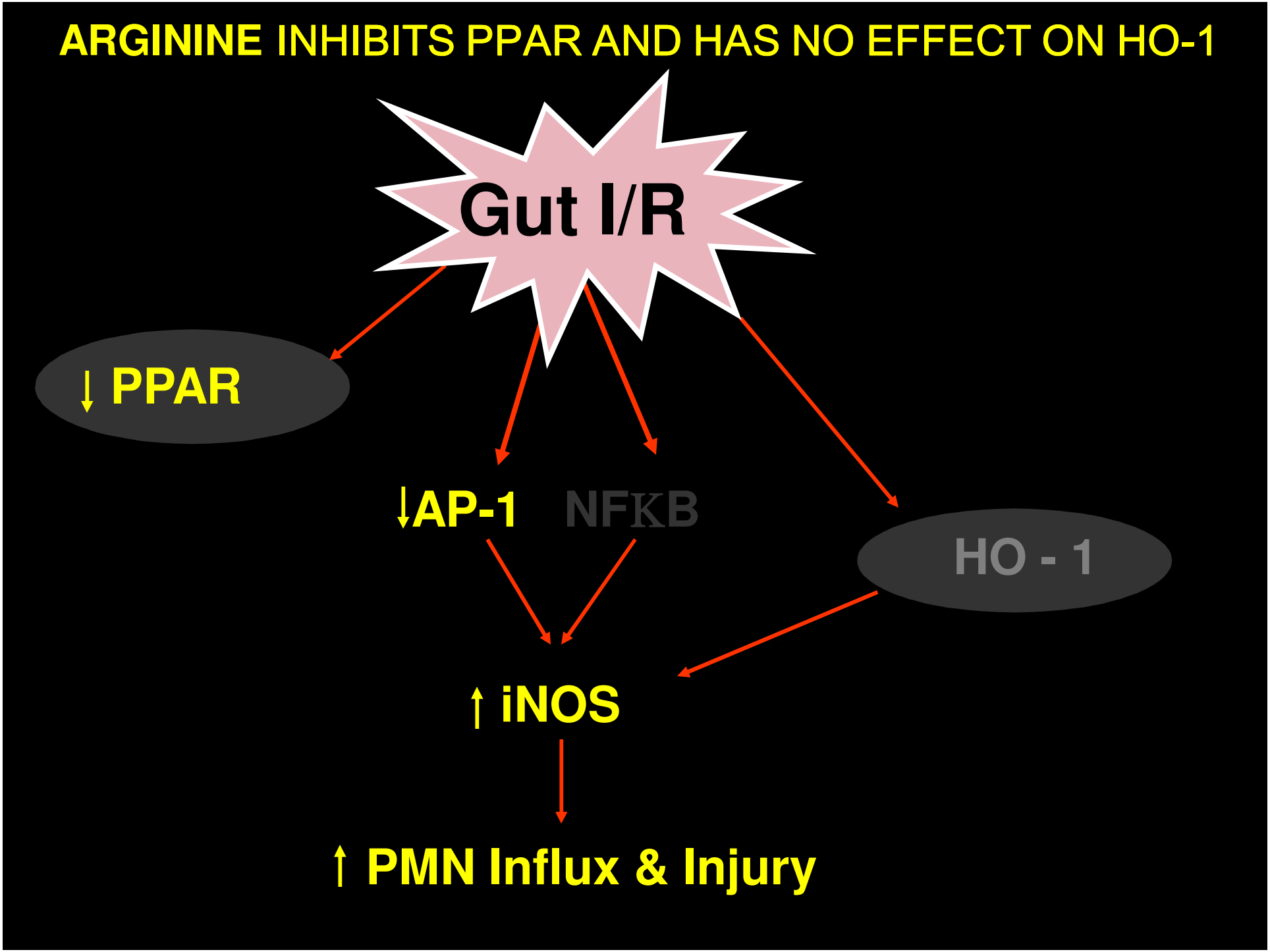
CLINICAL BENEFITS OF AN IMMUNE-ENHANCING DIET FOR EARLY POSTINJURY ENTERAL FEEDING

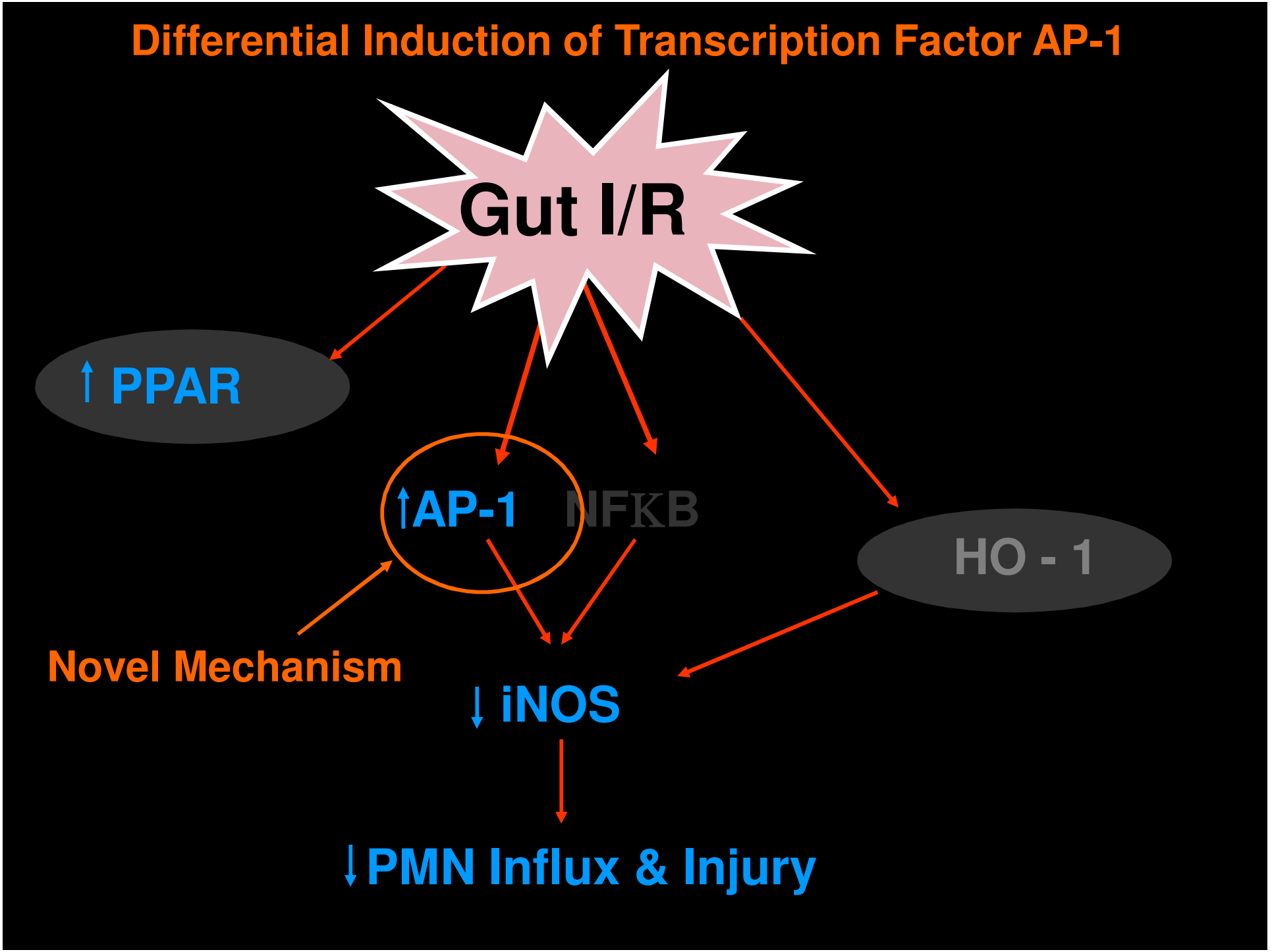
Frederick A. Moore, MD,[a] Ernest E. Moore, MD,[a] Kenneth A. Kudsk, MD,[b] Rex O. Brown, PharmD,[b] Robert H. Bower, MD,[c] Mark J. Koruda, MD,[d] Christopher C. Baker, MD,[d] and Adrian Barbul, MD[e]

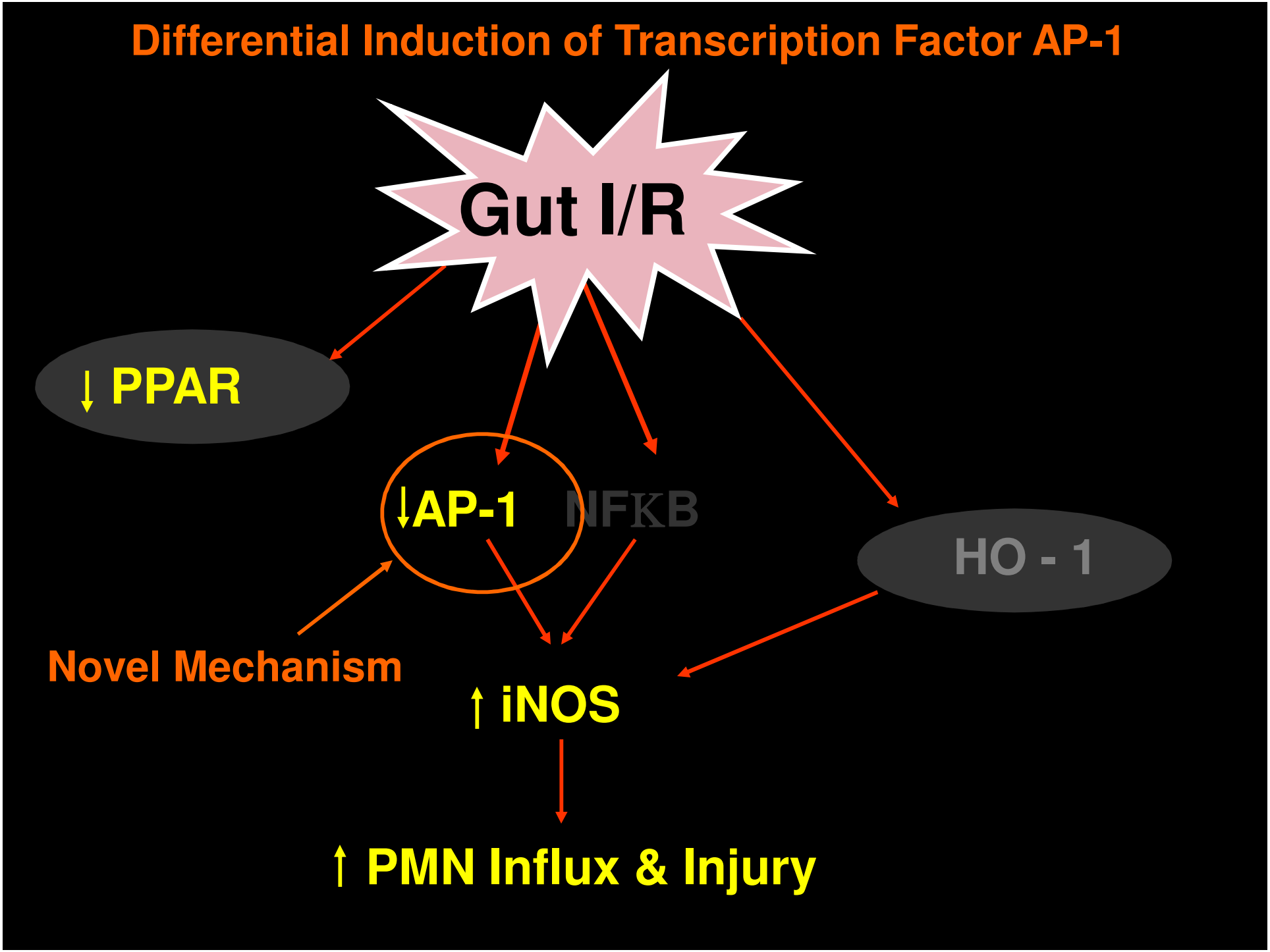
J Trauma 1994


HOW DO GLUTAMINE AND ARGININE MODULATE ?
Gut I/R
PPAR
AP-1
NFKB
HO - 1
iNOS
PMN Influx & Injury


GLUTAMINE INDUCES PPAR AND HAS NO EFFECT ON HO-1
Gut I/R
↑ PPAR
↑AP-1
NFKB
HO - 1
↓ iNOS
↓PMN Influx & Injury


ARGININE INHIBITS PPAR AND HAS NO EFFECT ON HO-1
Gut I/R
↓ PPAR
↓AP-1
NFKB
HO - 1
↑ iNOS
↑ PMN Influx & Injury


Differential Induction of Transcription Factor AP-1
Gut I/R
↑ PPAR
↑AP-1
NFKB
HO - 1
Novel Mechanism
↓ iNOS
↓PMN Influx & Injury


Differential Induction of Transcription Factor AP-1
Gut I/R
↓ PPAR
↓AP-1
NFKB
HO - 1
Novel Mechanism
↑ iNOS
↑ PMN Influx & Injury

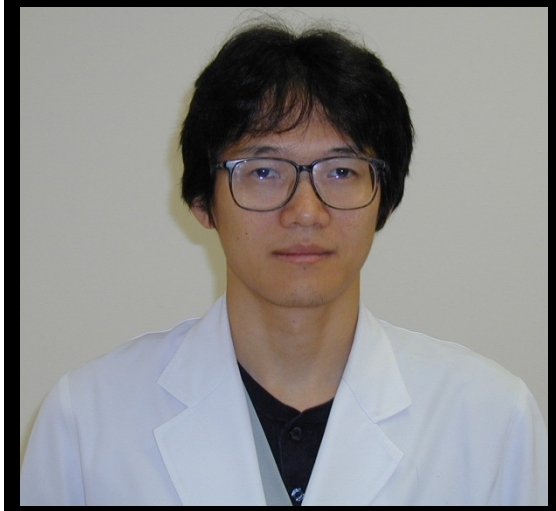
Differential induction of PPAR-γ by luminal glutamine and iNOS by luminal arginine in the rodent postischemic small bowel

N. Sato,[1] F. A. Moore,[1] B. C. Kone,[2] L. Zou,[2] M. A. Smith,[1] M. A. Childs,[1] S. Moore-Olufemi,[1] S. G. Schultz,[3] and R. A. Kozar[1]

Am J Physiol 2006

Funded R-01 Grant - 2007

Norio Sato



Glutamine activates PPAR γ via the LOX pathway

Arginine inhibits PPAR γ via the c-jun pathway

Enteral Glutamine During Active Shock Resuscitation Is Safe and Enhances Tolerance

Margaret McQuiggan, MS,RD; Rosemary Kozar, MD,PhD; R Matthew Sailors; Chul Ahn, PhD
Bruce McKinley, PhD; and Frederick A. Moore, MD

JPEN 2007

Maggie McQuiggan

Translational Research Project

Pilot Validation Study

Prospective & Randomized

Enteral Feeding Protocol Started After Shock Resuscitation

# of Intolerance Episodes	Early Glutamine (n=10)	Control (n=10)	
Diarrhea	0	2	
Vomiting	0	5	
High nasogastric output	5	23	*
Abdominal distention	3	12	*
Total instances of intolerance	8	42	*
# Patients requiring TPN PID #7	0	4	*

* $p < 0.05$


UT★HOUSTON
MEDICAL SCHOOL
HERMANN HOSPITAL
HH

The Methodist Hospital (TMH)

Chief of Acute Care Surgery 2006 - 2011

THE AMERICAN BOARD OF SURGERY
1617 John F. Kennedy Boulevard, Suite 860, Philadelphia, Pennsylvania 19103-1847
(215) 568-4000 FAX: (215) 563-5718 Internet: http://www.absurgery.org

March 1, 2004

H. Gill Cryer, M.D., President
American Association for the Surgery of Trauma (AAST)
Gregory J. Jurkovich, M.D., Chairman
AAST Committee for the Specialty of Trauma, Surgical Critical Care and Emergency Surgery
UCLA Medical Center
Department of Surgery
10833 LeConte Avenue, CH5 72-178
Los Angeles, CA 90024

Dear Gill and Greg:

I apologize for the very slow response to your letter of December 23 but your request has led to a great deal of discussion within the Board both during our January Meeting and in the period subsequently on a more informal basis. Your request for an Advisory Council to represent Trauma and Critical Care has stimulated a broader discussion of the general procedure for evolving new Advisory Councils in other areas, and has pointed out the need for us to have some specific guidelines for dealing with this on a continuing basis. At the January Meeting, the Board adopted a resolution to become more heavily involved in the oversight of post-residency fellowship training and the development of Advisory Councils in various areas will be a part of this entire plan. Chairman Ron Maier is appointing a group of Directors who will specifically meet to formulate guidelines for this in the next several weeks and then bring this issue back to the Board at its meeting in June. Hopefully, they will be in a position to be adopted at that time, so we can go forward with the creation of additional Advisory Councils. I think it is extremely likely that an Advisory Council in the area of Trauma, Critical Care, and Emergency Surgery will be created once these guidelines are formulated. At that time, we would look forward to sitting down with representatives of the AAST to determine the specifics of that structure.

