	1. REVIEW DATE (Leave Blank)	2. REVIEW GROUP (Leave Blank)

NOTE: Only new investigators who have not been provided with name labels should have items 3-7 typed in. Investigators already in the RDIS should affix their labels to provide this information.

PLACE LABEL HERE

3. HEALTH CARE FACILITY NO. (3 digit only)	4. LOCATION OF HEALTH CARE FACILITY (VAMC, OPC, MRO) City, State	5. PRINCIPAL INVESTIGATOR (Last name, first, middle initial) DEGREE
	North Chicago, Illinois	Astiz, Mark E., MD
6. SOCIAL SECURITY NO.	**7. VA TITLE**	
567-42-4024	Director, Medical/Surgical Intensive Care Unit	

8. TITLE OF PROGRAM (Not to exceed 72 typewriter spaces)

MECHANISMS OF SEPTIC SHOCK

9. AMOUNT REQUESTED EACH YEAR (Program 821, Cost Center 103)

1ST 53,547 ; 2ND 51,947 ; 3RD _____ ; 4TH _____ ; 5TH _____ ; TOTAL 105,494

10. VA EMPLOYMENT STATUS (Mark only one)	10A. VA SALARY SOURCE (Mark only one)	11. TYPE OF PROGRAM (Mark only one)
☐ FULL-TIME	☒ PATIENT CARE ☐ RER&D	I II III IV
☒ PART-TIME (5 ----/8 time)	☐ RESEARCH FUNDS CC 103 ☐ OTHER VA (Indicate below)	☒ NEW ☐ ☐ ☐
☐ CONSULTING (----hrs./week)	☐ RESEARCH FUNDS CC 104 _____	☐ ONGOING
☐ ATTENDING (----hrs./week)	☐ CAREER DEVELOPMENT _____	☐ SUPPLEMENTAL
☐ WOC (----hrs./week)	☐ HSR&D _____	12. NUMBER OF PROJECTS IN THIS PROGRAM

13. PRIMARY RESEARCH DEVELOPMENT PROGRAM AREA CODE 0 6

14. DEPARTMENT, LABORATORY, ETC. IN WHICH APPOINTMENT IS HELD

Medical Service

15. NAME OF ACADEMIC AFFILIATION AND TITLE OF MAJOR FACULTY APPOINTMENT

Assistant Professor of Medicine, University of Health Sciences/The Chicago Medical School

16. DEPARTMENT, LABORATORY, ETC. IN WHICH APPOINTMENT IS HELD

Division of Critical Care Medicine, Department of Medicine

17. SUMMARY OF RESEARCH/DEVELOPMENT SUPPORT FOR FIVE PREVIOUS YEARS:

PROGRAM NA, COST CENTER _____

		OTHER VA	TOTAL NON-VA
FY _____	$ _____	$ _____	$ _____
FY _____	_____	_____	_____
FY _____	_____	_____	_____
FY _____	_____	_____	_____
FY _____	_____	_____	_____

18. SIGNATURE OF PRINCIPAL INVESTIGATOR

[signature] M.D.

19. DATE 4/1/84

20. SIGNATURE OF ACOS FOR RESEARCH AND DEVELOPMENT

21. DATE

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CONTROL NO. 8667

SUMMARY DESCRIPTION OF PROGRAM [X] / PROJECT [ ]

PRINCIPAL INVESTIGATOR	LOCATION OF MEDICAL CENTER/CLINIC
Mark E. Astiz, M.D.	North Chicago, Illinois

TITLE OF PROGRAM/PROJECT (Not to exceed 72 typewriter spaces)

MECHANISMS OF SEPTIC SHOCK

BRIEF STATEMENT OF RESEARCH OBJECTIVES (Do not use continuation sheets)

Reports of abnormalities of mitochondrial function and abberations in the profile of oxygen utilization have prompted consideration of toxic cellular injury as the cause of impaired oxygen metabolism in patients with septic shock. However, recent studies suggest that aerobic metabolism and oxygen consumption may be flow limited in this syndrome. The present study is designed to determine if oxygen utilization is primarily dependent on capillary perfusion in patients with septic shock.

The objectives of the study are:

(1) to monitor systemic, regional and capillary perfusion during clinical septic shock.

(2) to examine the correlation of changes in systemic and regional blood flow and capillary perfusion during clinical septic shock.

(3) to determine the temporal relationship of blood flow to systemic and regional oxygen consumption during clinical septic shock.

CURRENT FUNDS AND FIRST YEAR REQUEST FOR PROGRAM [X] /PROJECT [ ]

(PROGRAM 821, COST CENTER 103 FUNDS)

PRINCIPAL INVESTIGATOR	LOCATION OF MEDICAL CENTER/CLINIC
Mark E. Astiz, M.D.	North Chicago, Illinois

TITLE OF PROGRAM/PROJECT

MECHANISMS OF SEPTIC SHOCK

DESCRIPTION (Itemize)			VA FUNDING	
PERSONNEL NAME	ROLE IN PROGRAM	% EFFORT	CURRENT YEAR	FIRST YEAR REQUEST
Mark E. Astiz, M.D.	PRINCIPAL INVESTIGATOR	20		
Eric C. Rackow, M.D.	Co-Investigator	5		
Max H. Weil, M.D.	Co-Investigator	5		
To be named	Research Assistant GS9	100		24,070
To be named	Lab Technician GS5	100		16,345
CONSULTANT SERVICES Statistical Consultant				1,000
EQUIPMENT (Justify any item over $2000)				
Mercury Strain-gauge Plethysmograph (D.E. Hokanson)				850
Pneumatic cuff inflator (D.E. Hokanson)				630
Gauge Set (D.E. Hokanson)				130
SUPPLIES				
Arterial catheters (25)				500
Pressure monitoring kits (25)				1,000
Blood gas collecting kits (225)				300
Chemical reagents				2,250
Xenon 133				1,500
Misc				700
ALL OTHER EXPENSES Support Services (Computer Center, Med. Illust)				750
Standard Assessment for VA Common Research Resources 16%				3,032
TOTAL OPERATING EXPENSES				53,547

VA FORM 10-1313.3 JUL 1979

CONTROL NO. 78667

ESTIMATED EXPENSES FOR EACH YEAR FOR PROGRAM [X] /PROJECT [ ]

DESCRIPTION	$ AMOUNT FOR EACH YEAR					FOOT-NOTE *
	1ST	2ND	3RD	4TH	5TH	
PERSONNEL*	40,415	40,415				
CONSULTANT SERVICES	1,000	1,000				
EQUIPMENT	1,600	--				
SUPPLIES	6,750	6,750				
ALL OTHER EXPENSES	3,782	3,782				
TOTAL OPERATING EXPENSES	53,547	51,947				

** Explain differences in the operating expenses between years.*

FOOT-NOTE	EXPLANATION
	We have requested the purchase of the following pieces of equipment for utilization in a research protocol entitled "Mechanisms of Septic Shock": 1. Mercury Strain-gauge Plethysmograph (D.E. Hokanson, Issaquah, WA) 850.00 2. Pneumatic cuff inflator 630.00 3. Gauge Set 130.00 $1,610.00 The investigators who will be utilizing the equipment are Mark E. Astiz, M.D.; Eric C. Rackow, M.D.; and the research assistant. We expect that the equipment will be utilized approximately four hours per week by the investigators as a group. This particular equipment was chosen because of the electrical calibration included in the system which makes it more adaptable to our needs. The Veterans Administration Medical Center at North Chicago, to my knowledge, does not own any of the equipment at the present time. The estimated duration of the study is two years. The upkeep of the plethysmograph will be covered during the time period by the manufacturer's warranty.

INVESTIGATOR'S BIOGRAPHIC SKETCH

NAME	SOCIAL SECURITY NO.
Mark E. Astiz, M.D.	567-72-4024

TITLE	ROLE IN PROGRAM
Director, Medical/Surgical ICU	Principal Investigator

EDUCATION *(Begin with Baccalaureate; include post doctoral training; do not include Honorary Degrees)*

NAME, LOCATION OF INSTITUTION AND TITLE OF COURSE OF TRAINING PROGRAM	DEGREE	YEAR AWARDED
University of California, Berkeley, California	B.A.	1974
Creighton University, Omaha, Nebraska	M.D.	1978
University of Southern California, Los Angeles, Calif.	Internal Medicine Residency	1978-1981
University of Health Sciences/The Chicago Medical School, North Chicago, Illinois	Critical Care	1981-1983

MAJOR RESEARCH INTEREST (S)

Pathophysiology of Septic Shock; Fluid Resuscitation

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Work backwards from present appointment)*

1983 - present	University of Health Sciences/ The Chicago Medical School	Dept. of Medicine	Asst. Professor of Medicine
1983 - present	North Chicago Veterans Administration Hospital	Dept. of Medicine	Director, Medical/ Surgical ICU

HONORS AND AWARDS

Diplomate Internal Medicine, American Board of Internal Medicine, 1981

INVESTIGATOR'S BIBLIOGRAPHY

NAME: Mark E. Astiz, M.D.