In the meantime, I urge you to consider within your organization the way in which trauma surgery, surgical intensive care, and emergency surgery can be combined, and how each of these areas should be represented within the structure of the American Board of Surgery. Although each is closely related to the other, they are not synonymous, and our current processes for issuing certificates in Surgical Critical Care do not entirely meet the needs of the other two areas. If the AAST could help with the development of a cohesive plan for integrating and addressing these it would be helpful to the Board as well.

If you want to discuss this further, please give me a call at any time. The Board is entirely sympathetic with your request and looks forward to entering into a productive dialogue in order to move the issue forward.

Sincerely,

Frank R. Lewis, Jr., M.D.
Executive Director

Barbara Bass

New TMH Chair

Division of Surgical Critical Care and Acute Care Surgery

Joe Sucher

Krista Turner

Laura Moore

Rob Todd

Division of Surgical Critical Care and Acute Care Surgery

Barbara asked: “what is going to be your research focus”

Sepsis in general surgery: a deadly complication

Laura J. Moore, M.D., Frederick A. Moore, M.D., Stephen L. Jones, M.D., Jiaqiong Xu, Ph.D., Barbara L. Bass, M.D.

Am J Surg 2009

n=363,897 Patients	Incidence	30-Day Mortality
No Sepsis	96.1%	1.1%
Sepsis	2.3%	5.4%
Severe Sepsis/Shock	1.6%	34%
Pulmonary Embolism	0.3%	9.1%
Myocardial Infarction	0.2%	32%

NSQIP 2005-2007 Database Analysis General Surgery

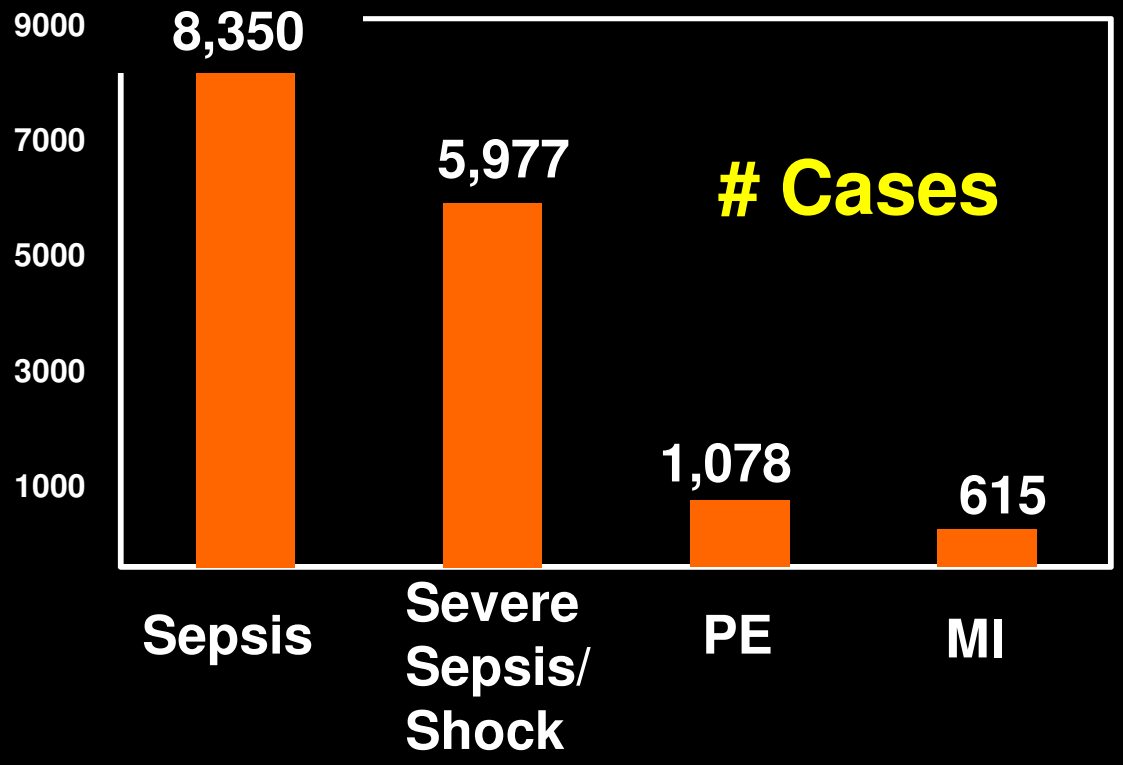
Sepsis in general surgery: a deadly complication

Laura J. Moore, M.D., Frederick A. Moore, M.D., Stephen L. Jones, M.D., Jiaqiong Xu, Ph.D., Barbara L. Bass, M.D.

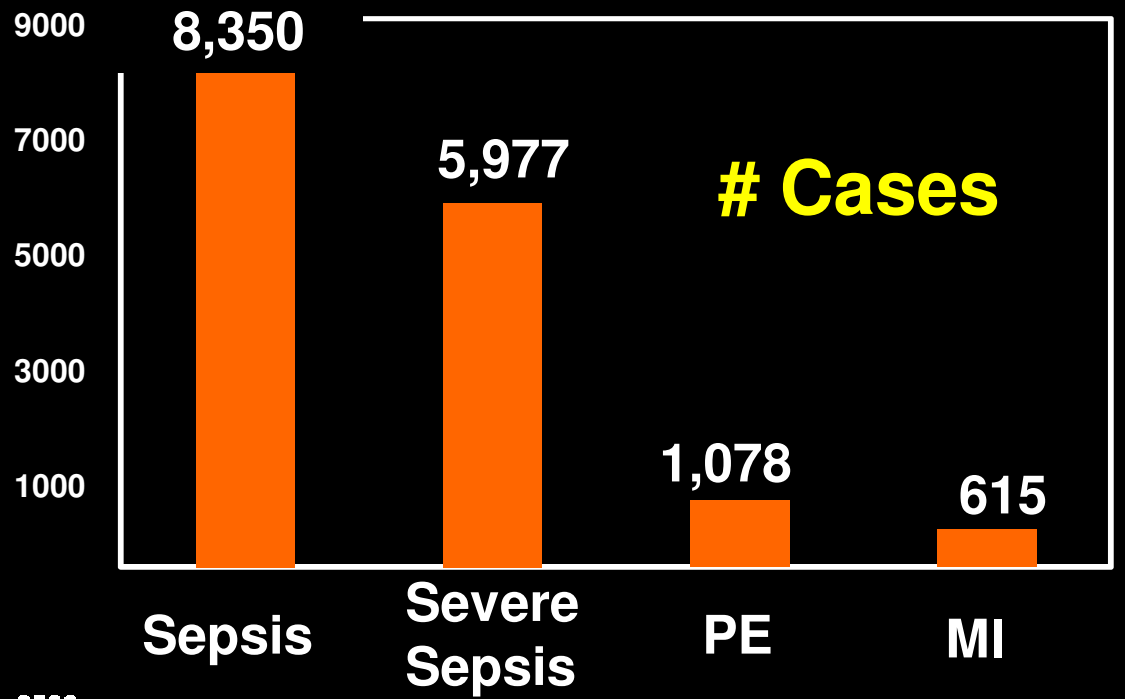
Am J Surg 2009

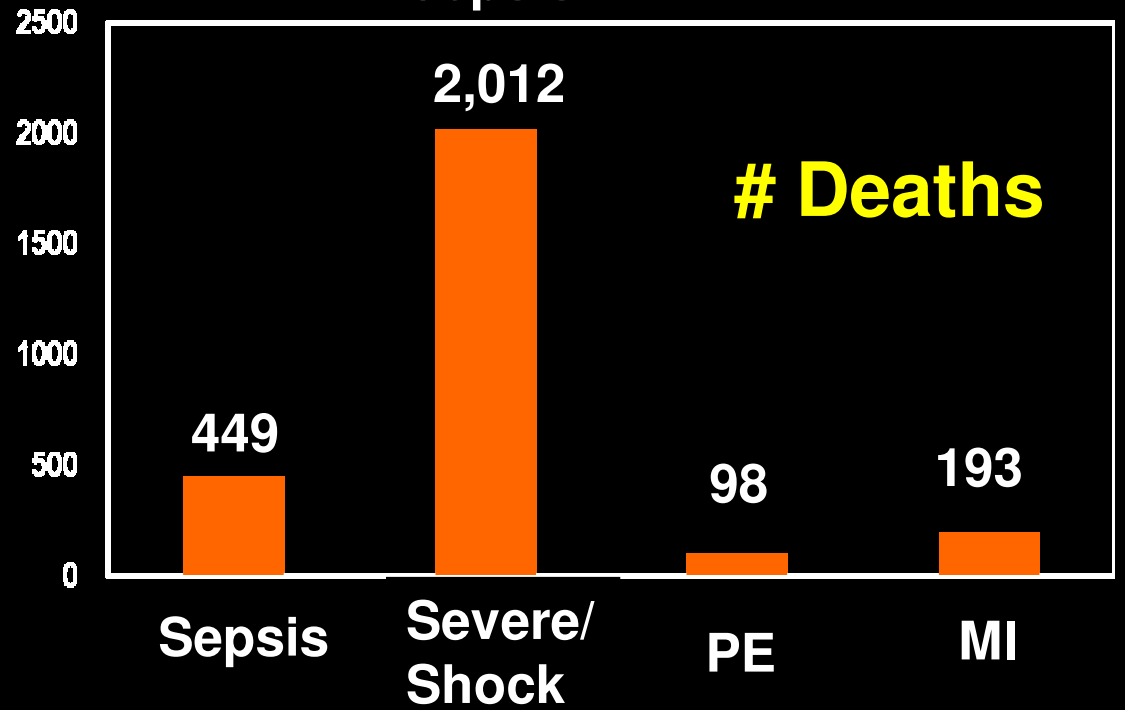
n=363,897 Patients	Incidence	30-Day Mortality
No Sepsis	96.1%	1.1%
Sepsis	2.3%	5.4%
Severe Sepsis/Shock	1.6%	34%
Pulmonary Embolism	0.3%	9.1%
Myocardial Infarction	0.2%	32%

NSQIP 2005-2007 Database Analysis General Surgery


9000
7000
5000
3000
1000
8,350
5,977
1,078
615
Cases
Sepsis
Severe Sepsis/ Shock
PE
MI

Do The Math


9000
7000
5000
3000
1000
8,350
5,977
1,078
615
Cases
Sepsis
Severe Sepsis
PE
MI


2500
2000
1500
1000
500
0
449
2,012
98
193
Deaths
Sepsis
Severe/ Shock
PE
MI

Linda Moore

Krista Turner

Joe Sucher

Rob Todd

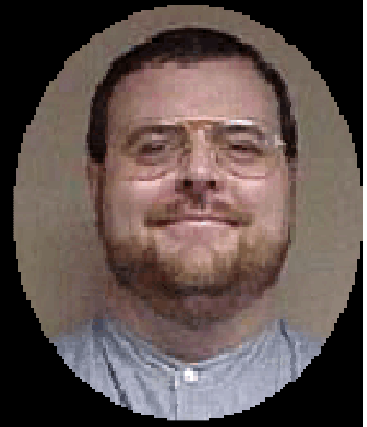
Alicia Valdivia

B McKinley

Nelda Wray

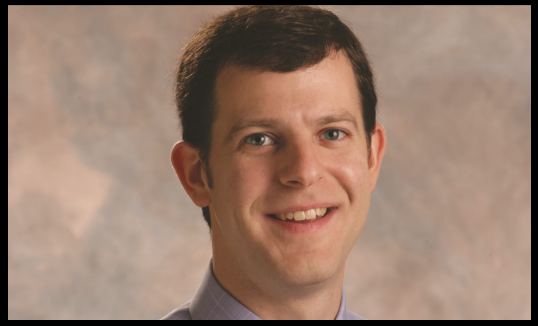
SEPSIS RESEARCH TEAM

Carol Ashton



M. Sailors

Laura Moore



Steve Pass

Steve Jones

Fred Moore

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

Crit Care Med 2004 Vol. 32, No. 3

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis*

Mitchell M. Levy, MD; R. Phillip Dellinger, MD; Sean R. Townsend, MD; Walter T. Linde-Zwirble; John C. Marshall, MD; Julian Bion, MD; Christa Schorr, RN, MSN; Antonio Artigas, MD; Graham Ramsay, MD; Richard Beale, MD; Margaret M. Parker, MD; Herwig Gerlach, MD, PhD; Konrad Reinhart, MD; Eliezer Silva, MD; Maurene Harvey, RN, MPH; Susan Regan, PhD; Derek C. Angus, MD, MPH; on behalf of the Surviving Sepsis Campaign

Crit Care Med 2010

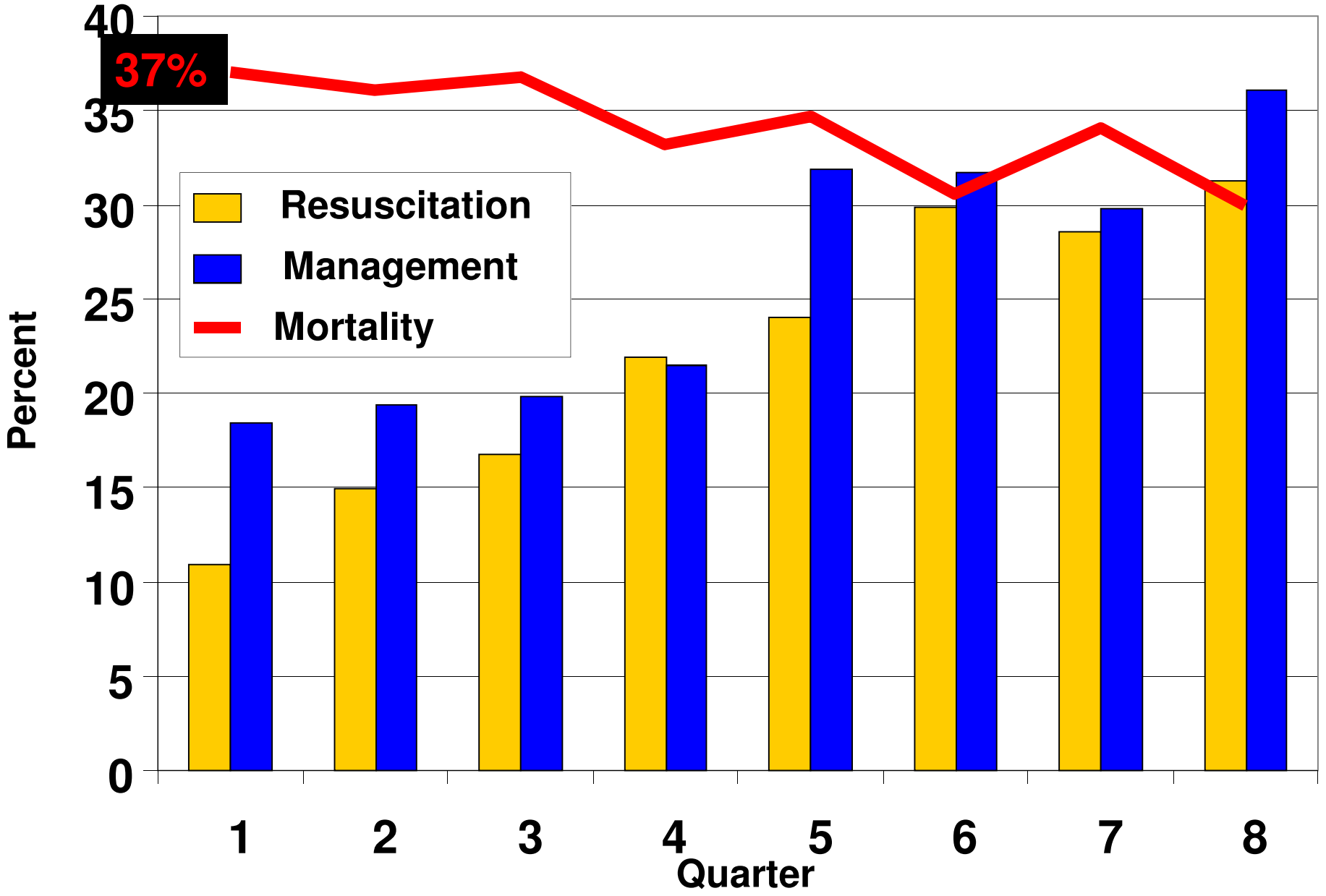
IHI Surviving Sepsis Campaign

Audit of Compliance and Effect on Mortality

(15,002 patients at 166 hospitals over 2 year implementation)