SOCIAL SECURITY NO.: 567-72-4024

PUBLICATIONS *(Not to exceed three pages for each investigator.)*

ARTICLES

(1). Astiz M, Weil MH, Rackow E. Hypovolemia in congestive heart failure, clinical and therapeutic implications. Practical Cardiology 1983;9:250.

(2) Case Study - Neurogenic Intrapulmonary Shunting in Head Trauma (In preparation).

(3) Correlation of Oxygen Transport Parameters in Human Septic Shock (In preparation)

ABSTRACTS

(1) Astiz M, Rackow E, Falk J, Kaufman B. Oxygen delivery and utilization in septic shock patients. Clinical Research 1983;31:256A.

(2) Astiz M, Rackow E, Falk J, Kaufman B. Assessment of oxygen utilization in septic shock patients. Critical Care Medicine 1983;11:250

(3) Kaufman BS, Rackow EC, Falk JC, Astiz ME, Weil MH. Systemic oxygen demand in patients with acute myocardial infarction. Clin Res 1984;31:84.

VA FORM JUL 1979 10-1313-7

INVESTIGATOR'S TOTAL VA AND NON-VA RESEARCH/DEVELOPMENT SUPPORT (I)

NAME

	AGENCY	GRANT/PROJECT NUMBER	% EFFORT	CURRENT YEAR: PERSONNEL	CONSULTANT SERVICES	EQUIPMENT	SUPPLIES	ALL OTHER EXPENSES	TOTAL CURRENT YEAR FUNDING	FUTURE YEARS: PROJECTED FUNDING	FUTURE YEARS: TOTAL PERIOD (Inclusive dates)
ACTIVE VA PROGRAMS										(NEXT YEAR)	
ACTIVE GRANTS AND AWARDS (GOVERNMENT)										(NEXT YEAR)	
ACTIVE GRANTS AND AWARDS (NON-GOVERNMENT)										(NEXT YEAR)	
PENDING REQUESTS (VA AND NON-VA)	Veterans' Administration		15%	11,250		12,400		1,419		(1ST YEAR OF PENDING SUBMISSION) $25,069	
TOTALS →										$25,069	

PAGE Astiz 7

INVESTIGATOR'S TOTAL VA AND NON-VA RESEARCH/ DEVELOPMENT SUPPORT (II)

NAME	SOCIAL SECURITY NO.
Mark E. Astiz, M.D.	567-72-4024

Instructions: 1. Provide a detailed explanation of the scientific, administrative and budgetary relationship of each program/project listed on VAF 10-1313-7 to total VA program.

2. In column below labeled "SORT," insert one of the following: AVA (active VA); AG (active government); ANG (active non-government); P (pending).

SORT	GRANT/PROJECT NO.	GRANT/PROJECT TITLE:
P		FLUID RESUSCITATION IN SEPTIC SHOCK

Currently pending as a proposal for the study of effects of different forms of volume therapy on the accumulation in lung water during resuscitation of patients with septic shock. The equipment requirements for that study are entirely different and there are no budget overlaps since each study will be done independently. Because the investigators involved in the two studies are the same, the administrative aspects will overlap. Although both studies involve septic shock, the scientific objectives posed by each study are independent and do not overlap.

SORT	GRANT/PROJECT NO.	GRANT, PROJECT TITLE:

CONTROL NO. 78667

INVESTIGATOR'S BIOGRAPHIC SKETCH

NAME	SOCIAL SECURITY #
Eric C, Rackow, M.D.	052-36-1758

TITLE	ROLE IN PROGRAM
Professor and Vice Chairman, Dept. of Medicine	Co-Investigator

EDUCATION *(Begin with Baccalaureate; include post doctoral training; do not include Honorary Degrees)*

NAME, LOCATION OF INSTITUTION AND TITLE OF COURSE OF TRAINING PROGRAM	DEGREE	YEAR AWARDED
Franklin & Marshall College, Lancaster, Pennsylvania	B.A.	1967
State Univ. of New York (SUNY), Brooklyn, New York	M.D.	1971
State Univ. of New York (SUNY), Brooklyn, New York	Internal Med. Residency	1971-1973
State Univ. of New York (SUNY), Brooklyn, New York	Cardiology Fellowship	1973-1975

MAJOR RESEARCH INTEREST (S)

Circulatory Shock; Fluid Resuscitation; Pulmonary Edema

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Work backwards from present appointment)*

Dates	Institution	Department	Rank/Function
1982-present	University of Health Sciences	Medicine	Professor and Vice-Chm Chief, Crit. Care Med.
1978-1982	Ellis Hospital, Schenectady, New York	Medicine	Chief, Sec. of Cardiol. and Crit. Care Med.
1978-1982	Albany Medical College of Union Univ., Schenectady, NY	Medicine	Assoc. Professor of Medicine
1978-1982	Albany Medical College of Union Univ., Schenectady, NY	Medicine	Director, Critical Care Fellowship
1977-1978	University of Southern California, Los Angeles	Critical Care	Director, Critical Care Fellowship
1977-1978	Institute of Critical Care Medicine, Univ. of So. Cal.	Critical Care Medicine	Asst. Prof. of Medicine Assistant Director
1976-1977	SUNY Downstate Medical Center	Medicine	Asst. Prof. of Medicine
1975-1977	SUNY Downstate Medical Center	Medicine	Dir. Crit. Care Units
1975-1976	SUNY Downstate Medical Center	Medicine	Instructor in Medicine
1972-1975	SUNY Downstate Medical Center	Medicine	Asst. Instructor in Medicine

HONORS AND AWARDS

Diplomate, Internal Medicine, American Board of Internal Medicine, 1975
Diplomate, Cardiovascular Diseases, American Board of Internal Medicine, 1977
Instructor, Advanced Cardiac Life Support, American Heart Association, 1978
Fellow, American College of Physicians
Fellow, American College of Cardiology
Fellow, American College of Chest Physicians
Affiliate Faculty, Chicago Heart Association

INVESTIGATOR'S BIBLIOGRAPHY

NAME: Eric C. Rackow, M.D. Co-Investigator

SOCIAL SECURITY NO.: 052-36-1758

PUBLICATIONS (Not to exceed three pages for each investigator.)

Representative Publications

Articles

1. Rackow EC, Fein IA, Leppo J. Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill. Chest 1977;72:709.
2. Rackow EC, Fein IA, Sprung C, Grodman R. Uremic pulmonary edema. Am J Med 1978; 64:1084.
3. Rackow EC, Fein IA, Leppo J. The relationship of colloid osmotic pressure and pulmonary capillary pressure to the development of pulmonary edema in the critically ill. Cardiovasc Med 1978;3:407.
4. Rackow EC, Fein I. Fulminany non-cardiogenic pulmonary edema in the critically ill. Crit Care Med 1978;6:630.
5. Fein IA, Rackow EC, Shapiro L. Acute non-cardiogenic pulmonary edema in plasmodium falciparum malaria: a case report. Am Rev Resp Dis 1978;118:425.
6. Sprung CL, Rackow EC, Fein IA. Pulmonary edema: a complication of diabetic ketoacidosis. Chest 1980;77:687.
7. Falk JL, Rackow EC, Blumenberg R, Gelfand M, Fein IA. Hemodynamic and metabolic effects of abdominal aortic crossclamping. Am J Surg 1981;142:175.
8. Sprung CL, Rackow EC, Fein IA, Isikoff SK. Differentiation of cardiogenic and non-cardiogenic pulmonary edema by edema fluid to serum globulin ratios. Am Rev Resp Dis 1982;124:718.
9. Fein IA, Rackow EC. Neurogenic pulmonary edema. Chest 1982;81:318.
10. Haupt MT, Rackow EC. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin and saline solutions. Crit Care Med 1982;10:159
11. Fein IA, Rackow EC, Sprung CL, Grodman R. Relation of colloid osmotic pressure to arterial hypoxemia and cerebral edema during crystalloid volume loading of patients with diabetic ketoacidosis. Ann Int Med 1982;96:570.
12. Rackow EC, Fein IA, Seigel J. The relationship of the colloid osmotic pulmonary artery wedge pressure gradient to pulmonary edema and mortality in critically ill patients. Chest 1982;82:433.
13. Haupt MT, Rackow EC. Resolution of fever and cardiac performance. Am Heart J 1983;105:763.
14. Packman MI and Rackow EC. Optimum heart filling pressure during fluid resuscitation of patients with hypovolemia and septic shock. Crit Care Med 1983:11:165.
15. Rackow EC, Weil MH. Recent trends in diagnosis and management of septic shock. Current Surgery 1983;40:181.
16. Astiz M, Weil MH, Rackow EC. Hypovolemia complicating acute heart failure. Practical Cardiology 1983;9:250.
17. Weil MH, Rackow EC. Critical Care Medicine. Arch Int Med 1983;143:1391.
18. Rackow EC, Fein IA. Adult respiratory distress syndrome. IN: Harrison's Principles of Internal Medicine. Patient Management Problems. Bollet AH (ed); New York; McGraw Hill Book Company, 1981:71-74.
19. Sprung CC, Rackow EC, Civetta JM. Direct measurements and derived calculations using the pulmonary artery catheter. IN: The Pulmonary Artery Catheter. Methodology and Clinical Applications. Sprung CC (ed); Baltimore: University Park Press 1983; 105-140.
20. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in shock: A comparison of cardiorespiratory effects of albumin, hetastarch and saline solutions in patients with hypovolemic shock. Crit Care Med 1983;12:11.
21. Rackow EC, Falk JL. Principles of intravascular volume management with crystalloids and colloids. IN: Critical Care: state of the art. Shoemaker WE, Thompson WL and Holbrook P (eds); WB Saunders Co, Philadelphia, 1983.

INVESTIGATOR'S BIBLIOGRAPHY

NAME

. Eric C. Rackow, M.D. Co-Investigator

SOCIAL SECURITY NO.

052-36-1758

PUBLICATIONS *(Not to exceed three pages for each investigator.)*

22. Kaufman BS, Rackow EC, Falk JL. The relationship between oxygen delivery and consumption during fluid resuscitation of hypovolemia and septic shock. Chest 1984;85:335.

Abstracts

Thirty-five abstracts have been published dating from 1976-1984 in such journals as American Journal of Cardiology, Chest, Critical Care Medicine, and proceedings of Conferences.

Books

Weil MH and Rackow EC. Diagnosis and Treatment of Shock. Williams & Wilkins (in press)

VA FORM JUL 1979 10-1313-6

INVESTIGATOR'S BIOGRAPHIC SKETCH

NAME	SOCIAL SECURITY NO.
Max Harry Weil, M.D., Ph.D.	055-20-9509

TITLE	ROLE IN PROGRAM
Professor and Chairman, Dept. of Medicine	Co-Investigator

EDUCATION *(Begin with Baccalaureate; include post doctoral training; do not include Honorary Degrees)*

NAME, LOCATION OF INSTITUTION AND TITLE OF COURSE OF TRAINING PROGRAM	DEGREE	YEAR AWARDED
University of Michigan, College of Literature, Sciences and Arts, Ann Arbor, Michigan	A.B.	1948
State University of New York, Brookoyn, New York	M.D.	1952
University of Minnesota Graduate School, Minneapolis, Minnesota	Ph.D.	1957

MAJOR RESEARCH INTEREST (S)

Cardiopulmonary Resuscitation

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Work backwards from present appointment)*

Dates	Institution	Department	Rank/Function
1982-present	University of Health Sciences The Chicago Medical School	Medicine	Professor and Chairman Department of Medicine
1981-present	University of California at Los Angeles	Anesthesia	Clinical Professor
1981-present	Univ. of Southern California	Medicine	Adjunct Professor
1958-1981	Univ. of Southern California	Critical Care Medicine	Professor of Clinical Med Division Chairman
1974-present	Institute of Critical Care Medicine		Director
1972-1981	Univ. of Southern California	Engineering	Prof. of Biomed. Engin.
1971-1981	Univ. of Southern California	Medicine	Prof. of Clinical Med.

HONORS AND AWARDS

1970-1971 President - Society of Critical Care Medicine
1966-1967 Committee on Shock & The Ad Hoc Subcommittee on Resuscitative Fluids, National Academy of Sciences, National Research Council
1968-1973 Chairman - Los Angeles County Commission on Emergency Medical Services
1974-1980 National Academy of Sciences - American Heart Association Panel for Cardiopulmonary Resuscitation and Emergency Cardiac Care (Member)
1981 - Chairman - American College of Cardiology Bethesda Conf. on Emerg. Cardiac Care

INVESTIGATOR'S BIBLIOGRAPHY

NAME
Max Harry Weil, M.D. (Co-Investigator)

SOCIAL SECURITY NO.
055-20-9509

PUBLICATIONS *(Not to exceed three pages for each investigator.)*

Author and co-author of more than 475 literature publications and chapter contributions and six (6) monographs on Shock and Critical Care Medicine.

Books

Weil MH and Shubin H. Diagnosis and Treatment of Shock. Baltimore, Williams and Wilkins Company, 1967.

Weil MH and Shubin H. Critical Care Medicine: Current Principles and Practices. Hagerstown, Maryland; Harper and Row, 1976.

Representative Publications

1. Weil MH, MacLean LD, Visscher MB, Spink WW. Studies on the circulatory changes in the dog produced by endotoxin from gram-negative microorgnisms. J Clin Invest 1956; 35:1191-1198.
2. Weil MH. Current concepts on the management of shock. Circulation 1957;16:1097-1105.
3 Weil MH, Spink WW. The shock syndrome associated with bacteremia due to gram-negative bacilli. Arch Intern Med 1958;101:184-193.
4. Udhoji VN, Weil MH, Sambhi MP, Rosoff L. Hemodynamic studies on clinical shock associated with infection. Amer J Med 1963;34:461-469.
5. Weil MH, Shubin H, Biddle M. Shock caused by gram-negative microorganisms: Analysis of 169 cases. Ann Intern Med 1964;60:384-400.
6. Broder G, Weil MH. Excess lactate: An index of reversibility of shock in human patients. Science 1964;143:1457-1459.
7. Udhoji VN, Weil MH. Hemodynamic and metabolic studies on shock associated with bacteremia: Observations on sixteen patients. Ann Intern Med 1965; 62:966-978.
8. Kwaan HM, Weil MH. Differences in the mechanism of hypotension (shock) caused by bacterial infections. Surg Gynecol Obstet 1969; 128:37-45.
9. Weil MH, Shubin H. Critical Care Medicine I: The VIP approach to the bedside management of shock. JAMA 1969;207:337-340.
10. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 1970;41:989-1001.
11. Nishijima H, Weil MH, Shubin H, Cavanilles JM. Hemodynamic and metabolic studies on shock associated with gram-negative bacteremia. Medicine 1973;52:287-294. Reprinted In: Gruninger RP, Hall WH (eds), Infectious Disease. Baltimore: Williams and Wilkins 1973:287-294.
12. Shubin H, Weil MH, Carlson RW. Bacterial shock. Am Heart J 1977;94:112-114.
13. Weil MH. Current understanding of mechanisms and treatment of circulatory shock caused by bacterial infections. Ann Clin Res 1977;9:181-191.
14. Weil MH, Nishijima H. Cardiac output in bacterial shock. Amer J Med 1978;64: 920-922.

A. RATIONALE

1. Introduction

Reports of abnormalities of mitochondrial function and abberations in the profile of oxygen utilization have prompted consideration of toxic cellular injury as the cause of impaired oxygen metabolism in patients with septic shock. However, recent studies suggest that aerobic metabolism and oxygen consumption may be flow limited in this syndrome. The present study is designed to determine if oxygen utilization is primarily dependent on capillary perfusion in patients with septic shock.

2. Hypothesis

On the basis of our clinical and experimental findings, we propose that the decrements in oxygen consumption observed in patients with septic shock reflect inadequate capillary perfusion rather than toxic cellular injury. Distributive alterations in systemic or microcirculatory flow could result in a decrease in nutritive flow despite a hyperdynamic circulation.[1,2,3] By simultaneous measurements of systemic, regional and capillary flow in combination with systemic and regional indices of oxygen utilization, delineation of the contribution of perfusion deficits to metabolic dysfunction can be assessed.

3. Specific Aims

The specific aims of the study are: (1) to examine the correlation of systemic and regional blood flow to capillary perfusion during septic shock, and (2) to determine the temporal relationship of blood flow to systemic and regional oxygen consumption during septic shock. The anticipated duration of the study is two years in order to enter a total of 50 patients.

4. Current Status of Work in the Area

Early observations of a hyperdynamic circulatory state in septic shock patients by Udhoji and Weil[4] implicated ineffective microcirculatory flow as part of the pathophysiologic defect in this syndrome. In the hyperdynamic patients described by Siegel et al,[5] oxygen consumption appeared to be independent of flow. Lloyd, et al,[6] also noted lactic acidosis in the presence of narrowed arteriovenous oxygen differences suggesting a defect in oxygen uptake. Siegel, Cerra, et al,[7] later observed progressive reductions in oxygen consumption with increased oxygen delivery and lactic acidosis in clinical septic shock. Moreover, studies on capillary flow in septic animals and patients not in shock showed increases in flow proportional to cardiac output.[8,9] In addition, both Schumer, et al,[10] and Mela, et al,[11,12] reported hepatic mitochondrial abnormalities after endotoxin challenge in vitro and in vivo that differed from changes induced by hypoxia. Using isolated perfused livers of rats with peritonitis, Clemens, et al,[13] also reported reductions in hepatic oxidative capacity. Taken together, these studies lead to the postulate that hepatic and peripheral defects in oxygen utilization existed in sepsis independent of tissue perfusion.