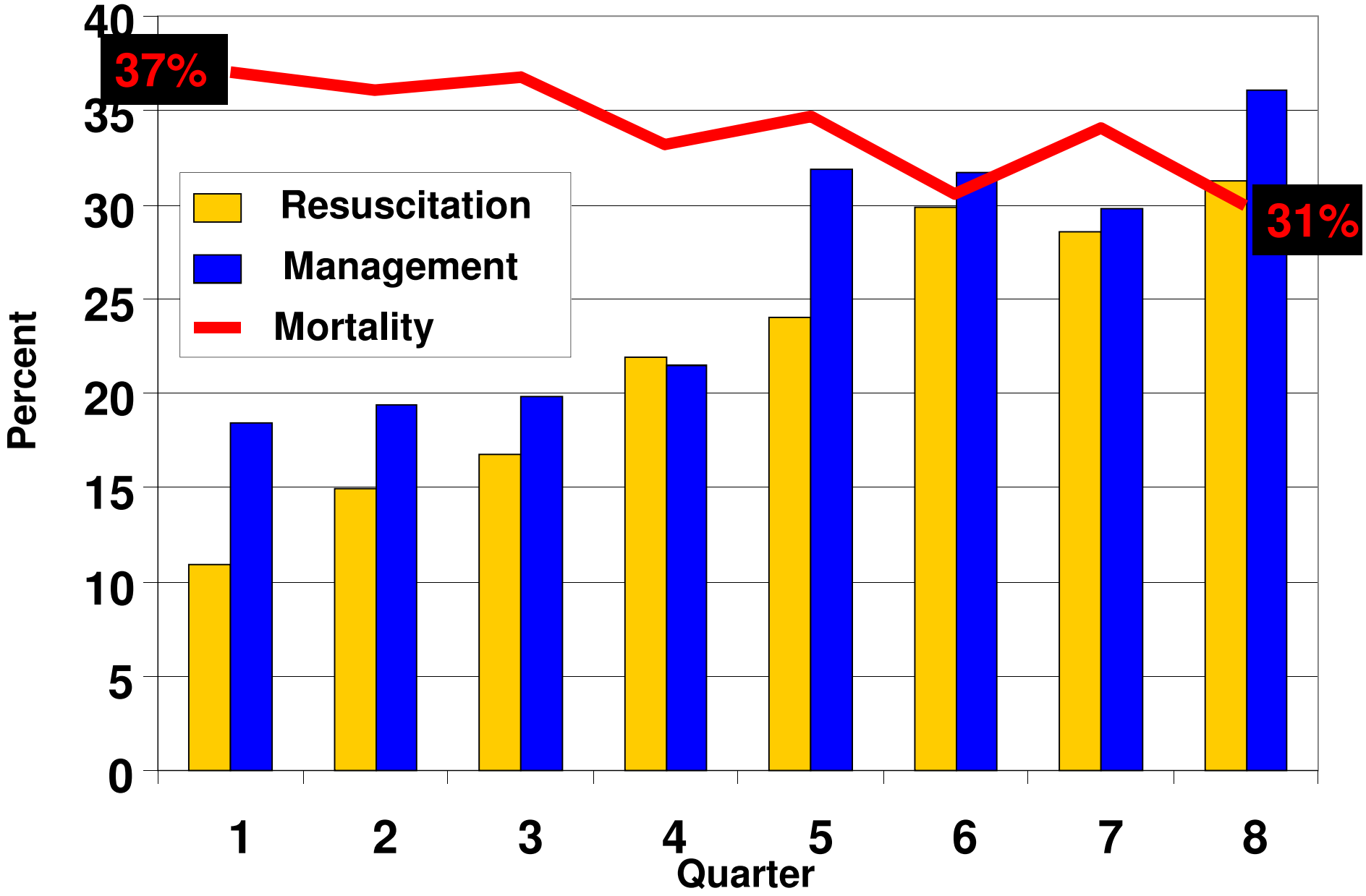
Compliance 6 hr Resuscitation Bundle = 12 %

Compliance 24 hr management Bundle = 18 %



Compliance 6 hr Resuscitation Bundle = 12 % → 32 %

Compliance 24 hr management Bundle = 18 % → 37 %



2/3 of patients did not receive evidence based care

Surviving Sepsis Campaign Guidelines 2008

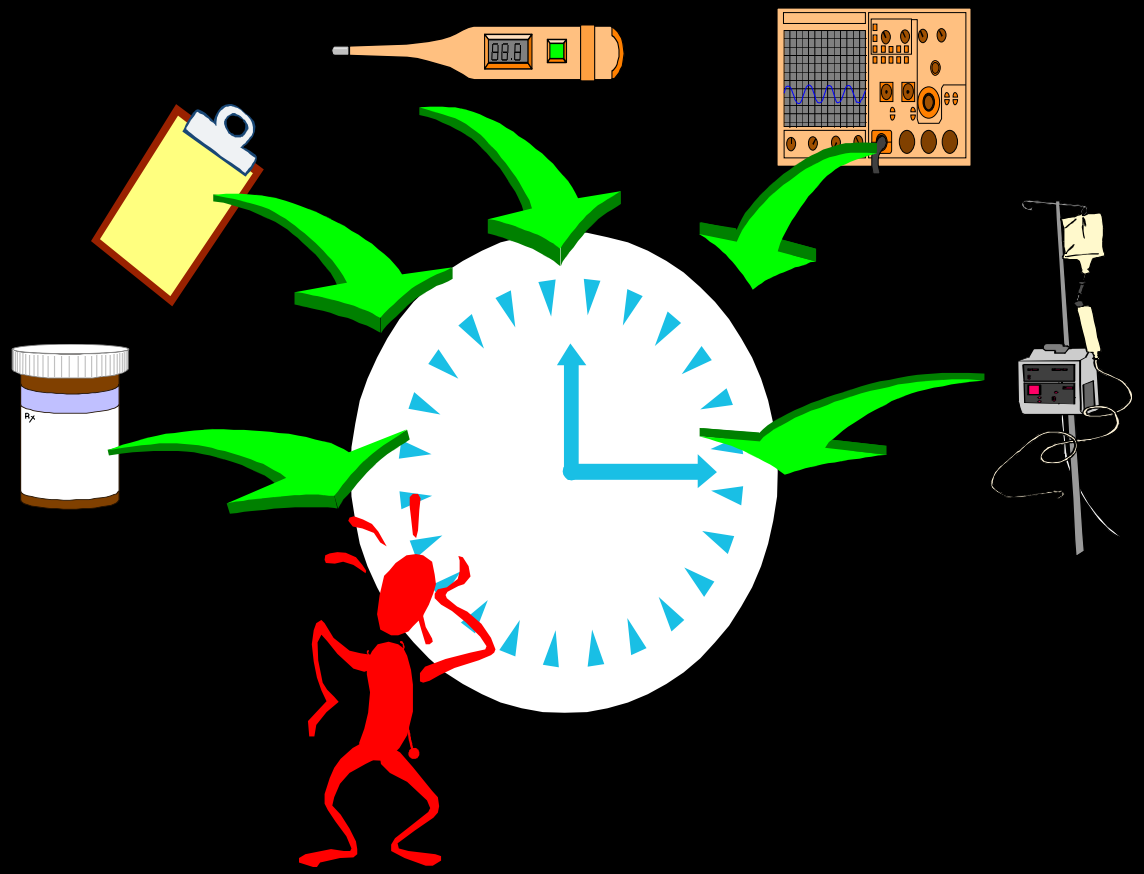
Grades of Evidence

Grade 1A	Grade 1B	Grade 1C	Grade 1D
Vent Weaning SBT Protocol	Broad Spectrum Antibiotics within 1 hour	Early Goal Directed Therapy	Source Control within 6 hours
DVT/PUD Prophylaxis	Conservative Transfusions	Cultures prior to antibiotics	Fluid Challenge for Hypovolemia
No Renal Dose Dopamine	IV Insulin Therapy	Early Source Identification	Limit Antibiotics to 7 -10 days
No High Dose Steroids	Sedation Protocol	De-escalate antibiotic Rx	Consider Limiting Support
	Avoid Bicarbonate	Norepinephrine or Dopamine	
	ALI Vent Protocol		

19 Recommendations

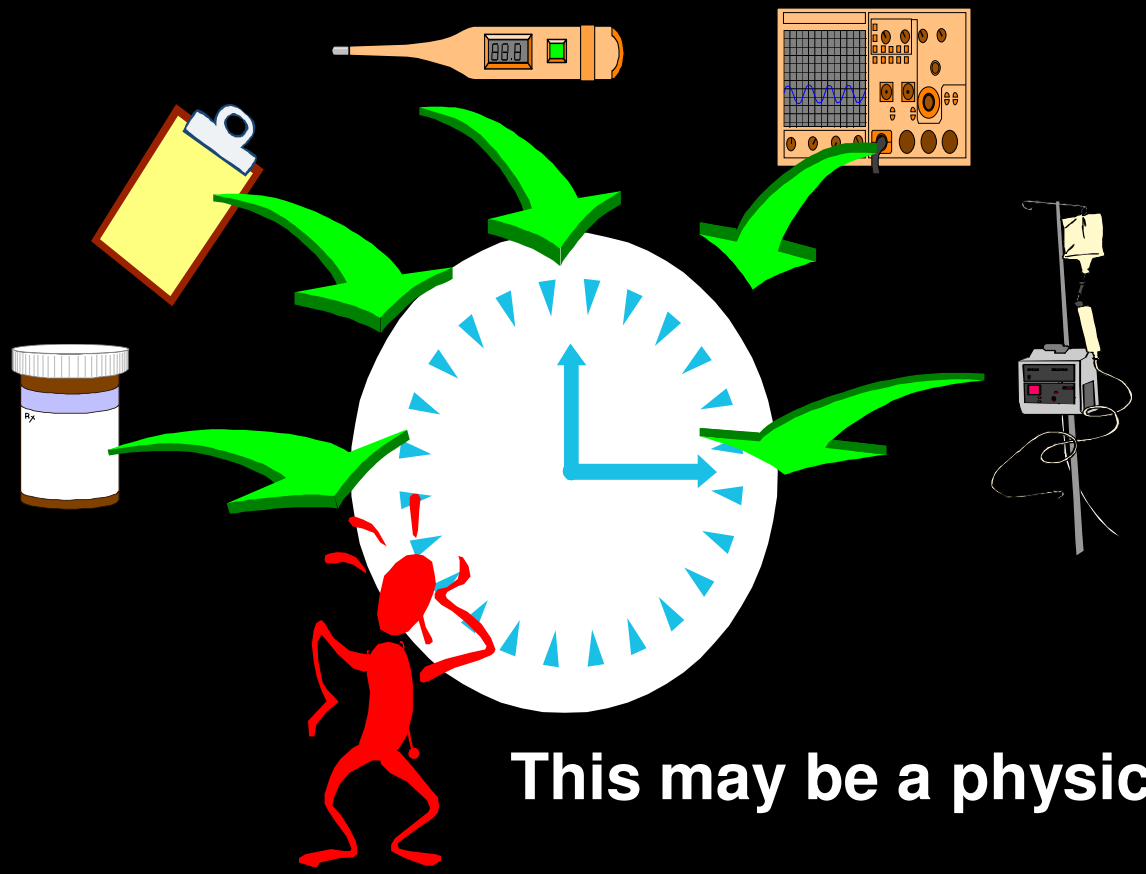
Difficult to Remember and Prioritize 19 Recommendations

Information overload !!!



Difficult to Remember and Prioritize 19 Recommendations

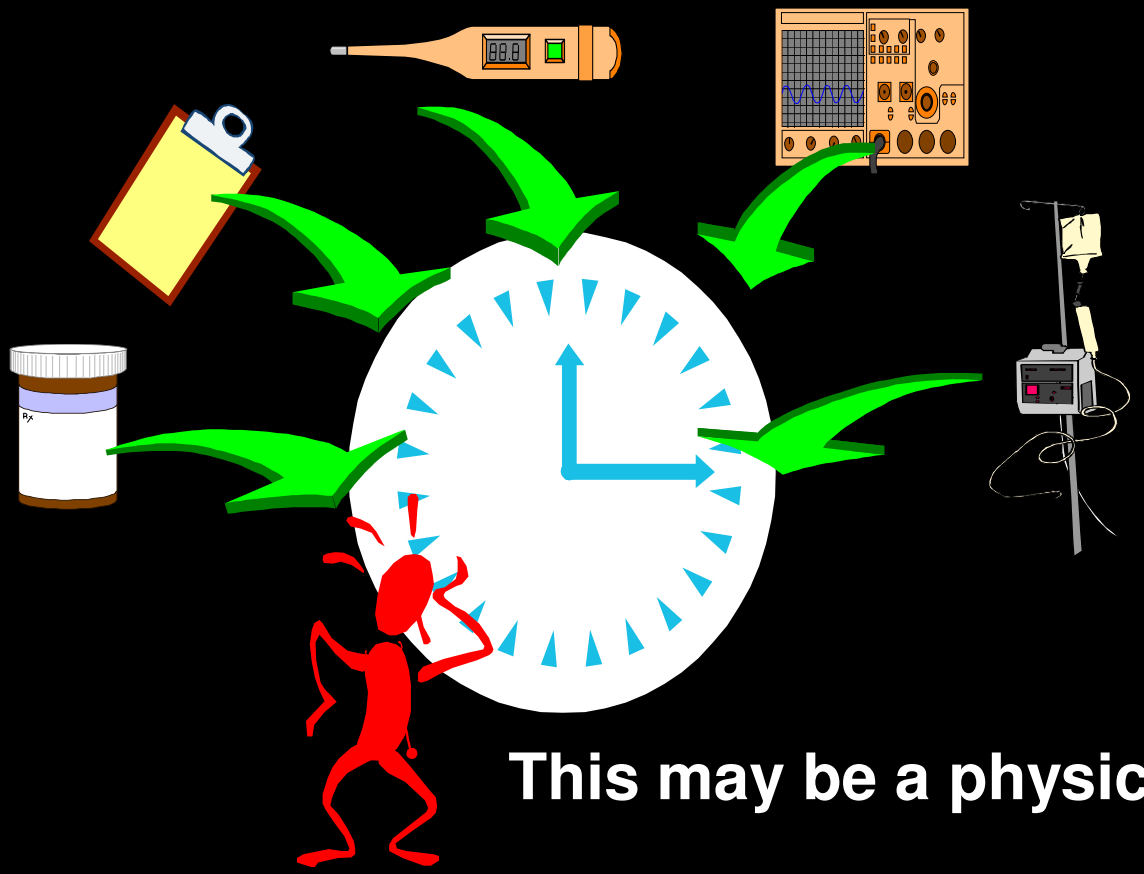
Information overload !!!



This may be a physician extender

Computerized Clinical Decision Support (CCDS)

Potential Solution for this Dilemma



This may be a physician extender

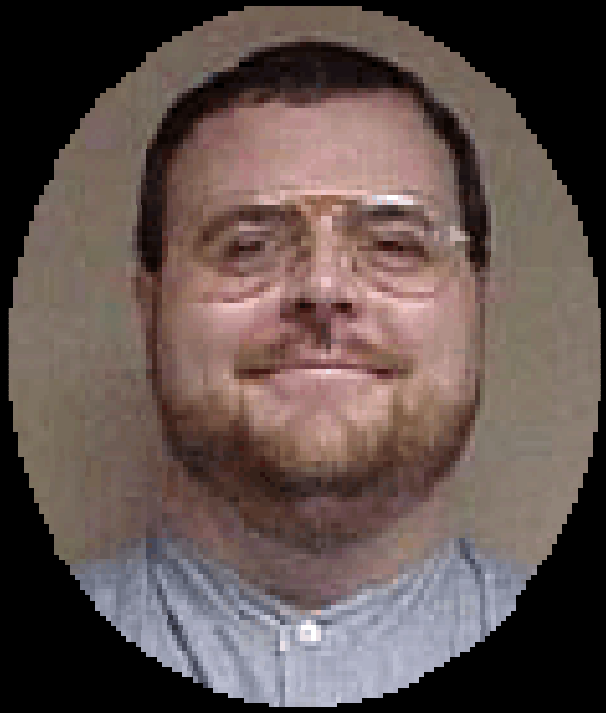
Computerized Decision Support for Mechanical Ventilation of Trauma Induced ARDS: Results of a Randomized Clinical Trial

Bruce A. McKinley, PhD, Frederick A. Moore, MD, R. Matthew Sailors, PhD, Christine S. Cocanour, MD, Alicia Marquez, RN, Roberta K. Wright, RRT, Alan S. Tonnesen, MD, C. Jane Wallace, RN, PhD, Alan H. Morris, MD, and Thomas D. East, PhD

Bruce McKinley

Bioengineer

Matt Sailors



Informatics Expert

Computerized Clinical Decision Support (CCDS)
Proof of Concept

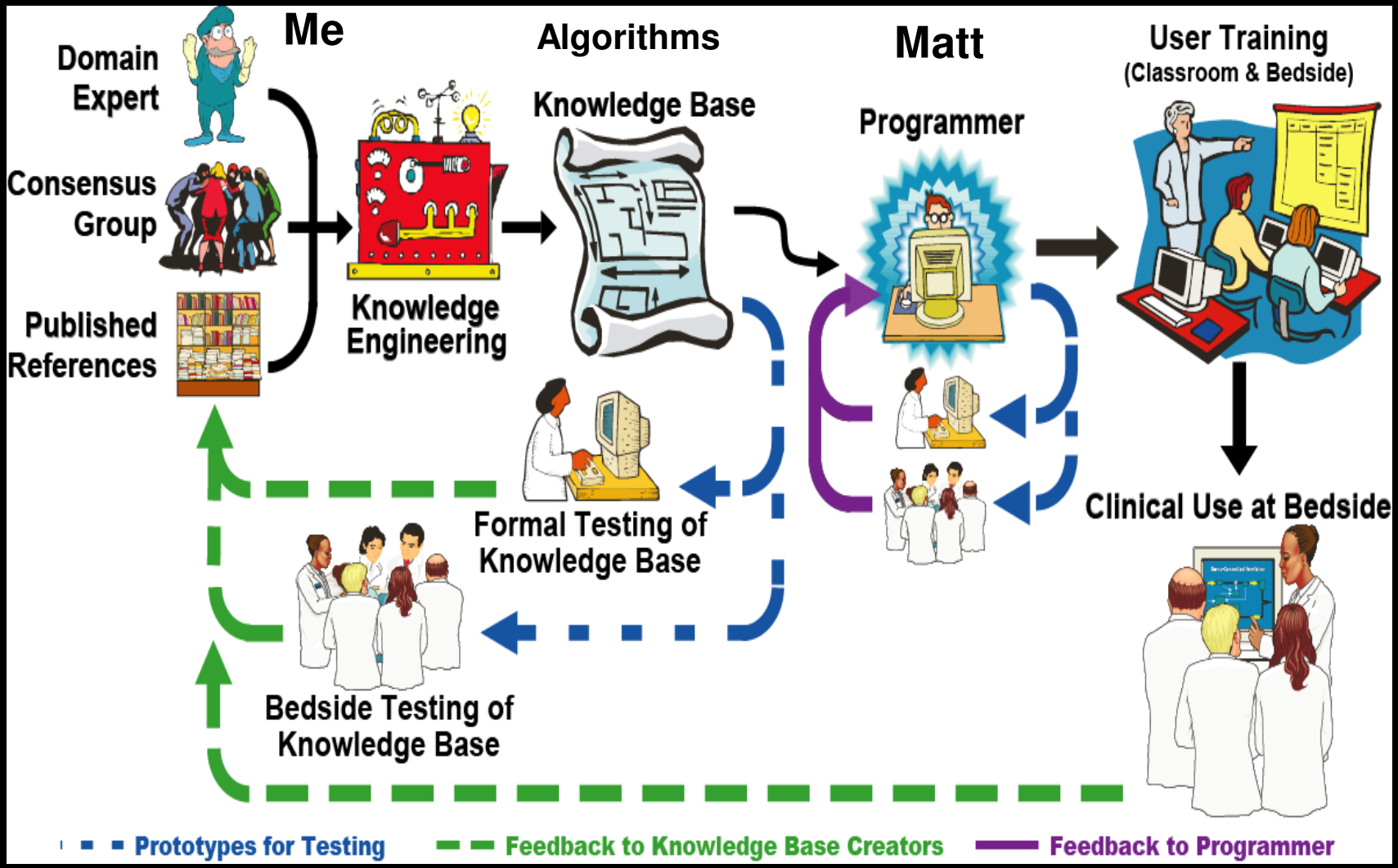
Mechanical ventilation of ARDS

Shock resuscitation

ICP management

Surviving Sepsis Campaign

DEVELOPMENT PROCESS



Fellow Using CCDS Application : Open Loop System

#10: Use CCDS to Control Confounding Variable Care

Difficulty in Diagnosis
Early Signs are not Recognized

A change in mental status: acute delirium

Hyperventilation: respiratory alkalosis

Hypotension & ↓ urine output: need for fluid bolus

Fever or hypothermia (especially in the elderly)

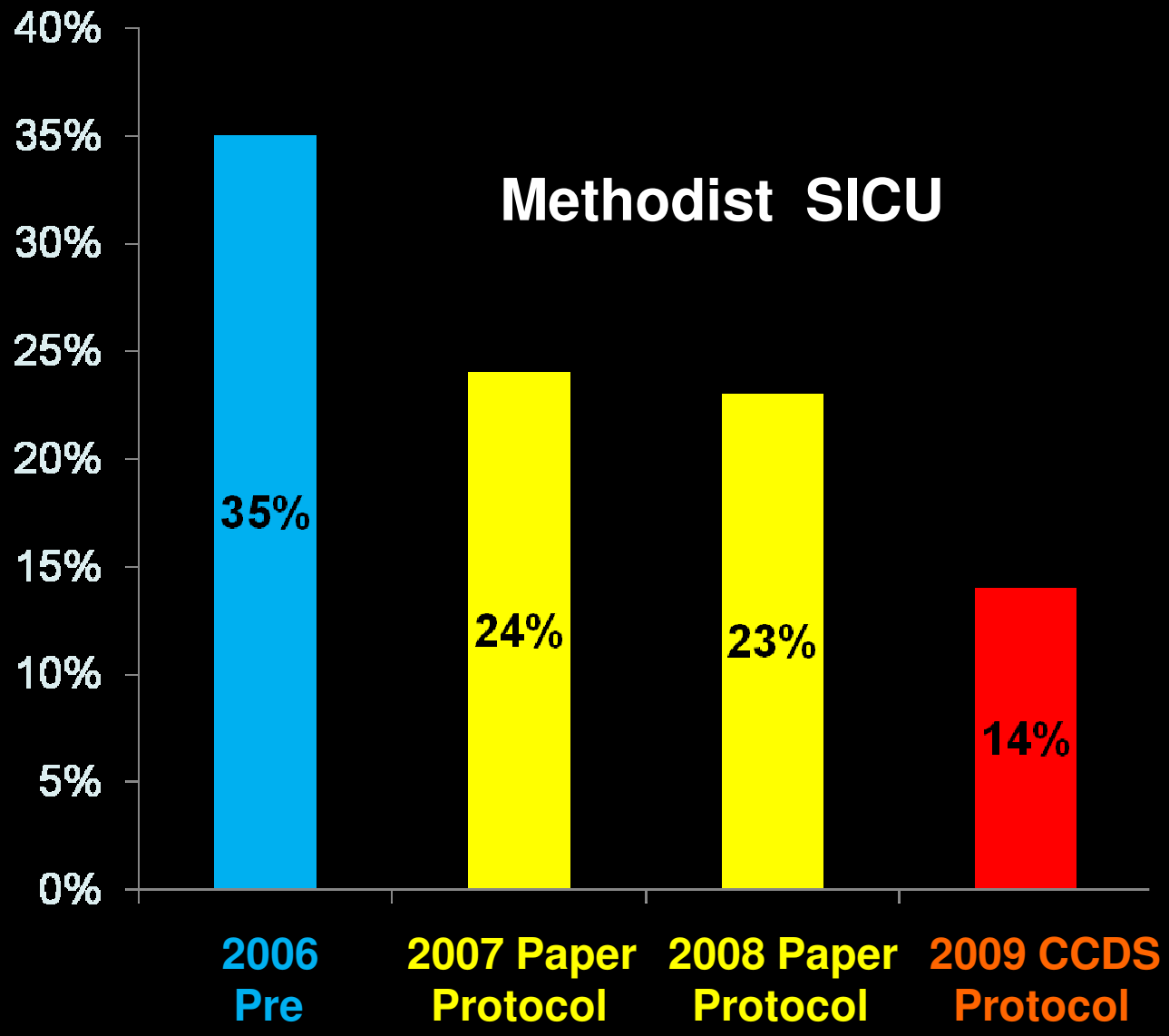
Validation of a Screening Tool for the Early Identification of Sepsis

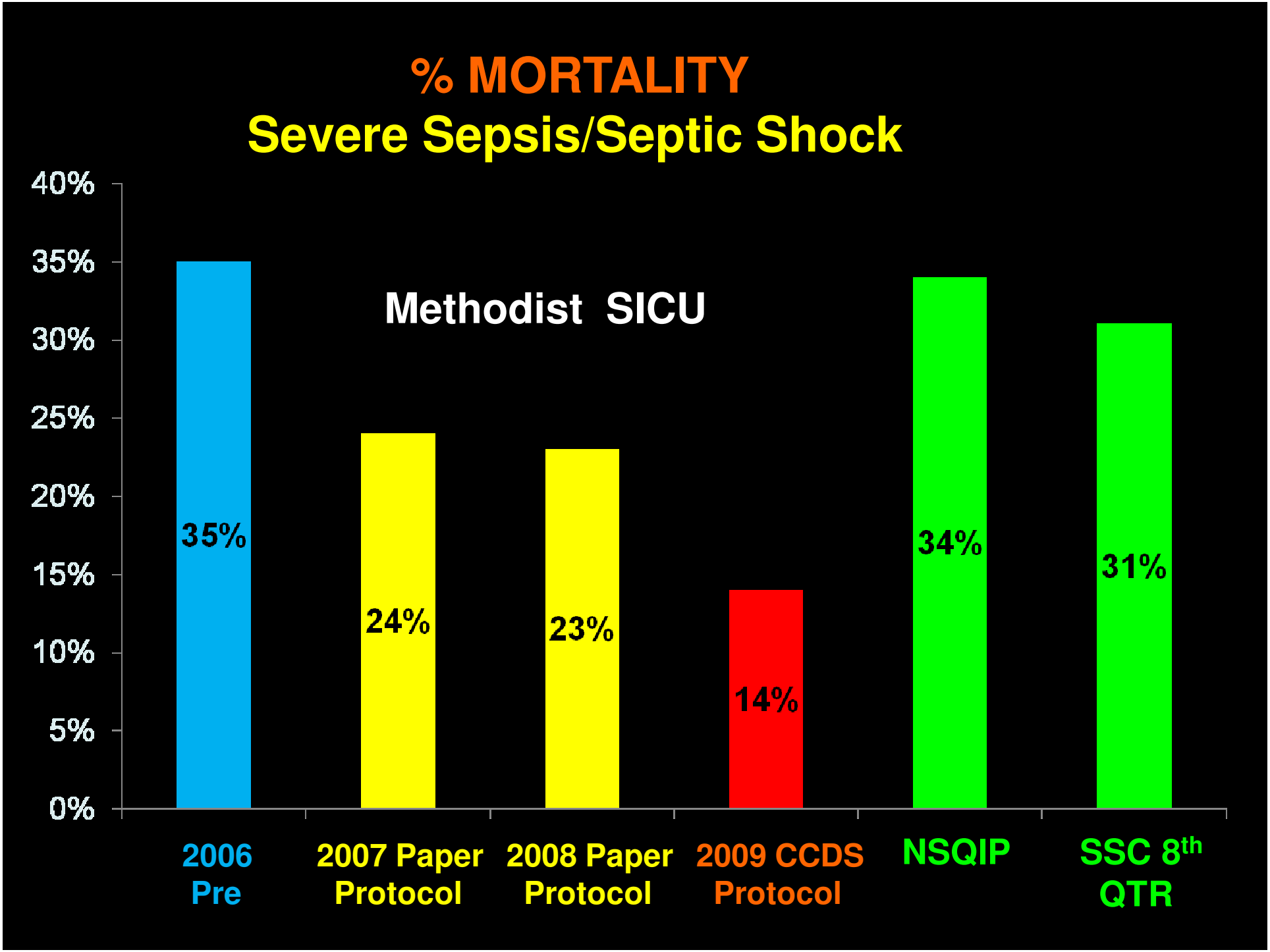
Laura J. Moore, MD, Stephen L. Jones, MD, Laura A. Kreiner, MD, Bruce McKinley, PhD, Joseph F. Sucher, MD, S. Rob Todd, MD, Krista L. Turner, MD, Alicia Valdivia, RN, and Frederick A. Moore, MD

J Trauma 2009

Sepsis Screening Champion

% MORTALITY
Severe Sepsis/Septic Shock




% MORTALITY
Severe Sepsis/Septic Shock
Methodist SICU
40%
35%
30%
25%
20%
15%
10%
5%
0%
35%
24%
23%
14%
34%
31%
2006 Pre
2007 Paper Protocol
2008 Paper Protocol
2009 CCDS Protocol
NSQIP
SSC 8th QTR

Shands Hospital at University of Florida

Chief of Acute Care Surgery – July 2011

Linc Moldawer PhD

Dr NIH Inflammation

Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team

PICS – the New Predominant Phenotype of MOF

A 12-Year Prospective Study of Postinjury Multiple Organ Failure Has Anything Changed?

David J. Ciesla, MD; Ernest E. Moore, MD; Jeffrey L. Johnson, MD; Jon M. Burch, MD; Clay C. Cothren, MD; Angela Sauaia, MD

Denver MOF Database

Arch Surg 2005

Epidemiology of MOF has again changed

2nd Peak in MOF Disappeared (Why ?)