In contrast, Kaufman, Rackow, et al,[14] and Astiz, Rackow, et al,[15] recently demonstrated increases in oxygen consumption accompanying increases in oxygen delivery with reversal of lactic acidosis in patients with septic shock. Examination of the data of Shoemaker, et al,[16] on uncomplicated septic shock shows oxygen consumption paralleling oxygen delivery. Gump, et al,[17] reported similar patterns when comparing cardiac output and oxygen consumption in patients with intra-abdominal sepsis. The strong correlation between survival and cardiac function described by Nishiyma, Weil, et al,[18] further emphasizes the importance

of adequate perfusion in clinical septic shock.

Using animal models of lethal peritonitis, both Deker, et al,[19] and Frey, et al,[20] found normal mitochondrial function during the terminal stages of shock. Frey, et al,[21] and Garrison, et al,[22] demonstrated increased tissue hypoxia with decreased hepatic flow suggesting that inadequate oxygen delivery was the primary defect in septic shock. Lundsgard-Hansen, et al,[23] evaluated the temporal relationship between metabolic and hemodynamic parameters in experimental endotoxin shock and concluded that circulatory deterioration was the major determinant of tissue metabolite changes. Similarly, Rink, et al,[24] found that changes in plasma lactate parallelled progressive hepatic hypoxia in endotoxic shock. In our own preliminary studies in a lethal model of rat peritonitis, we have observed marked increases in oxygen extraction with progression of the shock syndrome in both high and low cardiac output states. These findings suggest that impared oxygen utilization during septic shock is not primarily related to toxic cellular injury.

5. Significance

In spite of advances in the care of the critically ill, the mortality with septic shock ranges from 40% to 80%.[24,25] The geriatric age group which dominates the VAMC patient population is at increased risk for developing septic shock with the onset of a bacterial infection.[25] An improved understanding of the relative contributions of microcirculatory hypoperfusion and direct toxic derangments in this syndrome will help direct efforts toward therapeutic interventions aimed at either improving flow to systemic tissues are altering tissue metabolic milieu.

B. BACKGROUND

As mentioned, Udhoji and Weil in early studies described a hyperdynamic circulatory state in septic shock which suggested ineffective flow patterns.[4] Latter work by Nishiyma and Weil which indicated a strong correlation existed between cardiac function and survival in septic shock suggested that circulatory performance was the major determinant of clinical outcome.[15] More recently, Kaufman, Rackow, et al,[14] prospectively compared the effect of increasing oxygen delivery on eight hypovolemic patients with septic shock and five patients with hypovolemic shock. In both groups, increases in oxygen delivery were paralleled by increases in oxygen consumption. With no significant difference noticed between the two groups in these changes. Astiz, Rackow, et al,[15] retrospectively analyzed 35 patients with septic shock and found that oxygen consumption and oxygen delivery correlated significantly at both ends of the hemodynamic spectrum. In addition, a parallel animal project of rat peritonitis, including monitoring of systemic regional and microcirculatory flow, is currently under development at our labs. As discussed, preliminary data suggest that oxygen consumption is flow limited in this syndrome.

C. WORK PROPOSED

The North Chicago Veterans Administration Medical Center is a 1500 bed facility. Included is a large population residing in the incorporated nursing home and intermediate care areas which will serve as the major source of patients for this study. An average of four (4) patients per month are admitted to the medical-surgical intensive care unit with the diagnosis of septic shock and comprise the study population.

1. Methodology

A. Methods

Systemic and pulmonary artery pressures will be measured by femoral artery catheterization (Arrow, Reading, PA) and pulmonary artery catheterization (-Swan-Ganz, Edwards Laboratories, Santa Ana, Ca), respectively.[26] Catheters will be inserted by the standard Seldinger percutaneous technique under local xylocaine anesthesia. Pulmonary artery balloon-tipped floatation catheter placement will be guided by pressure monitoring and proper catheter position confirmed by chest x-ray. All pressures will be measured with the patient in the supine position using the mid-chest as a zero reference on strain-gauge pressure transducers calibrated to a known mercury standard. Hemodynamic measurements will be recorded by a bedside microprocessor-based monitor (Solo, Menen Medical, Clarence, NY).

Cardiac output will be determined by thermodilution utilizing tripligate injections of 10 mL of 5% dextrose in water cooled to less than 1°C.[27] Thermodilution curves will be strip chart recorded to confirm the validity of computed cardiac output determinations (5621A Computer, Edwards Laboratories, Santa Ana, Ca). Systemic oxygen delivery will be calculated as the product of cardiac output and arterial oxygen content. Oxygen consumption will be calculated using the Fick equation from the cardiac output and arterial-mixed venous oxygen content difference. Chapell, et al,[28] recently reported a close correlation between oxygen consumption as calculated by this method and that directly measured.

The washout rate of small molecules injected locally into tissue was proposed by Ketty as a means of measuring capillary flow.[29] Because substances such as water or lipid soluble inert gasses equilibrate rapidly with the blood during its passage through the tissues, their clearance can be used as a measure of capillary flow.[30] $Xenon^{133}$ has proven to be a particularly useful tracer for quantitating skeletal muscle capillary flow in studies on patients with peripheral vascular disease and in shock states.[9,31-34] One- to five-tenths mL of normal saline containing 50 uCi of $Xenon^{133}$ (New England Nuclear, Boston, Mass) is injected 1 cm into the thickest part of the brachioradialis muscle at an angle of 45°.[31] The needle will be withdrawn 30 seconds after the injection to reduce possible backflow of the injected material along the needle tract. After injection, the clearance of the isotope is determined over a 10 minute period from the decline in radioactivity over the intramuscular depot as imaged by a gamma scintillation camera (Sigma 420 Mobile Camera, Ohio Nuclear, Cleveland, Oh) and quantified by a digital computer (Technicure 500, Cleveland, Oh). Initial counting intervals will be set at 5 seconds. The clearance value is calculated from the formula $c = 100 \times \lambda \times k$, where c is the clearance in mL of blood flow/min/100 gms of tissue, λ is the partion coefficient and k is the fractional disappearance of the isotope from tissue.[33,35] A standard value of .7 mL/gm is utilized for λ and k is derived from the slope of the first phase of the clearance curve as plotted on a semilogarithmic scale.[31,35-37] Tonnensen[38] and Kjellmer, et al,[39] reported close agreement between directly measured blood flow and blood flow calculated from the initial phase of Xenon clearance.

$Xenon^{133}$ in saline will be prepared by the method of DiPiazza and Herbert.[40] This technique utilizes commercial saline gas and results in as much as 10% recovery. This is more than adequate for the amount (50 uCi) required for

tissue perfusion studies. To prepare the solution, sterile saline is added aseptically in 1 mL aliquots to 20 mCi vials of gaseous Xenon ^{133} (New England Nuclear, Boston, Mass). Following a 15 minute equilibration time, the activity of a .2 cc aliquot is determined and recorded using a dose calibratory (CRC-5, Capintic, Montvale, NJ). Pyrogens will be tested for using a Limulus kit (Limulus Lysate Assay, Mallinckrodt, St. Louis, Mo). The sterility of each vial will be determined by incubating .3cc of the solution in thioglycolate broth for three days at 40° C. Plating of the cultures will be done in the Nuclear Medicine Department. A stock solution previously tested for pyrogens and sterility will be stored at 4° C. Prior to each study, the quantity utilized will be determined by a dose calibrator in order to insure a 50 uCi injection.

Mercury strain-gauge plethysmography will be used to determine total forearm flow. The use of this technique was first reported by Whitney as a non-invasive method for measuring segmental flow.[41,42,43] A fine bore silicone rubber tube filled with mercury (strain gauge) is placed around the forearm of the patient in a supine position. Either end of the tube makes contact with a copper electrode and this system is in turn connected to an amplifier and recorder (Hokanson, Issaquah, Wash.). After obtaining a stable baseline, a pneumatic cuff placed just above the elbow is inflated to a pressure just below the diastolic arterial pressure to obstruct venous outflow. Initial increase in forearm volume is caused by a similar increase in venous blood volume equal to the rate of arterial inflow. The circumferential increase in length of the strain gauge after inflation of the cuff represents the change in forearm volume. Because relative changes in strain gauge resistance are proportionate to relative changes in strain gauge circumferential length, electrical calibration permits calculation of flow. The inflow deflection recorded after inflating the cuff is used to calculate flow from the equation $Q = s / c$, where Q is the flow in mL of blood flow/min/100 gms of tissue, s is the slope of the deflection and c is the calibration of the strain gauge such that a 1% resistance change equals a 1% volume change.[42-44] Raman, et al,[45] and Conrad and Green[46] observed an excellent correlation between flows measured plethysmographically and those measured directly.