The Changing Pattern and Implications of Multiple Organ Failure after Blunt Injury With Hemorrhagic Shock

Joseph P.Minei, MD; Joseph Cuschieri, MD; Jason Sperry, MD; Ernest E. Moore, MD; Michael A. West, MD, PhD; Brian G. Harbrecht, MD; Grant E. O'Keefe, MD; Mitchell J. Cohen, MD; Lyle L. Moldawer, PhD; Ronald Tompkins, MD, ScD; Ronald V. Maier, MD; the Inflammation and the Host Response to Injury Collaborative Research Program

Glue Grant Database

Crit Care Med 2012

Recognition That Traditional ICU Care is Harmful

- High Tidal Volume Mechanical Ventilation
- Liberal Blood Transfusion Practices
- High Volume Crystalloid Resuscitation
- Intermittent Dialysis
- Early TPN

Late MOF/Deaths are Iatrogenic

More Consistent Implementation of Evidence Based Care

IHI Surviving Sepsis Campaign

Our CCDS for Early Sepsis Management

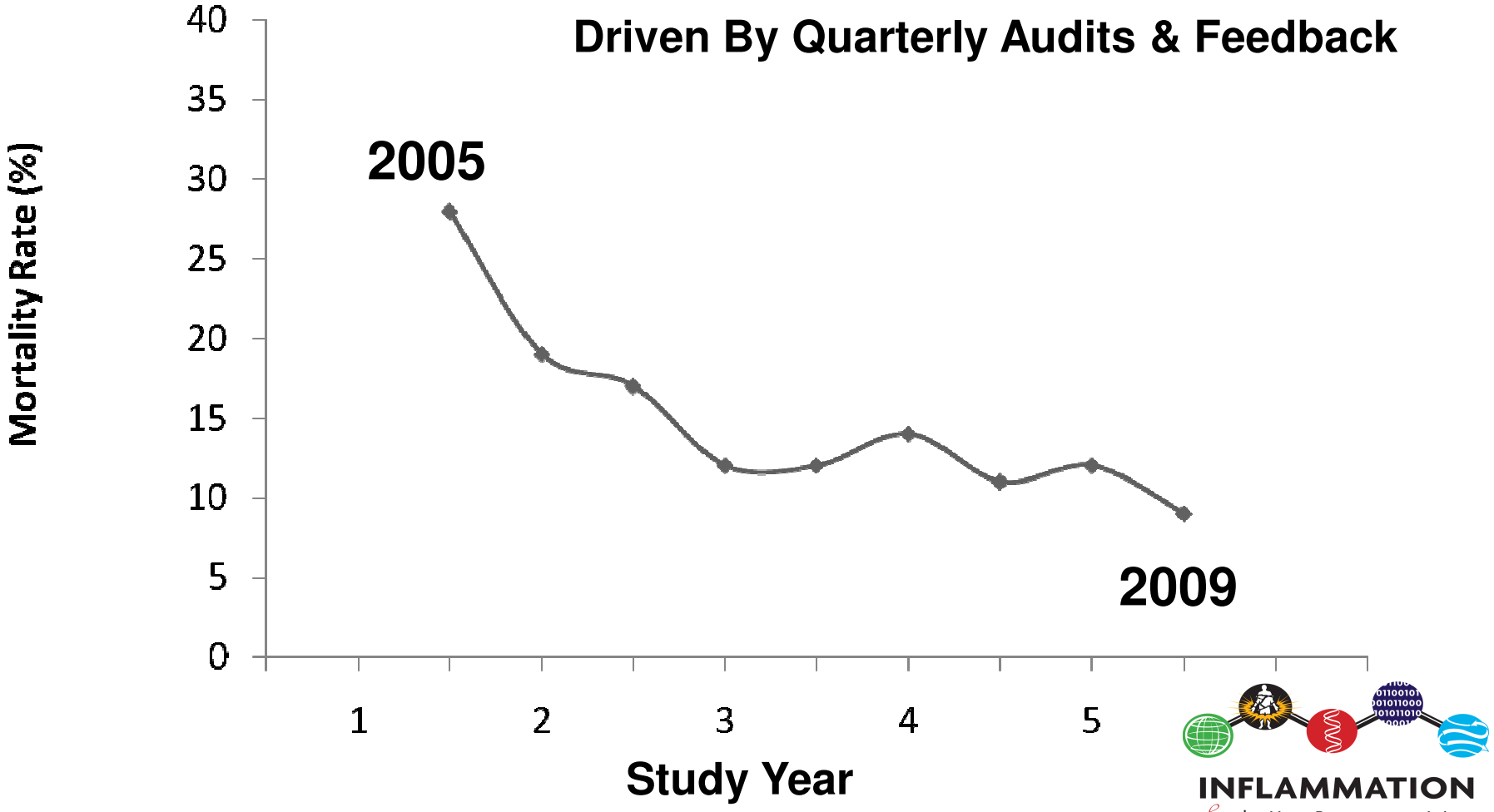
Glue Grant Experience of Increasing SOP Compliance

Benchmarking Outcomes in Critically Injured Trauma Patients

Joseph Cuschieri, MD; Jeffery L.Johnson, MD;Jason Sperry, MD; Michael A. West, M, PhD; Ernest E. Moore, MD; Joseph P.Minei, MD; et.al and the Inflammation and Host Response to Injury Large Scale Collaborative Research Program.

Ann Surg in press

Decreasing Mortality with Increasing Compliance to SOPs



INFLAMMATION & the Host Response to Injury

CARS is not Compensatory
Basic Lab Observations

Circulating Cytokine/Inhibitor Profiles Reshape the Understanding of the SIRS/CARS Continuum in Sepsis and Predict Mortality

Marcin F. Osuchowski, Kathy Welch, Javed Siddiqui, Daniel G. Remick

J Immunology 2006

Simultaneous Pro- & Anti-inflammation

Block Pro-inflammation & Improve Mortality

CARS is not Compensatory
Basic Lab Observations

Circulating Cytokine/Inhibitor Profiles Reshape the Understanding of the SIRS/CARS Continuum in Sepsis and Predict Mortality

Marcin F. Osuchowski, Kathy Welch, Javed Siddiqui, Daniel G. Remick

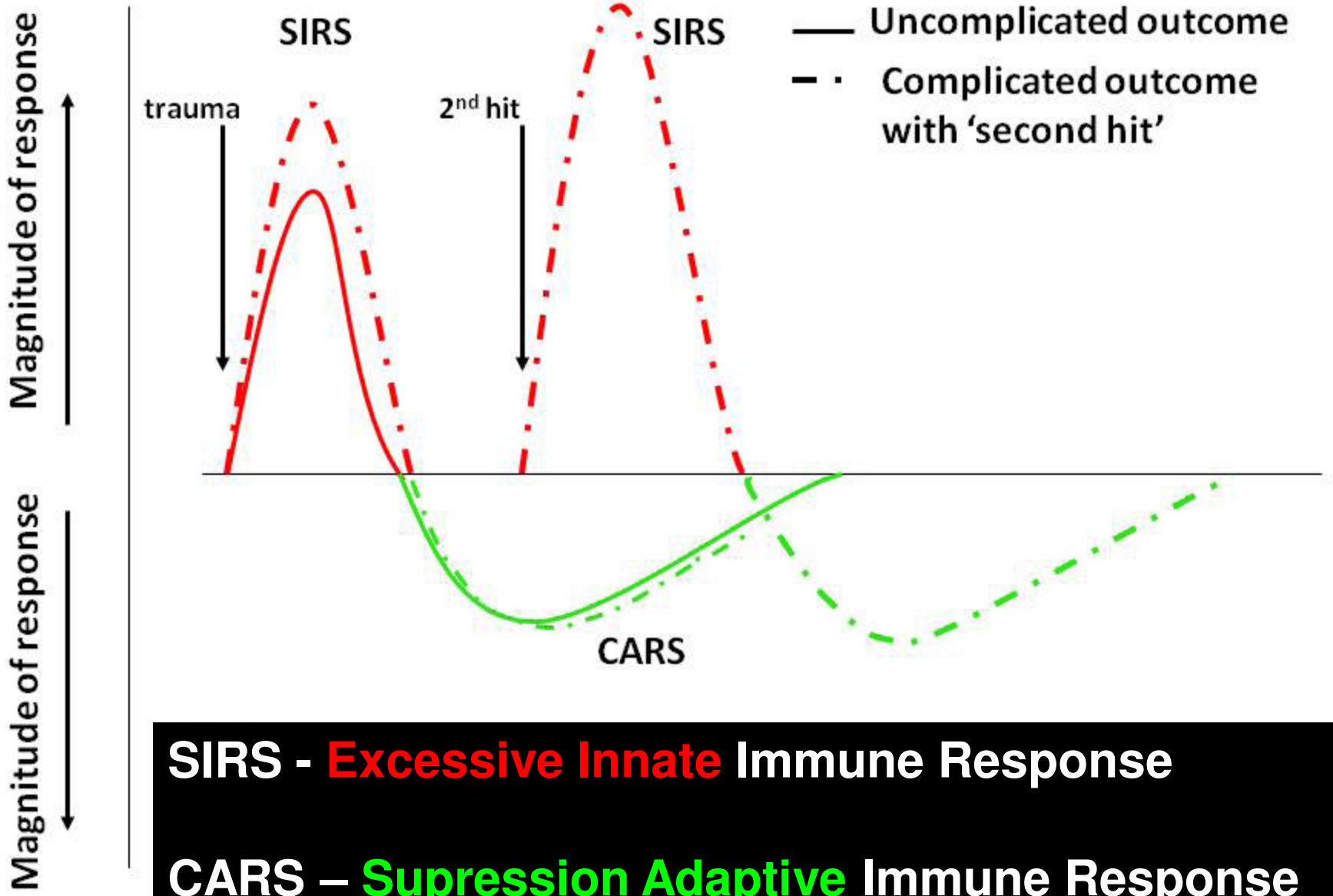
J Immunology 2006

Simultaneous Pro- & Anti-inflammation

Block Pro-inflammation & Improve Mortality

But has no Effect on Anti-inflammation & CARS

Glue Grant Hypothesis Tested in Humans



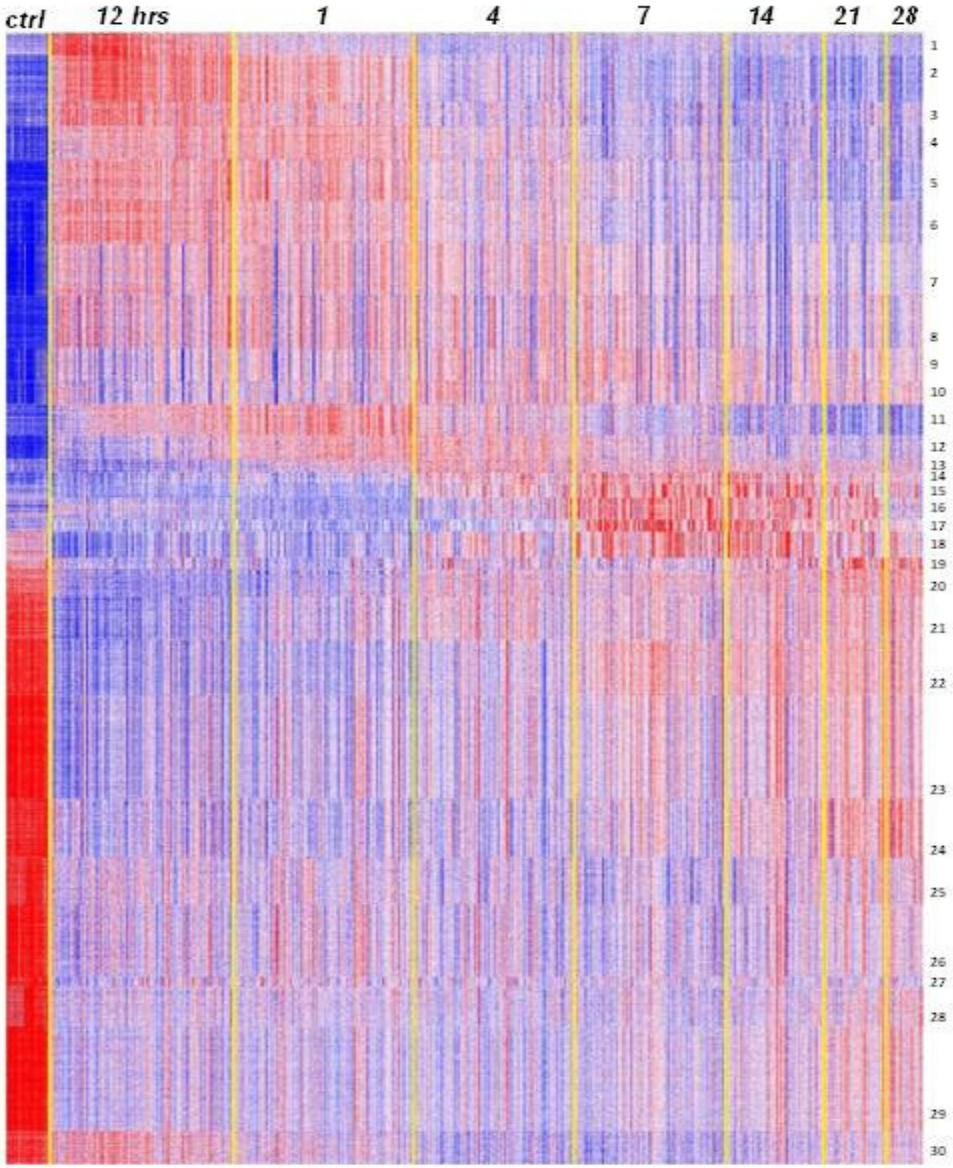
SIRS - Excessive Innate Immune Response

CARS – Supression Adaptive Immune Response

Looking at the Genomic Response After Severe Blunt Trauma

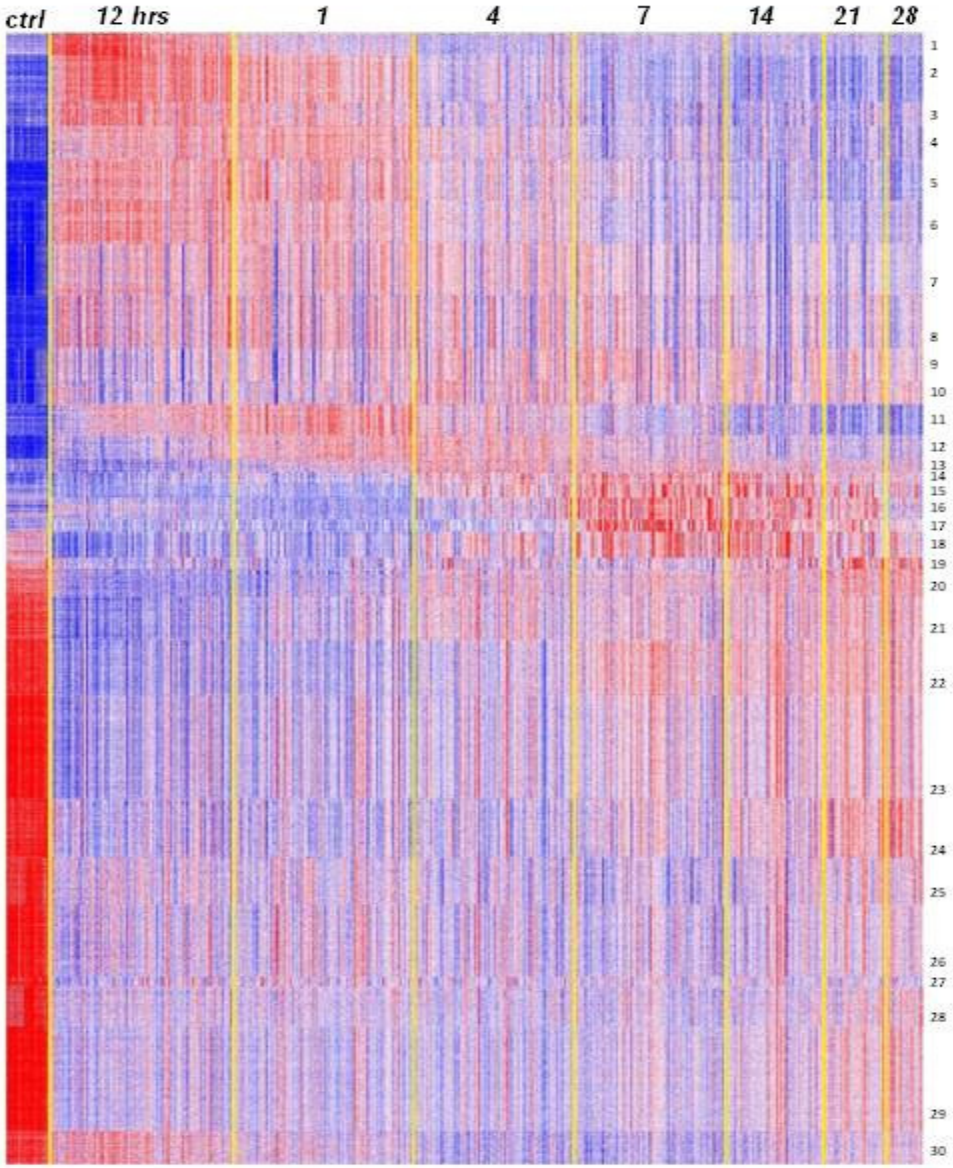
A Genomic Storm – 75% of Genes Up or Down Regulated

A. Heat Map of Gene Expression After Severe Trauma

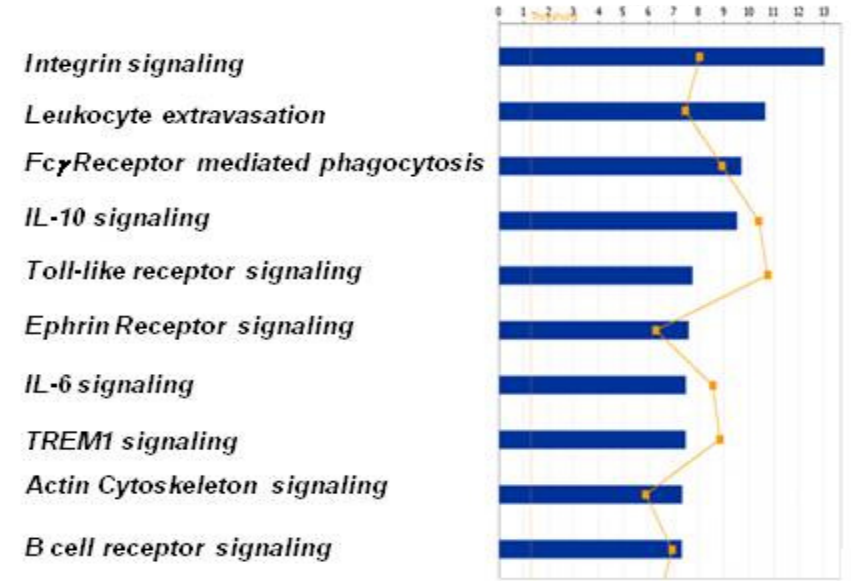


A Genomic Storm – 75% of Genes Up or Down Regulated

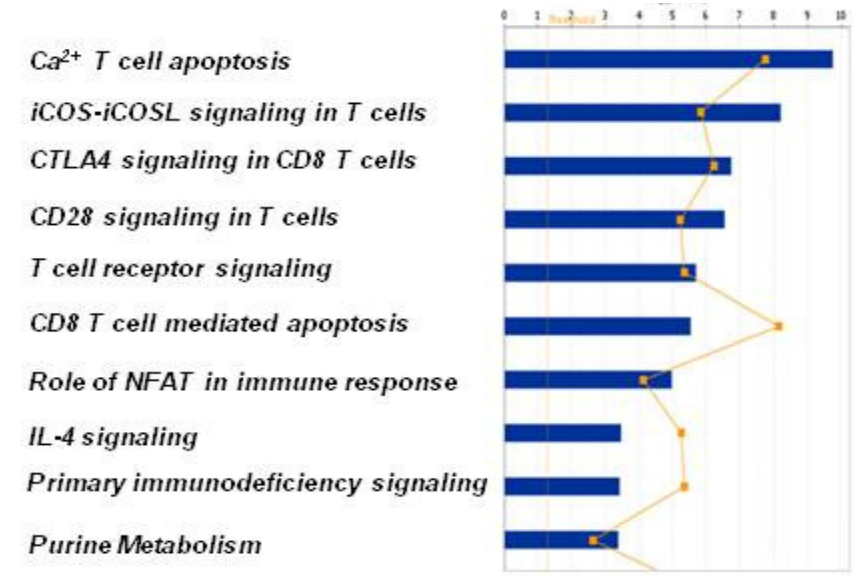
A. Heat Map of Gene expression After Severe Trauma



B. Up-regulated Innate Immunity



C. Down-regulated Adaptive Immunity



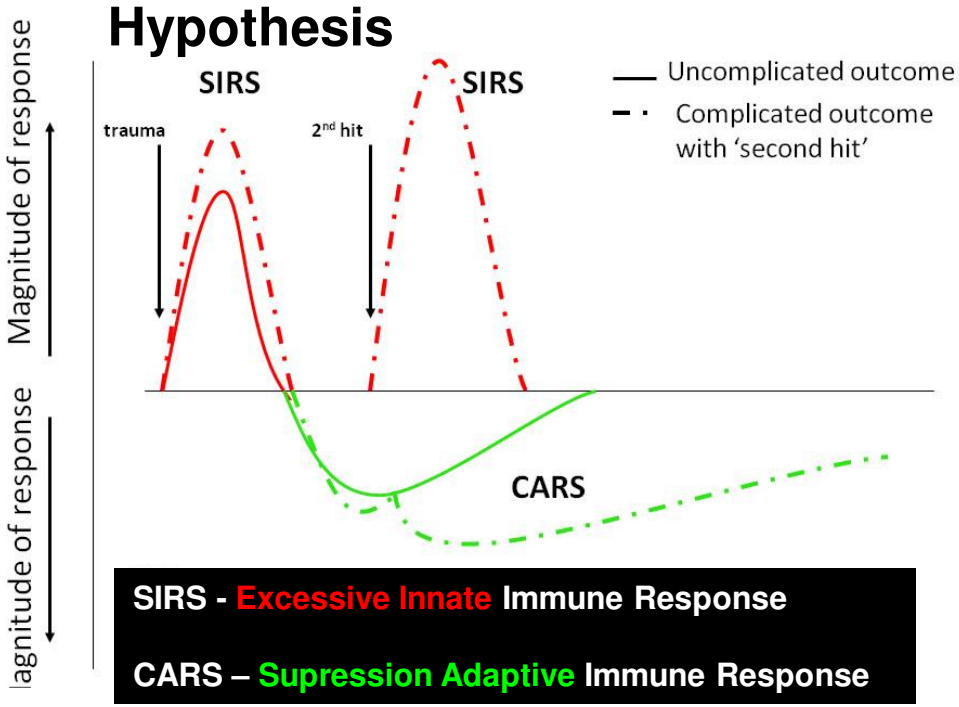
Significant Findings

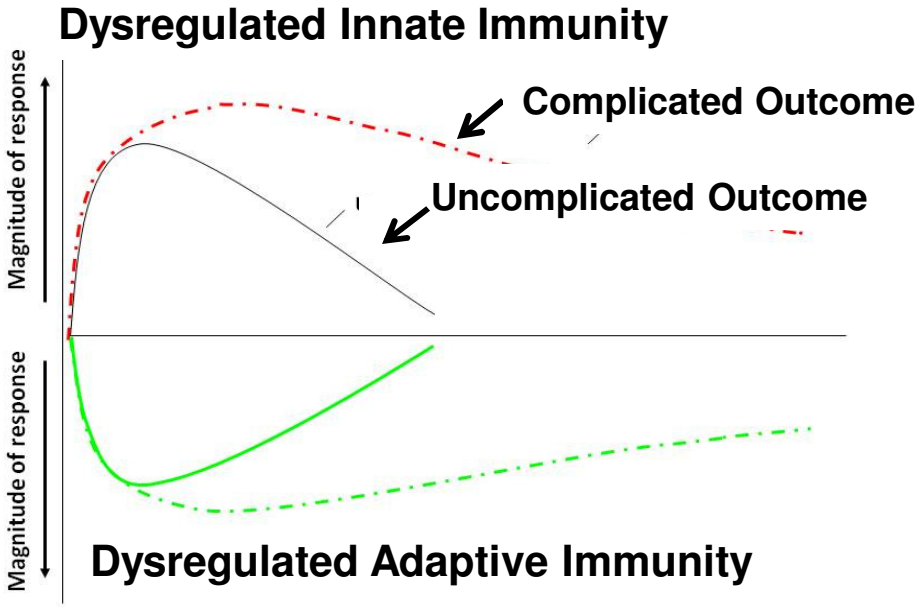
The SIRS/CARS phenomenon cannot be confirmed.

There is no evidence of a 2nd hit

Exaggerated and prolonged expression of genes involved in both innate and adaptive immunity discrimnates complicated outcome

Simultaneous pro- & anti-inflammation





NEW PHENOTYPE OF MOF EMERGES ?

Prolonged ICU stays

Manageable Organ Dysfunctions & no Overt Late MOF

Recurrent Infections (i.e. Hits) with Milder SIRS

NEW PHENOTYPE OF MOF EMERGES ?

Prolonged ICU stays

Manageable Organ Dysfunctions & no Overt Late MOF

Recurrent Infections (i.e. Hits) with Milder SIRS

Persistent Acute Phase Response & ↓↓ # Lymphocytes

Decreased Lean Body Mass – a Wasting Disease

NEW PHENOTYPE OF MOF EMERGES ?

Prolonged ICU stays

Manageable Organ Dysfunctions & no Overt Late MOF

Recurrent Infections (i.e. Hits) with Milder SIRS

Persistent Acute Phase Response & ↓↓ # Lymphocytes

Decreased Lean Body Mass – a Wasting Disease

Poor Wound Healing & Decubitus Ulcers

Transfer to LTACs for Indolent Deaths

A Paradoxical Role for Myeloid-Derived Supressor Cells In Sepsis and Trauma

Alex G Cuenca, Matthew J Delano, Kindra M. Scumpia, Claudia Moreno, Phillip O Scumpia, Drake M LaFace, Philip A Efron and Lyle L Moldawer

Mol Med 2011

Induction of myeloid - derived suppressor cells (MDSC)

Released from bone marrow after inflammatory insults

Immature innate immune cells

Poor antigen presentation but cause inflammation

A Paradoxical Role for Myeloid-Derived Supressor Cells In Sepsis and Trauma

Alex G Cuenca, Matthew J Delano, Kindra M. Scumpia, Claudia Moreno, Phillip O Scumpia, Drake M LaFace, Philip A Efron and Lyle L Moldawer

Mol Med 2011

Induction of myeloid - derived suppressor cells (MDSC)

Released from bone marrow after inflammatory insults

Immature innate immune cells

Poor antigen presentation but cause inflammation

Express arginase 1 which depletes arginine

Suppress T-cell responses that require arginine

A Novel Regulatory Cell Population

Myeloid Derived Suppressor Cells (MDSCs)

Historically referred to as “natural suppressor cells”

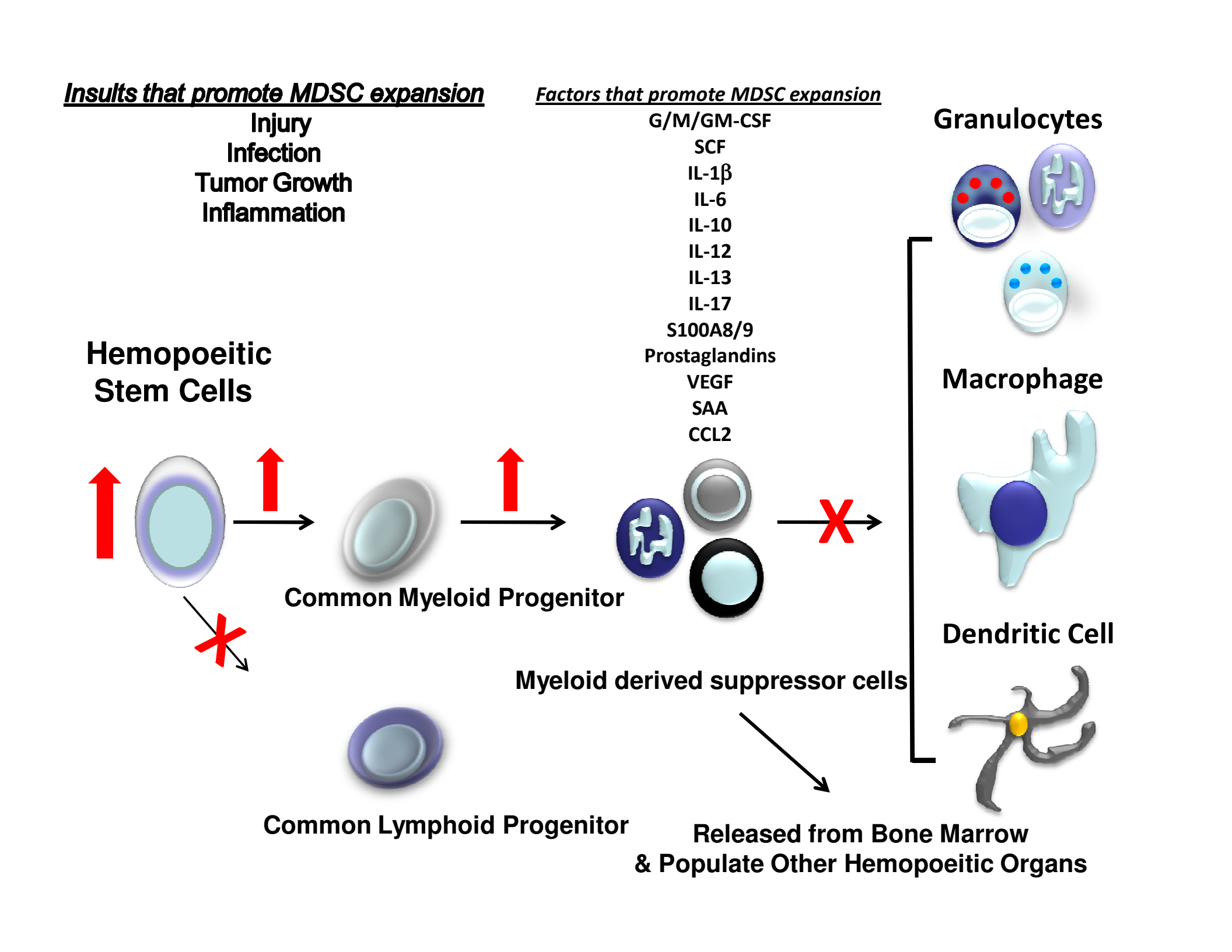
Bennette, *Proc Natl Acad Sci U S A*.10:5142-4, 1978

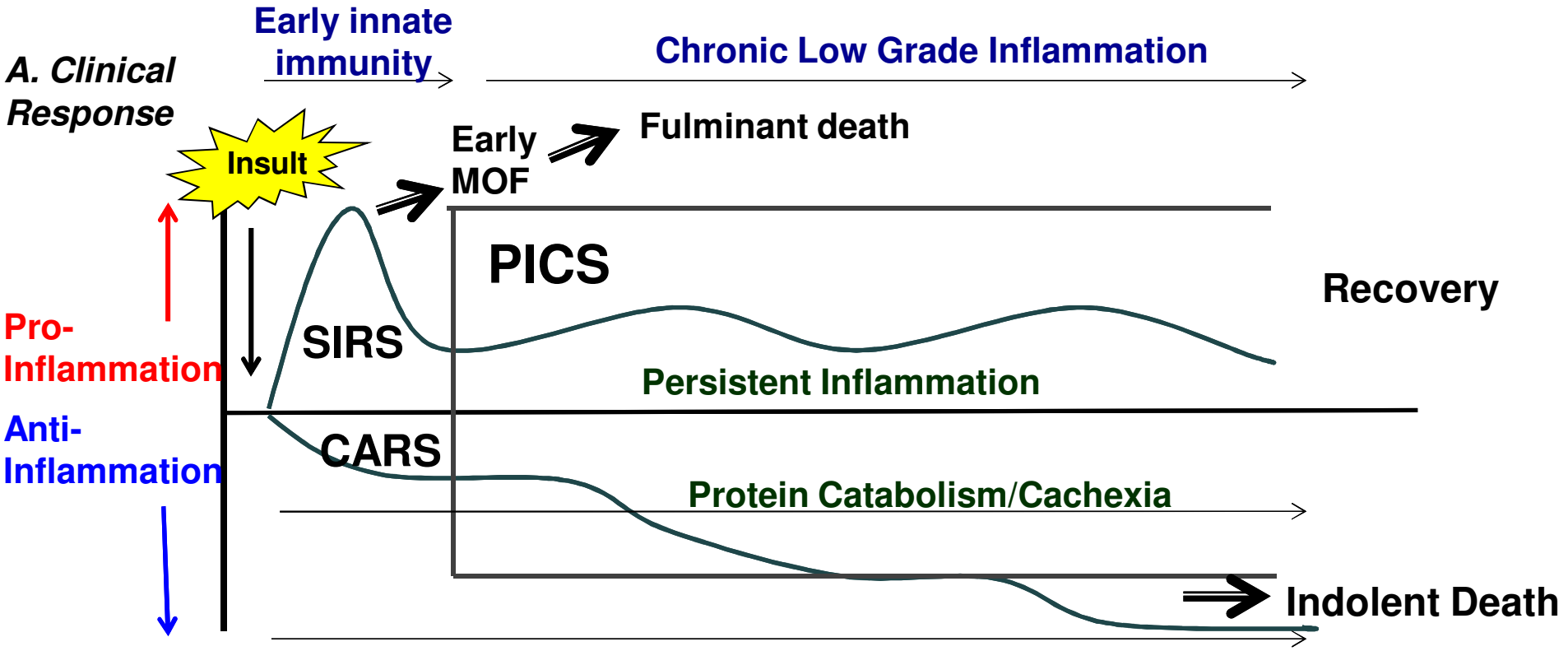
Arise with chronic inflammation and immunologic stress