Arterial-venous concentration differences have been applied in clinical and experimental studies to describe utilization and production of substrate in regional beds.[8,47,48] Regional oxygen consumption will be determined from the product of arterial-brachial venous oxygen content difference and forearm flow. Lactate production will be determined for the forearm from arterial and brachial venous samples in combination with flow measurements obtained from plethysmography.[46] Arterial and venous blood gases will be determined utilizing an IL1813 Blood Gas Analyzer. Oxygen content in venous and arterial samples will be measured using an IL28L co-oximeter (Instrumentation Laboratories, Waltham, Mass.). Lactate will be analyzed enzymatically using an NAD-lactate dehydrogenase reagent as previously described by our group.[49] Blood samples for lactate will be collected in tubes containing 0.9 mL of 0.6 mol/L perchloric acid and chilled on ice until assayed.

B. Protocol

1. Entrance Criteria

Patients identified as septic by either: (1) positive blood cultures or (2) an

identifiable site of infection in the lungs, abdomen or urinary tract are eligible for entry into the study. Criteria for the diagnosis of shock include one or more of the following: (1) serum lactate greater than 2 mm/L; (2) systolic arterial blood pressure at less than 90 mm Hg; (3) cardiac index less than 2.2 $L/min/M^2$. Patients will be excluded with either acute hemorrhage or acute myocardial infarction.

2. Experimental Flow

The study includes bedside and laboratory measurements prior to resuscitation (baseline) with subsequent measurements (study) to be repeated at the end of resuscitation.

a. Pre-entry Requirements

(1) Each patient will have a medical history and physical examination. The information will be recorded in the case report forms.
(2) The therapies given in the six hours before the treatment period will be reported in the case report forms.
(3) Each patient will be catheterized with a pulmonary artery thermodilution catheter (Swan-Ganz, Edwards Laboratories, Santa Ana, Ca.) and a femoral arterial line (Arrow, Reading, Pa.).
(4) Each patient will have a foley catheter placed.
(5) Patients will be placed on a face mask with supplemental oxygen to deliver an oxygen concentration resulting in 90% oxygen saturation of the arterial hemoglobin. Patients requiring intubation will be placed on controlled mechanical ventilation utilizing a volume cycled respirator with assist control and tidal volume set to provide an acceptable level of ventilation and an inspired oxygen concentration chosen to provide a 90% oxygen saturation of the arterial hemoglobin.

b. Baseline Bedside Measurements

(1) height
(2) weight
(3) temperature
(4) systolic, diastolic and mean systemic arterial and pulmonary artery blood pressures
(5) pulmonary artery wedge pressure
(6) central venous pressure
(7) cardiac output by thermodilution technique
(8) urine output
(9) pulse rate
(10) respiration rate
(11) forearm arterial flow by plethysmography
(12) capillary flow by xenon clearance

c. Baseline Laboratory Measurements

(1) hemoglobin and hematocrit
(2) arterial, brachial venous and mixed venous pH, PO_2 and pCO_2
(3) arterial, brachial venous and mixed venous oxygen saturation
(4) arterial and brachial venous lactate

d. Resuscitation

(1) Patients will be resucitated by fluid challenge utilizing a standard protocol of 250 mL of fluid every 15 minutes under continuous pulmonary artery pressure guidance until the pulmonary artery wedge pressure (PAWP) equals 15 mm Hg.[50,51] Previous studies by Rackow et al[50] and Packman and Rackow[51] have demonstrated effective fluid resuscitation in septic shock patients utilizing this protocol. Dopamine will be administered in increments of 3 g/kg/min in those patients with systolic arterial pressures less than 90 mm Hg following fluid resuscitation to a PAWP of 15 mm Hg or if the PAWP is $\geq$ 15 mm Hg on admission to the study.

(2) Patients will be treated with appropriate antibiotic therapy and recorded in the case report forms.

(3) Other intervening therapies will also be recorded in the case report forms.

e. Study Bedside and Laboratory Measurements

All measurements will be repeated after filling pressures have been optimized and any necessary dopamine dosage stabilized for one hour.[49]

3. Informed Consent

Informed consent will be obtained from each patient or his family prior to entry into the study (Forms 8,9).

4. Adverse Reactions

The protocol involves the use of two noninvasive proven tests in addition to the usual hemodynamic monitoring employed in patients with septic shock. Because of the nature of methods and lack of experimental intervention in the protocol, entrance in the study should not be associated with any increased incidence adverse reactions over that seen in the routine management of patients with septic shock.

5. Interpretation of the Data

Dopamine, through its interaction with dopaminergic and beta and alpha adrenergic receptors, can potentially effect the distribution of systemic and microcirculatory flow.[30,53] Therefore for data analysis, patients will be divided into two groups: (1) those resuscitated with fluid alone, and (2) those requiring pharmacologic support with dopamine (see text).

For each group, relative changes in cardiac output, forearm flow and capillary flow will be compared to delineate distributive blood flow abnormalities during septic shock. The relationship of distributive patterns in perfusion will also be compared to the systemic and regional forearm alterations in oxygen utilization and lactic acid production. When blood flow is critically decreased, oxygen delivery is no longer adequate to sustain aerobic metabolism, thereby creating an oxygen debt. The conversion of pyruvate to lactate constitutes a compensatory mechanism for partial anaerobic metabolism of glucose. The concentration of lactate in blood corresponds to the degree of oxygen deficit and, in turn, to the severity of perfusion failure.[54,55,56] Thus, the relationship of changes in blood flow to lactate production will be analyzed to delineate whether the decrements in oxygen utilization in septic shock patients reflect inadequate capillary perfusion.

6. Statistical Method

The effects of blood flow on oxygen utilization and lactate production will be

analyzed utilizing standard linear model techniques. The students T-test and one way Analysis of Variance will be used to compare the significance of observed differences from baseline measurements and between fluid and dopamine resuscitated groups. The SAS statistical software package will be used for statistical analysis.

7. Resources

The study will be carried out in the six bed Medical-Surgical Intensive Care Unit (ICU) of the North Chicago Veteran's Administration Medical Center which is fully equipped for bedside hemodynamic monitoring. The hemodynamic data will be collated utilizing a bedside microcomputer-based shock monitor (Solo, Menen Medical in Clarence, NY) with storage and tabulation on a centralized minicomputer (HP 5600A, Hewlett-Packard, Waltham, Mass.). The patient population has been previously described and consists of patients admitted to the ICU meeting the study entrance criteria. Laboratory analysis will be completed by the hospital STAT lab which is fully equipped for measurement of blood gases and lactate (Instrumentation Laboratories, Walthem, Mass.). Full time Nuclear Medicine staff will perform and interpret the Xenon clearance studies. The ICU is fully staffed by critical care nurses with a 1:1 nurse to patient ratio for the patient in circulatory shock and is further supported by respiratory therapy and biomedical specialists. The full-time critical care staff and fellow physicians provide 24 hours/day, 7 days/week bedside patient care.

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Charts

STUDY

Procedure	Baseline	End Resuscitation
Medical History	X	
Physical Exam	X	
Respiration, Pulse Temperature	X	X
Hemodynamic Pressures	X	X
Cardiac Output	X	X
Capillary Flow	X	X
Forearm Flow	X	X
Laboratory Measurements	X	X

Form 2
ENTRANCE CRITERIA

Answer each question to determine the patient's eligibility to enter the study.

	YES	NO
1. Is the patient a male or not known to be gravid female?	_____	STOP
2. Is the patient receiving any experimental medications?	STOP	_____
3. Is the patient in septic shock?	_____	STOP
4. Does the patient have: (check any applicable)		
a. Serum lactate greater than 2 mM/L	_____	_____
b. Systolic arterial blood pressure less than 90 mm Hg	_____	_____
c. Cardiac index less than 2.2 L min^{-1} M^{-2}	_____	_____

If none of the boxes marked STOP are checked and one or more of the criteria in #4 is checked, the patient is eligible for this study.

Investigator's Initials

Date Initialed

Form 3
MEDICAL HISTORY

Patient Number _____ Patient Initials _____ Date History Taken _____
Month/Day/Year

Date of Birth _____ Sex: _____ Male _____ Female Date of Hospital Admission _____
Month/Day/Year

Diagnosis on Admission (include etiology): _____

Please indicate whether or not the patient has had any known illness for each of the following. Explain all YES answers, identifying by system number.

SYSTEM	PAST ILLNESS NO	YES	DESCRIPTION: (identify by system number)
1. Neurological	____	____	
2. Respiratory	____	____	
3. Cardiovascular	____	____	
4. Blood	____	____	
5. Dermal	____	____	
6. Endocrine	____	____	
7. Genitourinary	____	____	
8. Hepatic	____	____	
9. Renal	____	____	
10. Lymphatic	____	____	
11. Musculoskeletal	____	____	
12. Gastrointestinal	____	____	
13. Other (specify)	____	____	

Investigator's Initials Date Initialed

Form 4
PHYSICAL EXAMINATION

Patient Number _____ Patient Initials _____ Date of Examination _____

Weight _____ pounds Height _____ inches Temperature _____ °F
or _____ kg or _____ cm or _____ °C

Please indicate whether or not abnormalities of any of the following are observed on physical examination. Describe all abnormalities.