Bronte, *Nat Rev Immunol* 5:641-654, 2005

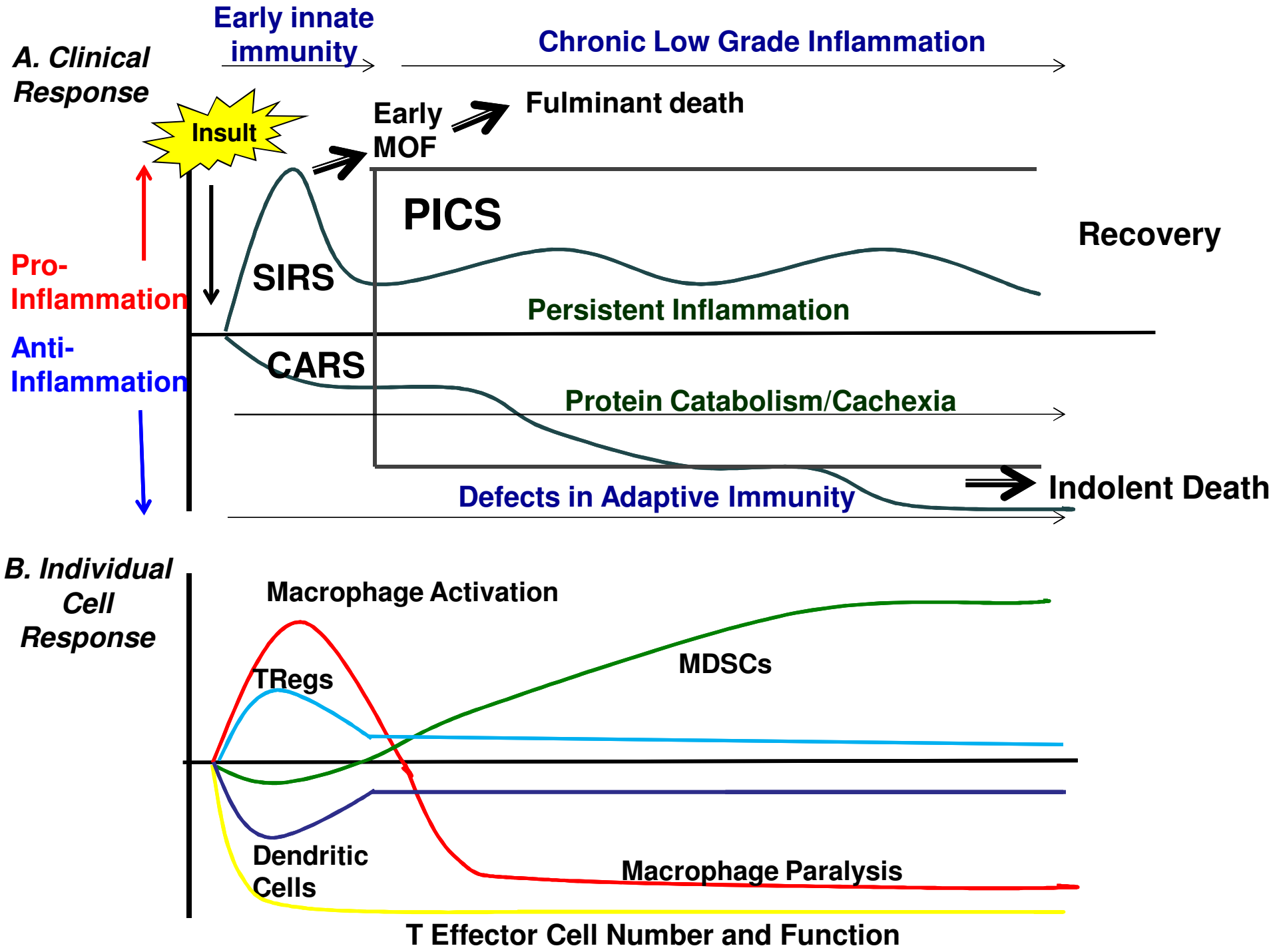
Highly conserved response to various inflammatory insults

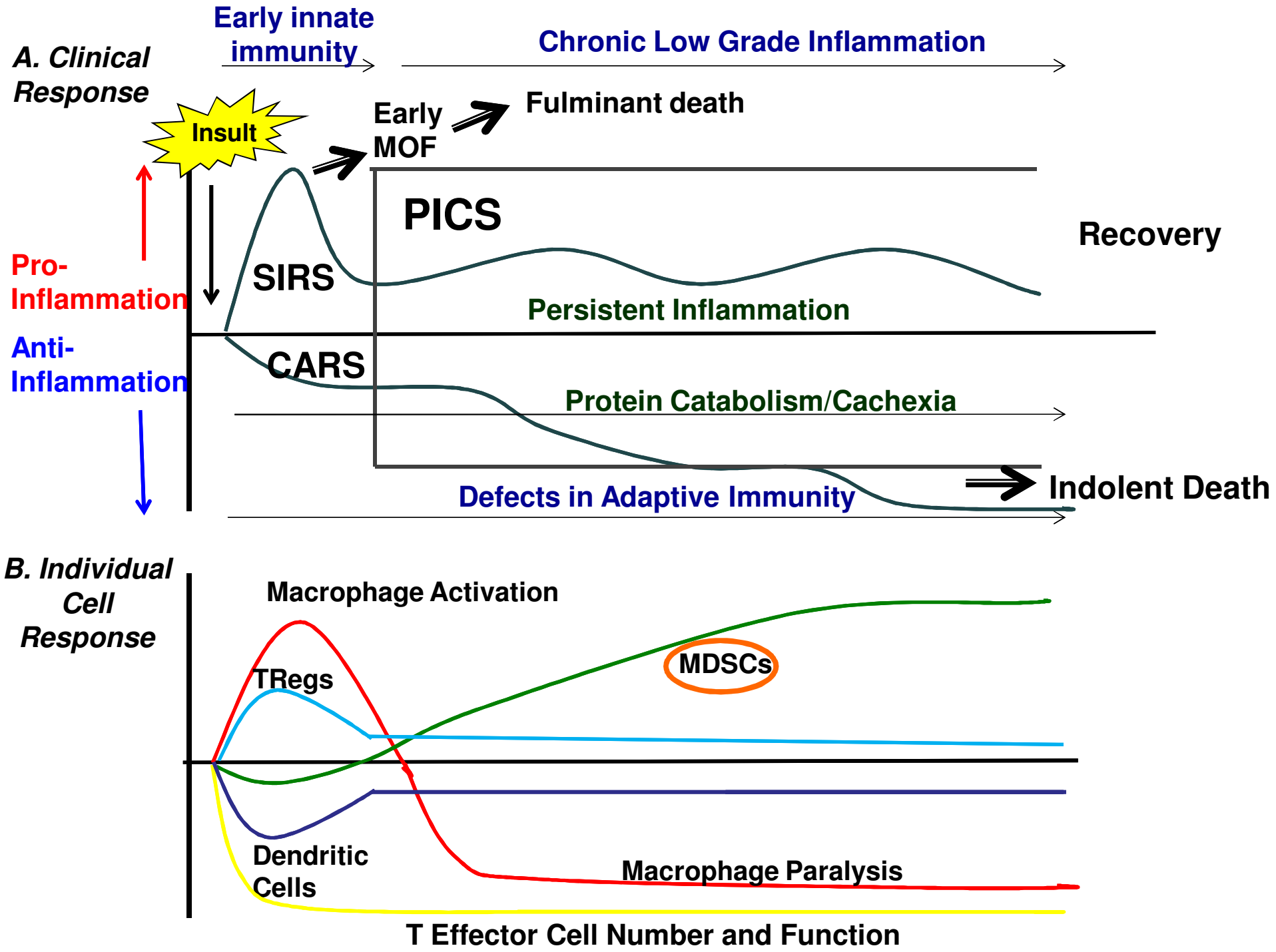
Bronte, *Nat Rev Immunol* 5:641-654, 2005


Insults that promote MDSC expansion
Injury
Infection
Tumor Growth
Inflammation
Factors that promote MDSC expansion
G/M/GM-CSF
SCF
IL-1β
IL-6
IL-10
IL-12
IL-13
IL-17
S100A8/9
Prostaglandins
VEGF
SAA
CCL2
Granulocytes
Macrophage
Dendritic Cell
Hemopoeitic Stem Cells
Common Myeloid Progenitor
Myeloid derived suppressor cells
Common Lymphoid Progenitor
Released from Bone Marrow
& Populate Other Hemopoeitic Organs



Persistent Inflammatory/immunosuppression Catabolism Syndrome (PICS)


A. Clinical Response
Early innate immunity
Chronic Low Grade Inflammation
Insult
Early MOF
Fulminant death
PICS
Recovery
Pro-Inflammation
SIRS
Persistent Inflammation
Anti-Inflammation
CARS
Protein Catabolism/Cachexia
Indolent Death
Defects in Adaptive Immunity
B. Individual Cell Response
Macrophage Activation
TRegs
MDSCs
Dendritic Cells
Macrophage Paralysis
T Effector Cell Number and Function


A. Clinical Response
Early innate immunity
Chronic Low Grade Inflammation
Insult
Early MOF
Fulminant death
PICS
Recovery
Pro-Inflammation
SIRS
Persistent Inflammation
Anti-Inflammation
CARS
Protein Catabolism/Cachexia
Indolent Death
Defects in Adaptive Immunity
B. Individual Cell Response
Macrophage Activation
MDSCs
TRegs
Dendritic Cells
Macrophage Paralysis
T Effector Cell Number and Function

Potential PICS Patients

Persistent Inflammatory Hits

Burns (> 30 % BSA)

Smoldering surgical sepsis

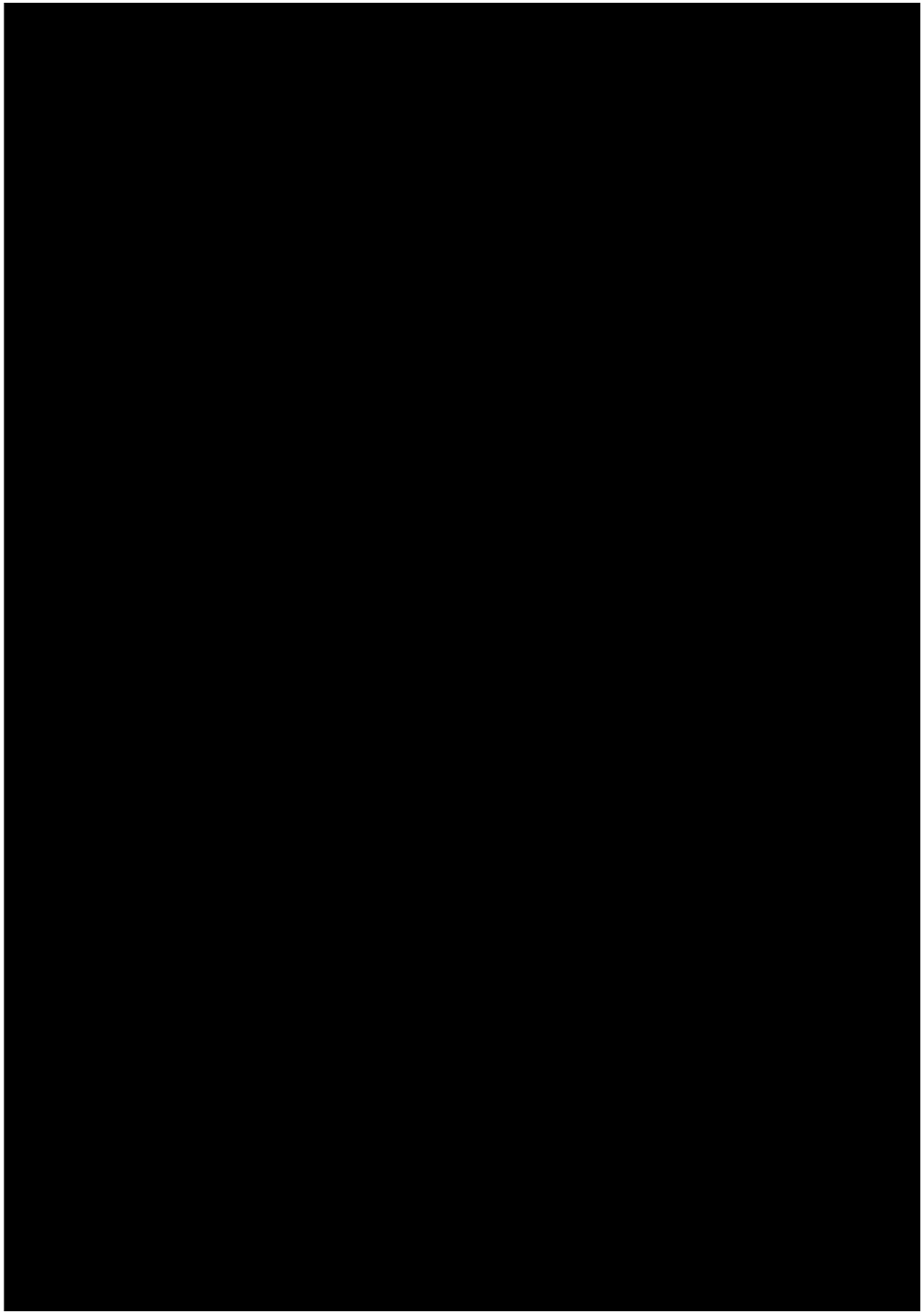
Necrotizing pancreatitis

Severe blunt trauma (ISS > 25)

Major surgery complicated by sepsis

Clinical Determinants of PICS

- **Persistent**
  - Prolonged hospitalization > 14 days
- **Inflammation**
  - C-reactive protein > 150 μg/dl
- **Immunosupression**
  - Total lymphocyte count < 800/mm^3
- **Catabolism**
  - Weight loss of >10% during hospitalization or BMI < 18
  - Creatinine Height Index < 80%
  - Albumin < 3.0 gm/dl
  - Pre-albumin < 10 mg/dl
  - Retinol binding protein < 10 μg/dl



Clinical Determinants of PICS

- **Persistent**
  - Prolonged hospitalization > 14 days
- **Inflammation**
  - C-reactive protein > 150 μg/dl
- **Immunosupression**
  - Total lymphocyte count < 800/mm^3
- **Catabolism**
  - Weight loss of >10% during hospitalization or BMI < 18
  - Creatinine Height Index < 80%
  - Albumin < 3.0 gm/dl
  - Pre-albumin < 10 mg/dl
  - Retinol binding protein < 10 μg/dl

Research or Laboratory Methodologies

- **Inflammation**
  - Luminex™ for cytokine concentrations- IL-6, IL-10, IL-1ra, procalcitonin
  - Leukocyte genome expression patterns, e.g. *ARG1, NOS2, IL-1RA,SILR2, MMP8, MMP9, MMP2*
- **Immunosupression**
  - 'Paralyzed Monocyte'
    - Reduced ex vivo cytokine production
    - Reduced HLA-DR expression
    - Reduced phagocytosis
  - Anergy or Exhausted T cell
    - Expression of suppressor molecules, e.g. PDL-1, CTLA-4, BTLA, HVEM
    - Reduced T-cell proliferation
    - T_{H2} polarization
  - Increased Treg numbers and suppressor activity

Summary

Myeloid derived suppressor cells drive persistent inflammation & catabolism that characterizes PICS