CATEGORY	NORMAL	ABNORMAL	DESCRIPTION
Eyes, Ears, Nose, Throat			
Head and Neck			
Heart			
Lungs			
Abdomen			
Pelvis			
Musculoskeletal			
Lymph Nodes			
Skin			
Genitourinary			
Neurological			

Investigator's Initials: Date Initialed:

Form 5
TREATMENT

Patient Number _____ Patient Initials _____

TREATMENT PRIOR TO STUDY

Fluid Expanders	Total Dose or Volume	Time of Administration (24 Hour Clock)	Reason for Administration

Drugs/Solutions

TREATMENT DURING THE STUDY

Fluid Expanders	Total Dose or Volume	Time of Administration (24 Hour Clock)	Reason for Administration

Drugs/Solutions

Investigator's Initials Date Initialed

Form 6
BEDSIDE MEASUREMENTS

Time Date Baseline End Resuscitation

Systemic Artery Pressures

Systolic

Diastolic

Mean

Pulmonary Artery Pressures

Systolic

Diastolic

Mean

Pulmonary Artery Wedge Pressures

Central Venous Pressures

Cardiac Output

Femoral Flow

Capillary Flow

Heart Rate

Temperature

Respiratory Rate

Form 7
LABORATORY MEASUREMENTS

Time	Date	Baseline	End Resuscitation
Hemoglobin gm%			
$F_{1}O_{2}$ %			
Arterial pH			
pO_2 mm Hg			
pCO_2 mm Hg			
Mixed Venous pH			
pO_2 mm Hg			
pCO_2 mm Hg			
Brachial Venous pH			
pO_2 mm Hg			
pCO_2 mm Hg			
O_2 cont a Vol %			
v Vol %			
bv Vol %			
Arterial Lactate mm/L			
Brachial Venous Lactate mm/L			

HUMAN STUDIES

Yes X No
(If Yes, complete this section)

1. Investigational studies: None. All tests to be done are routine and proven.

2. Investigational drugs: None

3. Drugs supplied by: ___Investigator ___Drug Company ___VA Pharmacy

___Other

RISKS AND BENEFITS EVALUATION

A. The purpose of the investigation may be briefly stated as follows:
To monitor systemic, regional and microcirculatory function and systemic and regional oxygen metabolism and thereby delineate the contributions of perfusion deficits to altered oxygen metabolism in septic shock.

B. The human subjects will be exposed to the following short term and long term risks by participation in this study:

1. Physical risks: None other than those the patient is exposed to with the usual intensive care therapy for shock.

2. Psychological risks: As above.

3. Risks to alternate or non-treatment control patients:
Protocol does not involve therapy.

4. State available toxicity data from animal studies:
None

5. State available toxicity data from human studies with references:
None, there is no therapy involved.

C. Summary of benefits to be expected:

1. Direct patient benefit: No acute benefit.

2. Value of knowledge to be gained:
Appreciation of the role of hyperperfusion versus toxic cellular injury in septic shock will lead to better directed therapeutic and investigative efforts.

HUMAN RIGHTS AND WELFARE SAFEGUARDS

A. Is specific protocol attached? X Yes ____ No

B. What procedures are provided to ensure that any potentially harmful results are recognized in time to protect the subject from harm?

The patient will be carefully monitored during the duration of the protocol in the Intensive Care Unit.

C. Confidentiality and security:

1. Does the investigation require the disclosure of information by the subject concerning his medical history or past or present behavior? (Attach a copy of all inquiries which will be directed to the subject. Where this information is contained in the protocol, a cross reference to the pertinent pages of the protocol will suffice.)

None other than the usual past medical history (See form 2).

2. What use may be made of this information and other results obtained in this study? They will be held in confidentiality and should not affect the study protocol.

3. What procedures will be used to maintain the confidentiality of this information? They information will be stored in locked files.

4. Before data concerning the results of the study or the subject's history or past or present behavior may be published or otherwise disseminated in such a manner that the identity of the subject may be disclosed, the subject's written consent shall be obtained.

RELATIONSHIP OF THE INVESTIGATOR TO THE EXPERIMENTAL SUBJECT

1. Does a doctor-patient relationship currently exist? No.

2. Are any of the subjects involved in this research either employees of the Veterans Administration, students or employees of the Chicago Medical School or one of its affiliated institutions? (If yes, please explain in detail) No.

3. Are any of the subjects classified as minors under current Illinois law (less than 18 years of age)? ____ Yes X No

4. Are any of the subjects in the proposed investigation either prisoners or of unsound mind? X Yes ____ No

5. Does any other special relationship exist? ____ Yes X No

CLINICAL RECORD

Report on INFORMED CONSENT TO BE READ BY THE SUBJECT
or
Continuation of S. F. ADDENDUM TO V.A. FORM 10-1086
(Strike out one line) (Specify type of examination or data)

(Sign and date)

Information about: Mechanism of Septic Shock

Principal Investigator: Mark E. Astiz, M.D. - Phone (312) 688-1900, Ext. 4506

The Research and Development Committee, and the Sub-Committee on Human Studies at the North Chicago Veterans Administration Medical Center approved the solicitati of subjects to participate in this research study.

The purpose of this investigation is to study changes in blood flow from the heart, and its relationship to blood flow to the arm and arm tissues in patients with serious infections. In spite of "adequate" blood flow, patients with serious infections still may die. The data collected from your participation in this research protocol may provide answers which will help us understand why this occurs. There are no experimental procedures in this research protocol. In addition to the usual procedures utilized in caring for patients with serious infections, two other tests will be done. One involves the placement of a blood pressure cuff over the arm and the measuring of changes in arm volume. It is a routine test that shoul not be associated with any discomfort and does not require any injections or surgic procedures. The second test requires the injection of a small amount of marker int the arm and taking pictures over that area for a period of 5 minutes. The needle to be used is extremely small and should be associated with minimal discomfort. These tests and associated laboratory tests will be repeated twice. There are no known risks of participating in this research protocol other than those caused by t disease state that led to your eligibility for this study. Patients who participate in this trial will be closely monitored by senior staff physicians. Patients who do not wish to participate in this study will receive identical care to patients who do participate. Data obtained from non-participants will not be utilized.

Authorized investigators may review my medical records. My physician may publish the results of the study in the medical literature. I know that my name will not be used.

If I have any questions concerning the procedures outlined above, my doctor will be glad to discuss them with me and give me any other information I desire.

I know I am free to withdraw my consent and discontinue participation in this study at any time without prejudice to my continued care, and I will continue to get the best care possible for my condition.

(Continue on reverse side)

PATIENT'S IDENTIFICATION (For typed or written entries give: name—last, first, middle; grade; date; hospital or medical facility)

REGISTER NO.

WARD NO.

REPORT ON _____ or CONTINUATION OF _____

CONTROL NO. 78667

I have read the above and understand it and hereby consent to the procedures set forth above.

Patient/Guardian	Witness

PART I AGREEMENT TO PARTICIPATE IN RESEARCH
BY OR UNDER THE DIRECTION OF THE VETERANS ADMINISTRATION

DATE

1. I, _____, voluntarily consent to participate as a sul
(Type or print subject's name)

in the investigation entitled _____
(Title of study)

2. I have signed one or more information sheets with this title to show that I have read the description including the purpose and nature of investigation, the procedures to be used, the risks, inconveniences, side effects and benefits to be expected, as well as other courses of action open to and my right to withdraw from the investigation at any time. Each of these items has been explained to me by the investigator in the presence of a witn The investigator has answered my questions concerning the investigation and I believe I understand what is intended.

3. I understand that no guarantees or assurances have been given me since the results and risks of an investigation are not always known beforehan have been told that this investigation has been carefully planned, that the plan has been reviewed by knowledgeable people, and that every reasona precaution will be taken to protect my well-being.

4. In the event I sustain physical injury as a result of participation in this investigation, if I am eligible for medical care as a veteran, all necessary appropriate care will be provided. If I am not eligible for medical care as a veteran, humanitarian emergency care will nevertheless be provided.

5. I realize I have not released this institution from liability for negligence. Compensation may or may not be payable, in the event of physical inj arising from such research, under applicable federal laws.

6. I understand that all information obtained about me during the course of this study will be made available only to doctors who are taking care of and to qualified investigaters and their assistants where their access to this information is appropriate and authorized. They will be bound by the s requirements to maintain my privacy and anonymity as apply to all medical personnel within the Veterans Administration.

7. I further understand that, where required by law, the appropriate federal officer or agency will have free access to information obtained in this st should it become necessary. Genetally, I may expect the same respect for my privacy and anonymity from these agencies as is afforded by the Veter Administration and its employees. The provisions of the Privacy Act apply to all agencies.