Better understand these cells & how to modulate them

Understand how co-morbid conditions contribute to PICS

Embrace early immunonutrition

Develop strategies for anabolic nutrition

Conclusion

Strategy # 1

Translational research needs to be a core value

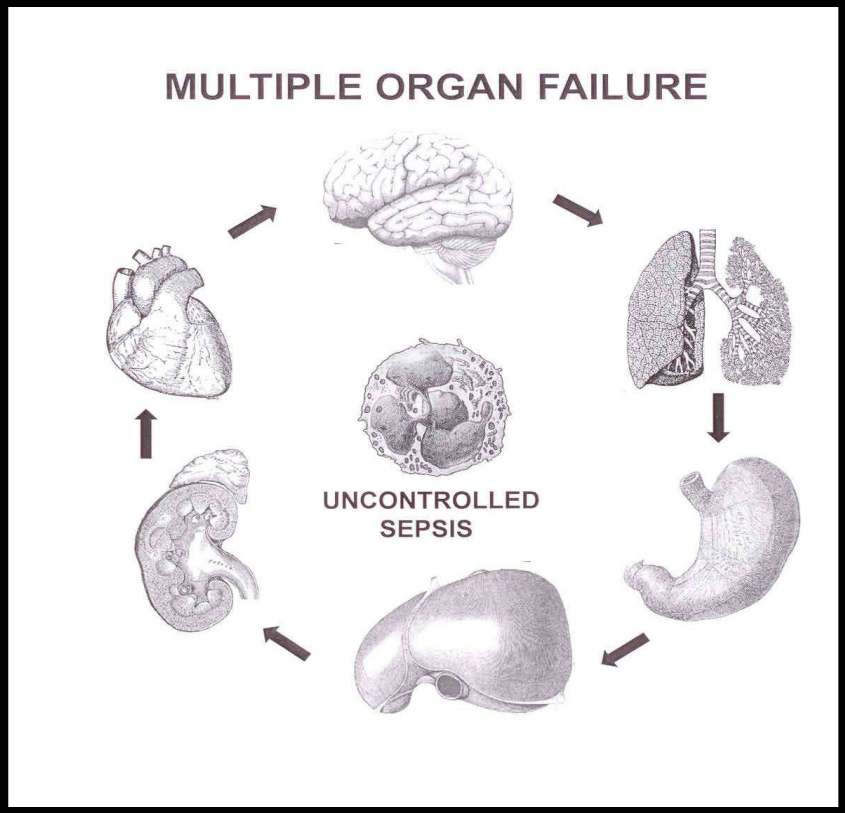
Create the Culture

Thank You Dr Eiseman

Conclusion

Strategy # 2

Pick a Topic and Stick with it

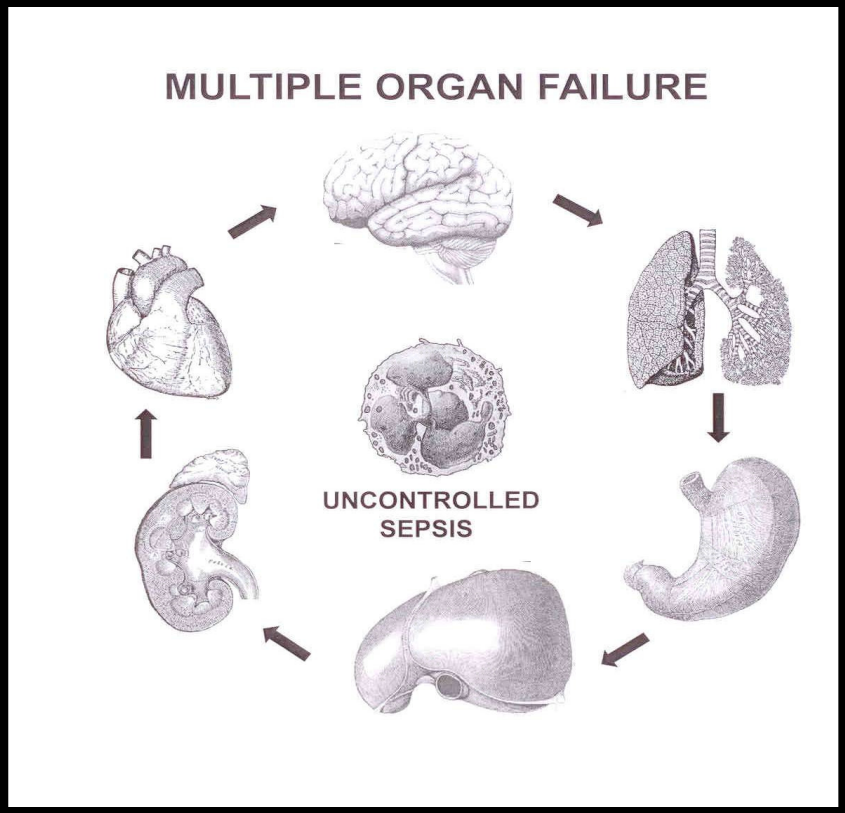


I have been studying MOF for over 25 years

Conclusion

Strategy # 2

Pick a Topic and Stick with it

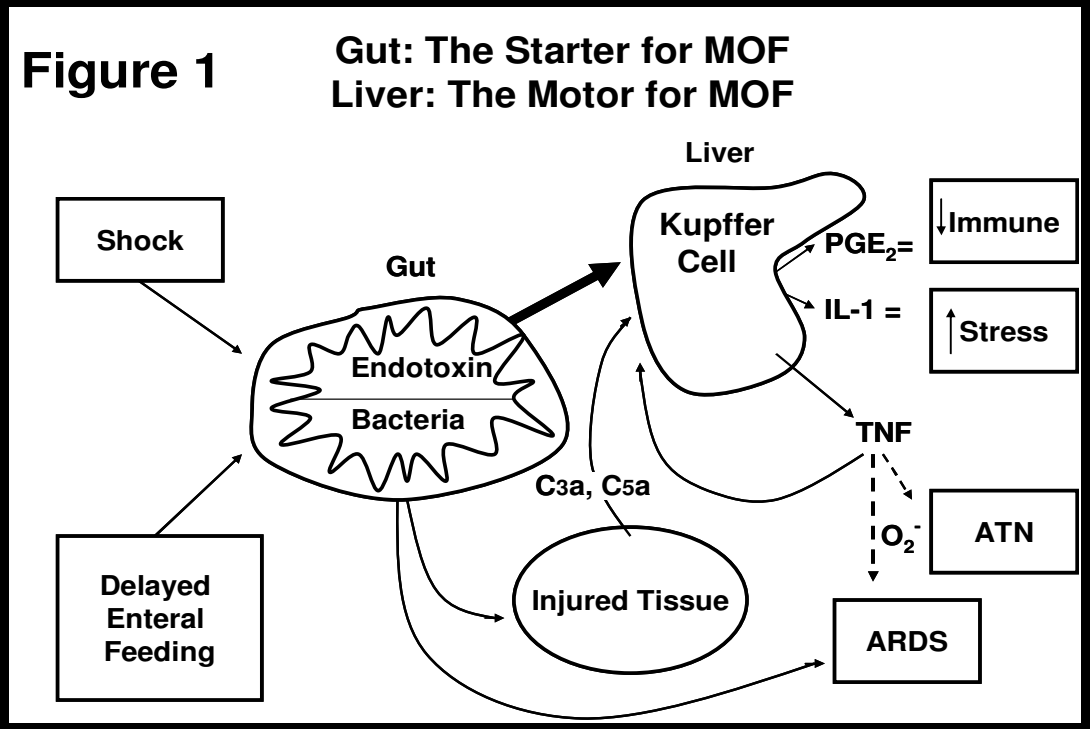


and the story just gets better as the syndrome evolves

Conclusion

Strategy # 3

Draw cartoons and generate "win:win" hypotheses

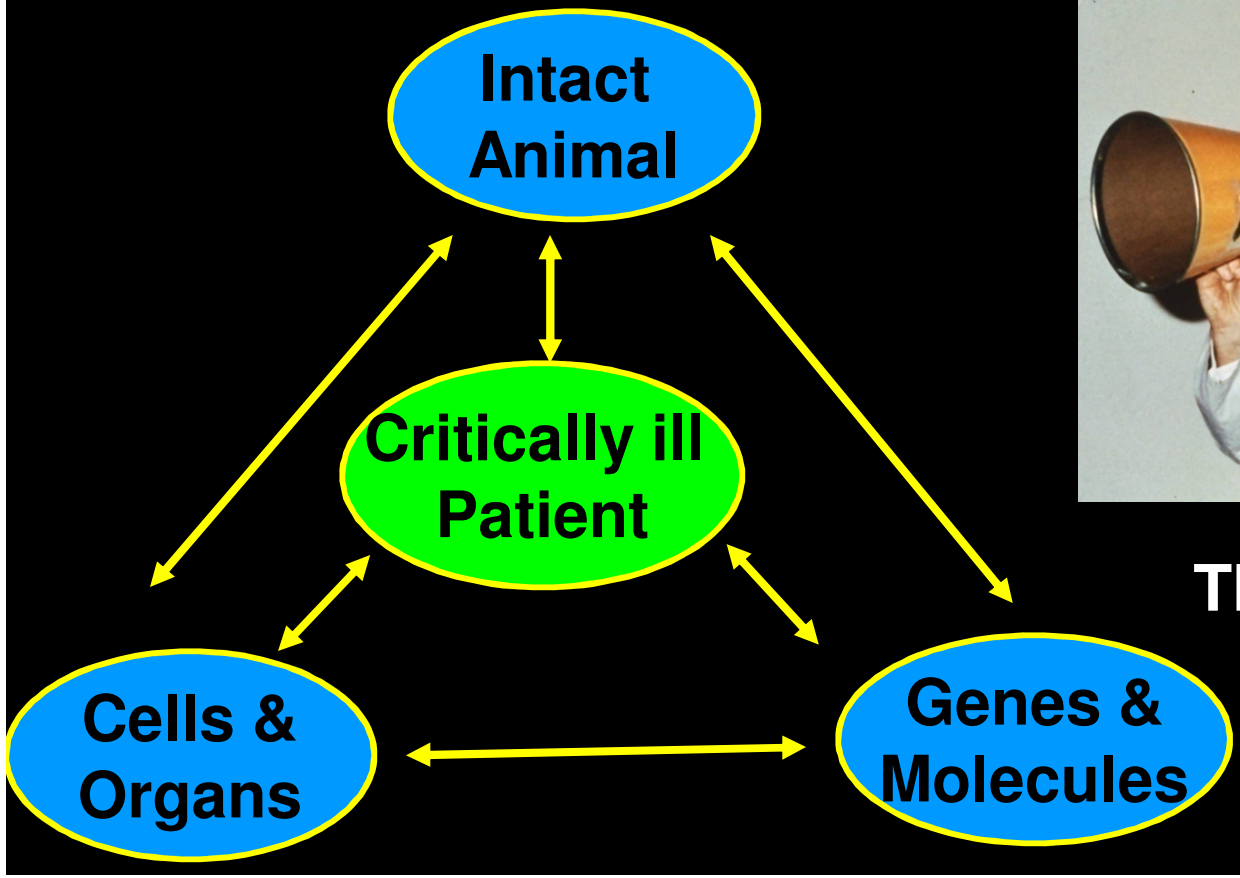


Thank You Gene

Conclusion

Strategy # 4

Be a Cheer Leader and Focus on Your Patients



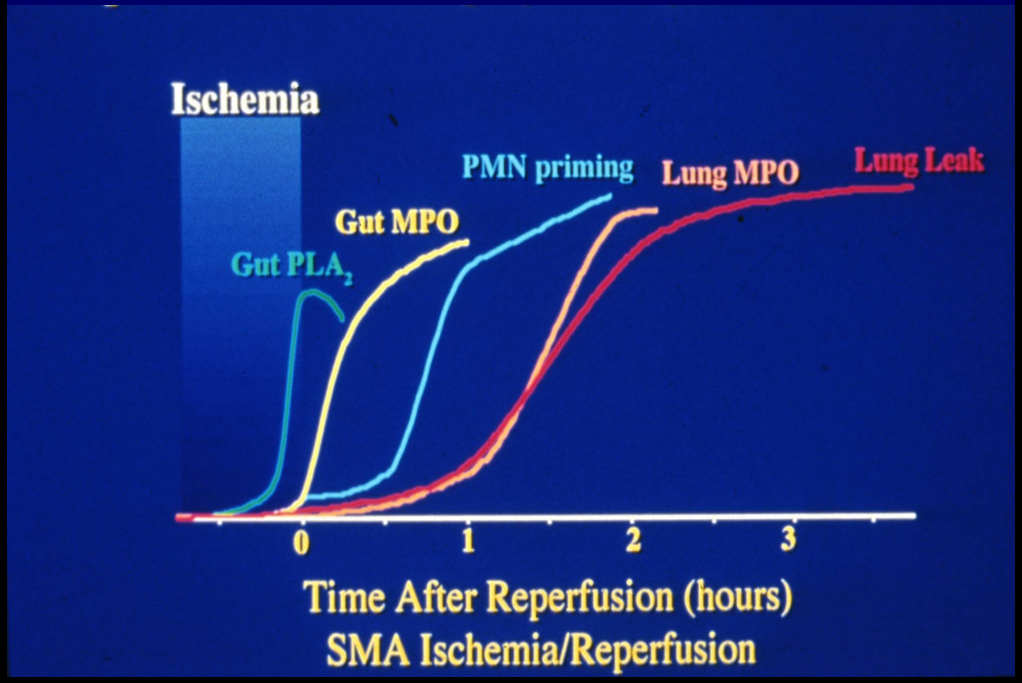
Thank You Dr Harken

Conclusion

Strategy # 5

Create clinically relevant lab models

Pathophysiologic Sequence



Denver SMAO Model

Thank you Renato

Conclusion

Strategy # 6

Develop a clinical database & study epidemiology

Denver MOF Database

Thank You Angela

Conclusion

Strategy # 7

Write review articles & propose new paradigms

POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,*
Norman W. Weisbrodt,‡ and Frederick A. Moore*

Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

The Role of the Gut in Late MOF

Thank You Heitham

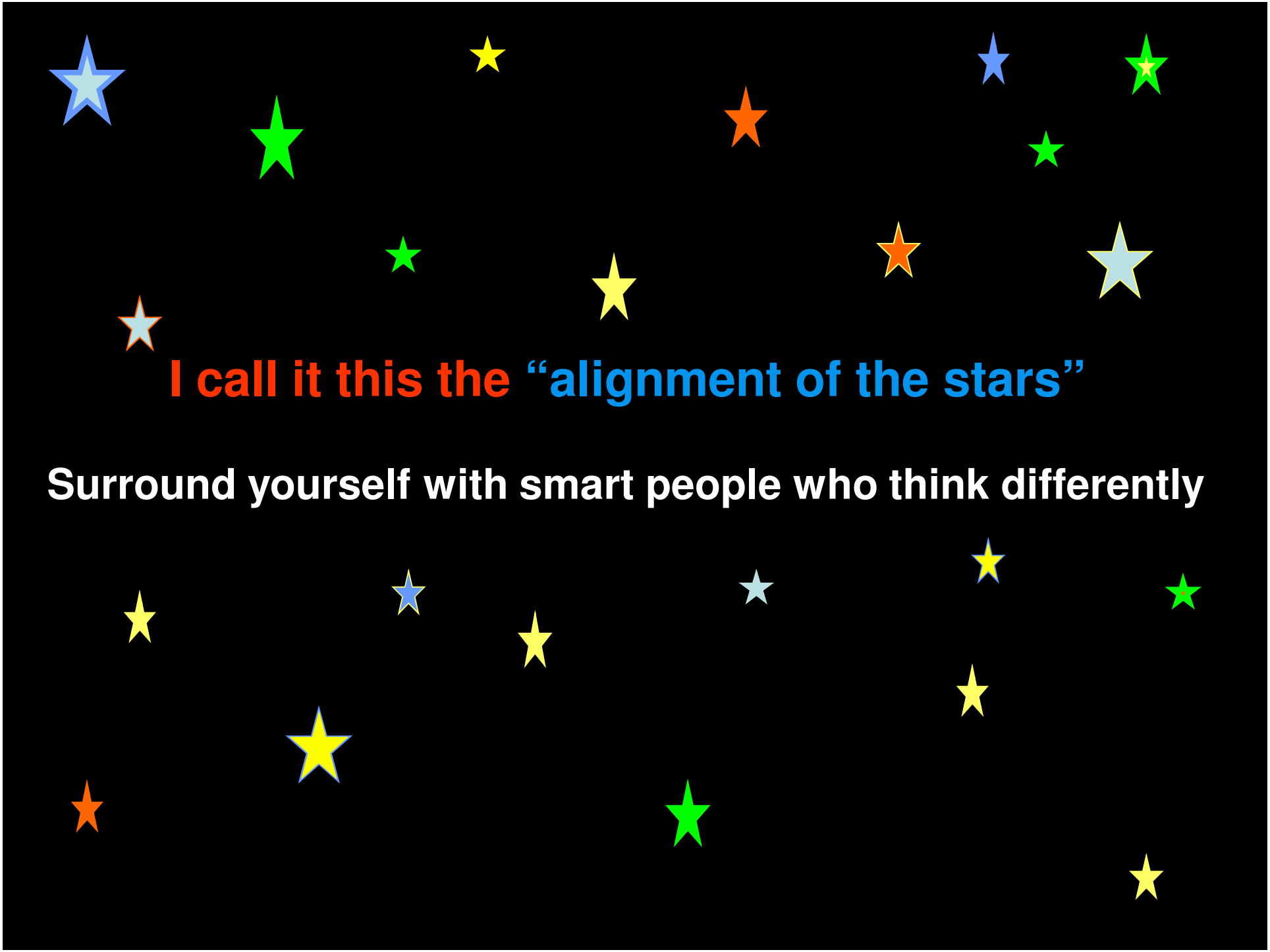
Conclusion

Strategy # 8

Develop “win, win” research relationships

- Foreign research fellows
- Institutional “super stars”
- Use senior scientists as mentors

Too Many to Thank


I call it this the “alignment of the stars”
Surround yourself with smart people who think differently

Conclusion

Strategy # 9

Train the next generation to be translational scientists

Formal Didactics

- Bioethics
- Statistics
- Epidemiology
- Clinical Trial Design
- Outcomes Research

Basic Laboratory Studies

- Critical Thinking
- Hypothesis Driven Research

Thank You David

Conclusion

Strategy # 10

Use CCDS to control confounding effect of variable care

Thank You Bruce

“ The connection between cause and effect has no beginning and can have no end ”

Leo Tolstoy
War and Peace

“ The connection between cause and effect has no beginning and can have no end “

Leo Tolstoy
War and Peace

“ Imagination is more important than knowledge ”

Albert Einstein

Growing PICS Research Team at UF