8. In the event that research in which I participate involves certain new drugs, information concerning my response to the drug(s) will be supplied to sponsoring pharmaceutical house(s) that made the drug(s) available. This information will be given to them in such a way that I cannot be identified.

I _____
NAME OF VOLUNTEER

HAVE READ THIS CONSENT FORM. ALL MY QUESTIONS HAVE BEEN ANSWERED, AND I FREELY AND VOLUNTARILY CHOOSE TO PARTICIPATE. I UNDERSTAND THAT MY RIGHTS AND PRIVACY WILL BE MAINTAINED. I AGREE TO PARTICIPATE AS A VOLUNTEER IN THIS PROGRAM.

9. Nevertheless, I wish to limit my participation in the investigation as follows:

VA FACILITY	SUBJECT'S SIGNATURE
WITNESS'S NAME AND ADDRESS (Print or type)	WITNESS'S SIGNATURE
INVESTIGATOR'S NAME (Print or type)	INVESTIGATOR'S SIGNATURE

☐ Signed information sheets attached. ☐ Signed information sheets available at:

SUBJECT'S IDENTIFICATION (I.D. plate or give name - last, first, middle)

SUBJECT'S I.D. NO.

WARD

AGREEMENT TO PARTICIPATE IN RESEARCH BY OR UNDER THE DIRECTION OF THE VETERANS ADMINISTRATION

VA FORM 10-1086 SEP 1979

SUPERSEDES VA FORM JUN 1975, WHICH WILL N USED.

REPORT OF SUBCOMMITTEE ON HUMAN STUDIES

PROJECT OR PROGRAM TITLE	NUMBER
MECHANISMS OF SEPTIC SHOCK	

PRINCIPAL INVESTIGATOR'S NAME	VA FACILITY
Mark E. Astiz, M.D.	VAMC North Chicago, IL

INSTITUTION OF SUBCOMMITTEE *(or the equivalent body)*

DATE OF REVIEW: June 19, 1984

This subcommittee has reviewed the above described project with respect to the rights and safety of the human subjects. The following are our findings:

1. RISKS *(Check one)*

[X] The planned research involves little foreseeable risk and the subjects safety is adequately protected unless the plan is modified.

[ ] The foreseeable risk is justified by the potential benefit to the subjects or by the anticipated benefit to society and the plans include adequate and appropriate measures to reduce the risk insofar as feasible.

[ ] The risk is justified but further measures seem advisable to protect the subject, including _____

_____

_____

[ ] The risk seems greater than can be justified by the research as planned and the project or program is not approved as presented.

2. INFORMATION FOR THE SUBJECT *(Check one)*

[X] The information to be given the subjects *(or their legal representatives)* is complete and accurate enough for them to reach a valid decision concerning participation in the research.

[ ] The information for the subjects as presented is incomplete or defective in that _____

_____

_____

3. CONSENT METHOD *(Check one)*

[X] The format and manner of obtaining informed consent from the subjects *(or their legal representatives)* is satisfactory.

[ ] The method of obtaining informed consent is defective in that _____

_____

4. FURTHER COMMENTS

CONTROL NO. 7866

5. RECOMMENDATION *(Check one)*

[X] The project or program be approved as submitted.

[ ] The plan or protocol be revised in keeping with our comments and resubmitted.

[ ] The proposal as described be rejected.

SIGNATURE OF CHAIRMAN

SANT P. SINGH, M.D.

VA FORM 10-1223

VETERANS ADMINISTRATION MEDICAL CENTER
NORTH CHICAGO, ILLINOIS

Research and Development Committee Meeting
June 21, 1984

PRESENT: S.P. Singh, M.D., Executive Secretary; Lester Cohn, M.D., Maria R. Couper, R.N., Ph.D.; Ediz Z. Ezdinli, M.D.; Timothy R. Hansen, Ph.D.; Robert E. Kuttner, Ph.D.; Joseph J. Ryan, Ph.D. (f/Orville Lips, Ph.D.); Frederick Sierles, M.D.; Conrad M. Swartz, Ph.D., M.D.; A.J. Vazquez, M.D.; Patricia Schipula, AO/R&D (ex officio)

Observer: Larry Blacik

EXCUSED: Y.B. Kim, M.D.; Jean Kowal, M.D.

GUESTS: Mark E. Astiz, M.D.; Clarke Halfman, Ph.D.; Michael A. Taylor, M.D.

1. The new committee members were introduced. The functions of the committee were reviewed and discussed. Dr. Ediz Z. Ezdinli was nominated and unanimously approved as Chairman, Research and Development Committee.

2. Minutes. The minutes of the meeting of May 17, 1984 were unanimously approved as submitted. They will be signed and forwarded to VACO as required.

3. Old Business.

a. The minutes of the meeting of May 17, 1984 are corrected to reflect that Dr. Moira Breen has a letter from VACO which indicates funding support "through May 1984" vice "end of April" as shown in paragraph 7, line 7, of the minutes of April 19, 1984.

4. Research proposal Neuropsychological Dysfunction in Affective Disorders by Michael A. Taylor, M.D. The study proposes to assess the ability of specialized measures of neuropsychological function to discriminate among depressed, pseudodemented and demented patients. It is proposed to study 25 patients in each of these diagnostic categories admitted to the short-term psychiatric treatment units. The neuropsychological testing will not interfere with the treatment of the patients. Details of the testing procedures, obtaining informed consent as well as criteria for consent, and entering information in the patients' charts were discussed at length. Dr. Ryan suggested that the personnel administering the tests inform the ward personnel of the purpose of the tests as part of a research project so as not to be confused with psychology testing functions. After further discussion, the proposal was unanimously approved.

5. Research proposal Mechanisms of Septic Shock by Mark E. Astiz, M.D. The proposal was reviewed and approved for submission to VACO Merit Review Board.

6. Research proposal Optimization of Fluorescence Immunoassays Based Upon Polarization by Arthur S. Schneider, M.D. Dr. C. Halfman, Co-investigator, discussed the proposal with the committee. The project has a potentially significant impact on laboratory technology, particularly in endocrinology and therapeutic drug monitoring, and enhancement to patient care. The proposal was approved for submission to VACO Merit Review Board.

7. Research proposal High-Dose R022-1319 in Schizophrenia by Richard Abrams, M.D. The committee requested more information on animal and human studies (e.g., toxicity) with the proposed dose of the drug. Action was deferred pending the clarifications.

8. Research proposal Effects of Patient Education on Compliance: A Meta-Analysis of Studies by Maria R. Couper, R.N., Ph.D. The proposal was discussed and approved for submission to VACO Health Services Research and Development Service.

9. Research proposal The Characterization of Effective Electroconvulsive Therapy by Conrad M. Swartz, Ph.D., M.D. The proposal is similar to the RAG approved study being conducted by Dr. Swartz. The subjects will be patients who have received ECT according to their physician and the ECT is not part of this project per se and requires drawing blood specimens only. The proposal was approved for submission to VACO Merit Review Board.

10. Research proposal Endocrine Management of The Assaultive Geripsychiatric Male by Conrad M. Swartz, Ph.D., M.D. After a detailed discussion of the proposed use of progesterone, the dose of 40 mg b.i.d. p.o., and informed consent, the committee recommended a pilot study on 5 patients using a 20 mg b.i.d. dose. If supportive information is obtained, then consideration be given to develop a proposal for submission for merit review.

11. Research proposal Metabolic Effects of Maternal Alcoholism by Sant P. Singh, M.D. The proposal is an extension of the ongoing research program of the investigator and after discussion it was approved for submission to VACO Merit Review Board.

12. Research proposal Entamoeba hystolytica Toxin Action: Role of Second Messengers by Harvey S. Kantor, M.D./Srinivasa V. Achar, Ph.D. Due to the tardiness of the proposal, committee members were requested to review it and cast their vote by telephone to the Research Office in order to meet the deadline for submission to VACO for merit review. Approval will be confirmed at the next committee meeting.

13. Research proposal Oral Activated Charcoal in Chronic Renal Failure by Michael Phillips, M.D. The proposal is a pilot study to determine the effects of orally ingested activated charcoal (AC) on the blood chemistry of patients suffering from chronic renal failure. The proposal was approved with one abstention.

14. There being no further business, the meeting was adjourned at 5:00 p.m.

Sant P Singh MD.

SANT P. SINGH, M.D.
Executive Secretary

APPROVED:

For And In Absence Of

JONATHAN D. HAWK
Acting Medical Center Director

EDIZ Z. EZDINLI, M.D.
Chairman

DISTRIBUTION: 00, 001, 11, Committee members

VETERANS ADMINISTRATION MEDICAL CENTER
NORTH CHICAGO, ILLINOIS

Subcommittee on Human Studies Meeting
June 19, 1984

PRESENT: Sant P. Singh, M.D., Chairman; George English, Ph.D.; Robert Harms; Reverend Shirley Herman; Carole Johnson, R.Ph.; Jean Kowal, M.D.; Suleyman Sarpel, M.D.

EXCUSED: Alfred Lewis

GUESTS: Mark E. Astiz, M.D.; Michael Phillips, M.D.; Conrad M. Swartz, Ph.D., M.D.; Michael Taylor, M.D.

1. New members, Dr. Sarpel, Oncology Section, and Dr. English, Psychology Service, were introduced to the Subcommittee.

2. Minutes. The minutes of the meeting of May 15, 1984 were approved as written.

3. Old Business.

a. Research proposal Growth Hormone Deficiencies in Old Age by Daniel Rudman, M.D. ACOS/R&D received a letter from Dr. Rudman stating that he has decided not to do the total body water test. Therefore, no radioactive material will be given to the subjects who participate in this study. The proposal will not be submitted to the Medical Isotopes Committee for consideration.

4. Research proposal Neuropsychological Dysfunction in Affective Disorders by Michael Taylor, M.D. The study proposes to assess the ability of specialized measures of neuropsychological function to discriminate among depressed, pseudodemented, and demented patients. It is proposed to study 25 patients in each of these diagnostic categories admitted to the short-term psychiatric treatment units. Testing will be done by technicians trained for this and will not interfere with patients' treatment. After further discussion the proposal was unanimously approved.

5. Research proposal Pinacidil vs Placebo: Parallel Double-Blind Study in Hypertension by Michael Phillips, M.D. The proposed study is an extension of the ongoing pinacidil study. The purpose of the study is to determine if pinacidil is more effective than placebo in the treatment of hypertension. Subjects will be carefully monitored for possibility of hypertension becoming uncontrolled in placebo group. In which case, conventional therapy will be resumed. The proposal was unanimously approved with recommendation that the consent form be revised to include the adverse effects of the drug (page 21, paragraph 3), and that the form be prepared on an SF 507 as required for proper processing.

6. Research proposal Mechanisms of Septic Shock by Mark E. Astiz, M.D. A similar proposal on septic shock has been submitted to the Research Advisory Group. The current proposal will be submitted to VACO for merit review. The details of obtaining informed consent were discussed. The investigator will obtain consent from the family. After further discussion, the proposal was approved with recommendation for minor corrections/changes to the consent form, e.g., investigator signature line, as well as a letter of concurrence from the Chief, Nuclear Medicine Service.

7. Research proposal Characterization of Effective Electroconvulsive Therapy by Gonrad M. Swartz, Ph.D., M.D. This study is similar to the RAG-approved study being conducted by Dr. Swartz. Subjects will be patients who have received ECT by order of their physician, and blood samples will be obtained from them for evaluation. After further discussion, the proposal was approved with the recommendation that the investigator administer the blood sampling as part of the treatment and include this information in the protocol and the consent form.

8. Research proposal Endocrine Management of the Assaultive Geripsychiatric Male by Conrad M. Swartz, Ph.D., M.D. The proposed use of progesterone in assaultive male patients was discussed at length. It was indicated that there are patients who assault staff, patients, and doctors. Of primary concern is the demented patients who cannot control what they are doing. In this case, consent must be obtained from the family. It was noted that the investigator must obtain an IND number for progesterone. After further discussion the proposal was approved.

9. Research proposal High-Dose RO22-1319 in Schizophrenia by Richard Abrams, M.D. Dr. Abrams has been doing this study using this drug in this hospital and requests approval to increase the dose. Request approved.

10. Research proposal Effects of Patient Education on Complicance: A Meta-Analysis of Studies by Maria R. Couper, R.N., Ph.D. This study is a survey of searches in the library and not a matter for the Subcommittee. Human rights are not involved.

11. There being no further business, the meeting was adjourned.

SANT P. SINGH, M.D.
Chairman

VETERANS ADMINISTRATION MEDICAL CENTER
NORTH CHICAGO, ILLINOIS

Research and Development Committee Meeting
June 21, 1984

PRESENT: S.P. Singh, M.D., Executive Secretary; Lester Cohn, M.D., Maria R. Couper, R.N., Ph.D.; Ediz Z. Ezdinli, M.D.; Timothy R. Hansen, Ph.D.; Robert E. Kuttner, Ph.D.; Joseph J. Ryan, Ph.D. (f/Orville Lips, Ph.D.); Frederick Sierles, M.D.; Conrad M. Swartz, Ph.D., M.D.; A.J. Vazquez, M.D.; Patricia Schipula, AO/R&D (ex officio)

Observer: Larry Blacik

EXCUSED: Y.B. Kim, M.D.; Jean Kowal, M.D.

GUESTS: Mark E. Astiz, M.D.; Clarke Halfman, Ph.D.; Michael A. Taylor, M.D.

1. The new committee members were introduced. The functions of the committee were reviewed and discussed. Dr. Ediz Z. Ezdinli was nominated and unanimously approved as Chairman, Research and Development Committee.

2. Minutes. The minutes of the meeting of May 17, 1984 were unanimously approved as submitted. They will be signed and forwarded to VACO as required.

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14. There being no further business, the meeting was adjourned at 5:00 p.m.

Sant P. Singh M.D.

SANT P. SINGH, M.D.
Executive Secretary

APPROVED:

JONATHAN D. HAWK
Acting Medical Center Director

EDIZ Z. EZDINLI, M.D.
Chairman

DISTRIBUTION: 00, 001, 11, Committee members

CONTROL NO. 7865

VETERANS ADMINISTRATION MEDICAL CENTER
NORTH CHICAGO, ILLINOIS

Subcommittee on Human Studies Meeting
June 19, 1984

PRESENT: Sant P. Singh, M.D., Chairman; George English, Ph.D.; Robert Harms; Reverend Shirley Herman; Carole Johnson, R.Ph.; Jean Kowal, M.D.; Suleyman Sarpel, M.D.

EXCUSED: Alfred Lewis

GUESTS: Mark E. Astiz, M.D.; Michael Phillips, M.D.; Conrad M. Swartz, Ph.D., M.D.; Michael Taylor, M.D.

1. New members, Dr. Sarpel, Oncology Section, and Dr. English, Psychology Service, were introduced to the Subcommittee.

2. Minutes. The minutes of the meeting of May 15, 1984 were approved as written.

3. Old Business.

a. Research proposal Growth Hormone Deficiencies in Old Age by Daniel Rudman, M.D. ACOS/R&D received a letter from Dr. Rudman stating that he has decided not to do the total body water test. Therefore, no radioactive material will be given to the subjects who participate in this study. The proposal will not be submitted to the Medical Isotopes Committee for consideration.

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5. Research proposal Pinacidil vs Placebo: Parallel Double-Blind Study in Hypertension by Michael Phillips, M.D. The proposed study is an extension of the ongoing pinacidil study. The purpose of the study is to determine if pinacidil is more effective than placebo in the treatment of hypertension. Subjects will be carefully monitored for possibility of hypertension becoming uncontrolled in placebo group. In which case, conventional therapy will be resumed. The proposal was unanimously approved with recommendation that the consent form be revised to include the adverse effects of the drug (page 21, paragraph 3), and that the form be prepared on an SF 507 as required for proper processing.

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11. There being no further business, the meeting was adjourned.

SANT P. SINGH, M.D.
Chairman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 24,978

JAN 23 1984

Mark E. Astiz, M.D.
Department of Nuclear Medicine (115)
Veterans Administration Medical Center
North Chicago, Illinois 60064

Dear Dr. Astiz:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND 24,978) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for the use of the diagnostic radiopharmaceutical drug product, Xenon Xe 133 in Saline for the evaluation of regional blood flow by intramuscular administration. The specific aims of the study are (1) to examine the correlation of systemic and regional blood flow to capillary perfusion during septic shock and, (2) to determine the temporal relationship of blood flow to systemic and regional oxygen consumption during septic shock.

We also refer to your telephone conversations with Division personnel on October 17, November 5, and November 16, 1984 concerning the supplier of your raw material Xenon Xe 133 Gas.

We acknowledge the receipt of your amendment dated November 28, 1984 which names your supplier of the raw material Xenon Xe 133 Gas, and provides the procedure you will use to prepare the final dosage form.

The IND Exemption provides for the clinical use of this approved drug for an approved indication, and by the approved route of administration. Unfortunately, the drug is not commercially available as a sterile and apyrogenic product at this time. The license issued to your institution by the U.S. Nuclear Regulatory Commission limits the use of radiopharmaceutical drug products to material which has been prepared under an FDA approved New Drug Application or to those radiopharmaceuticals compounded in-house under an IND Exemption.

We have completed our review of your submission and have concluded that your clinical study may proceed as planned. In the event that the product becomes commercially available again, please notify the Division so that this Exemption may be discontinued.

CONTROL NO. 78667

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions, an agreement to provide for any significant changes in your clinical protocol by means of an amendment, and the submission of a progress report detailing the course of your study at intervals not to exceed one year.

Thank you for your cooperation.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics