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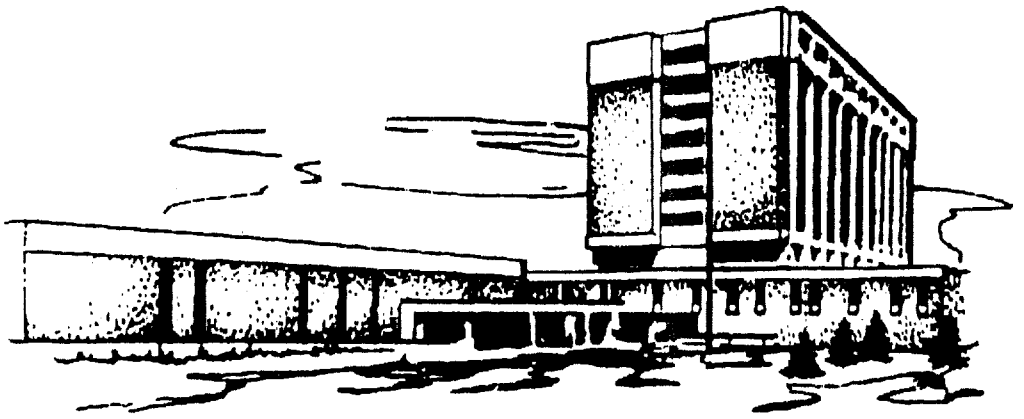
Annual Progress Report

Fiscal Year 1990



Department of Clinical Investigation
William Beaumont Army Medical Center
El Paso, Texas 79920-5001

REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	25 Mar 91	Annual 1 Oct 89-30 Sep 90

4. TITLE AND SUBTITLE
Annual Research Progress Report FY 90

5. FUNDING NUMBERS

6. AUTHOR(S)
COL Manuel Schydlower, MC

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Department of Clinical Investigation
William Beaumont Army Medical Center
El Paso, TX 79920-5001

8. PERFORMING ORGANIZATION REPORT NUMBER
RCS-MED-300 (R1)

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of The Surgeon General
Department of the Army
Washington, DC 20314

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release. Distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Subject report serves to identify the research activities conducted at William Beaumont Army Medical Center investigators who had protocols approved by the Clinical Investigation Committee, the Institutional Review Board, and the Animal Use Committee. This report includes all protocols registered with the Department of Clinical Investigation during FY 1990. All known presentations and publications are also included. The research protocols described were conducted under the provisions of AR 40-38 (Clinical Investigation Program); AR 40-7 (Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Substances; AR 70-25 (Use of Volunteers as Subjects of Research); HSC 40-23 (Management of Clinical Investigation Protocols and Reports); and AR 70-18 (The Use of Animals in DOD Programs).

14. SUBJECT TERMS	15. NUMBER OF PAGES
Clinical Investigations; Publications; Presentations; Detail Summary Sheets (Study Objective, Technical Approach, Progress, & Status)	245
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	

NSN 7540-01-280-5500

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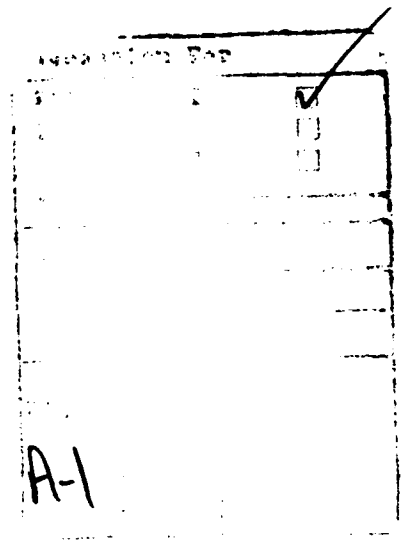


Headquarters
William Beaumont Army
Medical Center
El Paso, Texas 79920-5001

Annual Progress Report
Fiscal Year 1990

Clinical Investigation Program
RCS MED-300 (R1)

This report was prepared under the direction of
Colonel Manuel Schydlower
Chief, Department of Clinical Investigations
William Beaumont Army Medical Center
El Paso, Texas 79920-5001

FORWARD

Highlights in the Department of Clinical Investigation at William Beaumont Army Medical Center, during Fiscal Year 1990, included seeking and obtaining additional extramural and collaborative research projects. Among these, our medical center became a funded participant in an Army Medical Research and Development Command/Department of Veteran Affairs cooperative multicenter efficacy study of passive immunization in the prevention of Klebsiella and Pseudomonas infection. We also received notification of approval from MRDC of a major grant for mucin gene research and investigation of environmental toxic exposures. During this period, continued progress occurred in our joint Navy/Army sickle cell trait/human exercise physiology projects. Additionally, our Jackson Foundation account was reactivated, and utilized for support of education projects at WBAMC.

Our department was very active in supporting clinical projects throughout the medical center, and collaborated in finalizing several studies of important clinical significance. For example, the Departments of Pediatrics and Clinical Investigation jointly studied the measles revaccination immune response in a military dependent population and further defined the need and best timing for revaccination. An MRDC-funded Orthopedic project, studying lower extremity injuries in soldiers involved in basic training, reached the final stages of data collection. This project will greatly advance knowledge on the mechanisms, diagnosis, and prevention of these injuries.

The American Association for Accreditation of Laboratory Animal Care (AAALAC) conducted an inspection of our Biological Research Service. We were impressed with their detailed scrutiny of the program, and felt confident that the high standards in our care and use of laboratory animals would result in a reaccreditation decision. Additionally, our animal lab provided early and ongoing support of Operation Desert Shield by collaborating with the Department of Surgery in conducting Advanced Trauma Life Support Training for deploying personnel.

The cohesive, dependable and enthusiastic members of the clinical investigation team at WBAMC are together responsible for another year of progress and accomplishment. On behalf of our soldiers, patients, faculty and houseofficers, thank you for making clinical investigation a healthy and thriving activity at WBAMC. It is a privilege to serve with you.

Manuel Schydlower, M.D.

MANUEL SCHYDLOWER
Colonel, Medical Corps
Chief, Department of Clinical Investigation

Objectives

The Department of Clinical Investigation is responsible for providing the facilities and atmosphere of inquiry necessary to support and stimulate basic and clinical medical investigation within William Beaumont Army Medical Center.

Technical Approach

The Department of Clinical Investigation provides support for staff, fellows and housestaff research projects under the guidelines of the Clinical Investigation Program (AR 40-38); Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances (AR 40-7); Use of Volunteers as Subjects of Research (AR 70-25); Management of Clinical Investigation Protocols and Reports (HSC Reg 40-23); and The Use of Animals in DOD Programs (AR 70-18). Research protocols utilizing laboratory animals also adhere to the guidelines set forth in the "Guide for Laboratory Animal *Facilities and Care*" (published by the National Academy of Sciences-National Research Council) and the criteria established by the American Association of Laboratory Animal Care.

Research is conducted under protocols approved by the WBAMC Clinical Investigation Committee, Human Use Committee, Radioisotope Committee and Animal Use Committee, as applicable. Committee membership is governed by WBAMC Reg 15-1.

MANPOWER: Listed below is the current strength of the Department of Clinical Investigation.

Description	Grade	MOS	Br	Req	Auth	Name	Rank
C, Dept Cl Inv	06	60P	MC	1	1	Schydlower	06
Dir, HP/SCT	05	60F	MC	1	1	Weisman	05
Immunologist	03	68E	MS	1	1	Martig	05
Biochemist	03	68C	MS	1	1	Smith	03
C, Bio Res Svc	03	64C	VC	1	1	O'Hair	04
Animal Care NCO	E6	91T	NC	2	1	Ribble	E5
Biol Sci NCO	E5	01H	NC	1	1	Fama*	E6
Biol Sci Asst	E4	01H		1	1	Ezukanma	E5
Biol Sci Asst	E4	01H		0	0	Delgado	E4
Biol Sci Asst	E4	01H		0	0	Barlan	E4
Animal Care Sp	E4	91T		1	1	Kahn	E4
Animal Care Sp	E3	91T		2	1	Brown	E3
Supv Res Chem	12	1320	GS	1	1	Bhattacharyya	12
Microbiologist	12	403	GS	1	1	Veit	12
Chemist	09	1320	GS	1	1	Enriquez	09
Microbiologist	09	403	GS	1	1	Smiley	09
Med Technician	07	645	GS	2	1	Lund	07
Med Technician	07	645	GS	2	1	Mana	07
Med Technician	07	645	GS	2	1	McIntyre	07
Health Tech	07	640	GS	1	1	Revels	07
Cl Prot Coord	07	303	GS	1	1	McCollum	07
Edit Asst Typ	07	1087	GS	1	1	Lamonde	07
Sup Clk (Typ)	04	2005	GS	1	1	Turner	04
Anm Caretaker	04	5048	WG	1	1	Sigholz	04
Anm Caretaker	01	5048	WG	2	1	Burton	01

* Detailed to WBAMC Security Force

Civilian Personnel with Special Project Funding

Co-Director HP/SCT				Zeballos
Exer Physiol	09	413	GS	Connery
Health Technician	07	640	GS	Walker
Med Technician	06	645	GS	Lopez
Edit Asst	05	1087	GS	Angerman
Res Proj Clerk	04	303	GS	Morillo
Data Transcriber	03	356	GS	Brungs

PERSONNEL

	Required	Authorized	Assigned
Officers	7	5	5
Enlisted	7	5	7
Civilian	18	13	20*

* 7 civilians are funded through special projects

GRANTS:

USA Medical Research and Development Command

Prevention of Stress Fractures Through Modification of Basic Combat Training Physical Training Activities Based on Biodynamics. (Continuation of last year's grant) $174,111.60

Combat Trauma Surgery Using a Portable Contact Nd-(YAG) Laser in the Porcine and Ovine Models. $107,000

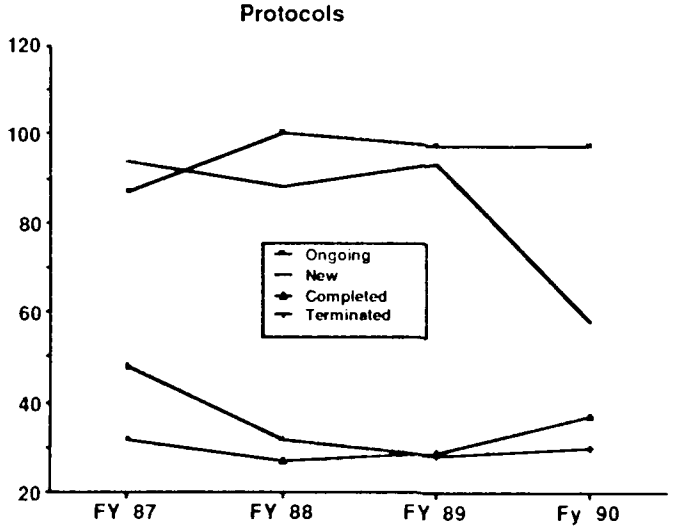
Comparison of Cranial and Iliac Autologous Bone Grafts and Their Effect on the Success Rates of Subsequent Osseointegrated Intra/Extraoral Implant Application in the Miniature Swine. $28,092.00

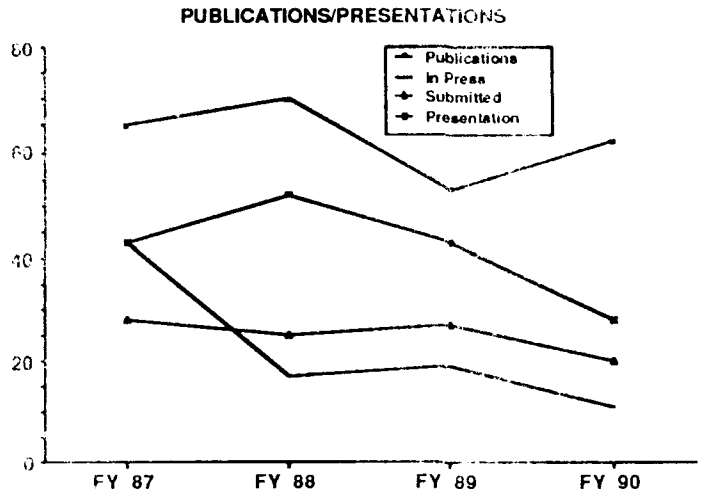
Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model. $40,482.00

USN Medical Research and Development Command

Joint Navy-Army Human Performance/Sickle Cell Trait Research Project at WBAMC. (Continuation of last year's grant) $74,894.00

PROTOCOLS, PRESENTATIONS, PUBLICATIONS:





EXPENDITURES	FY 87	FY 88	FY 89	FY90
Personnel (Civ)	363,094	375,197	405,498	572,958
Consumable Supplies	236,662	141,175	187,846	221,572
Capital Equipment	8,743	34,726	23,835	91,748
TDY	5,272	3,092	4,605	6,128
Printing and Publications	28,821	26,338	4,103	3,019
TOTAL	642,592	580,528	625,887	895,425
MEDCASE Equipment	89,105	434,064	361,427	62,116
Military Pay	457,879	417,265	510,814	538,711
TOTAL	1,189,576	1,431,857	1,498,128	1,496,252

PROGRESS FY 90

Biological Research Service

The Biological Research Facility is accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). It has a total of 6,984 sq ft and during FY 90 had an average daily inventory of 95 animals. During this year, the facility underwent a reaccreditation inspection by AAALAC, and received no major negative findings. Reaccreditation is expected early in FY 91.

The facility supports the total animal research and training mission for William Beaumont Army Medical Center and additionally, provides direct support to other MEDDAC's in this geographical region. The biomedical training utilizing animal models is primarily for the physician resident training programs. There are 11 ongoing training protocols for physicians encompassing emergency trauma life support, general surgery, laser surgery, and microsurgery. In addition, there are two protocols for training field medics and paramedics in emergency trauma life support procedures. There are a total of 16 active research protocols including microsurgery, general surgery, oral surgery, therapy and techniques for the management of soft tissue and orthopedic trauma, laser surgery for visceral trauma repair, microstructural changes with stress reaction in bone, drug efficacy, and immunology.

The Department of Surgery collaborated with the Biological Research Service to provide early and ongoing support of Operation Desert Shield in the form of Advanced Trauma Life Support (ATLS) training for deploying personnel, both from Ft Bliss and other facilities. As more medical reservists arrive at WBAMC, this training is expected to occupy a considerable amount of time, effort, and resources.

Chemistry Section

The on going research activities of the Chemistry Section of DCI include studies concerning the role of mucin in respiratory disease, the role of vitamin B_6 in human health and disease and analysis of drug metabolites in children of addicted parents.

Antibody against human tracheal mucin peptide, P_1, has been raised in rabbit and the antibody has been purified. The peptide is being utilized to examine the cross-reactivity between human mucin and the mucin isolated from different sources. The major aim of this research is to utilize this antibody to study the control of production of mucin in cell culture systems at the gene level. Tracheal epithelial cell culture systems from both rabbit and rat have been successfully maintained in the Chemistry laboratory for over one year now. Different drugs and chemical reagents are being utilized now to study the release of mucin by these cell cultures. In addition, mucin RNA from pig trachea has been isolated and experiments are on the way to isolate and screen the library with the antibody cited above. Also, attempts are being made to study the effects of different toxic substances on the production of mucin in a rat tracheal epithelial cell culture system. The last study will be assisted by a grant from USAMRDC, which has been awarded to DCI for FY 91.

The major projects are continuing on with research being centered on using the rabbit model to study the effect of B_6 supplementation on morbidity and survival of seriously ill patients, and the effect of L asparaginase on vitamin B_6 levels and amino acid profile, with or without the vitamin supplementation.

An additional protocol is being developed concerning the determination of the prevalence of drug affected babies in the military population. The protocol involves the use of GC/ mass spectroscopy techniques. In addition to the research activities cited above, we are involved in two co-operative efforts. The first is with Dr William Becker of the Army Institute of Surgical Research at Ft Sam Houston, involving the analysis of plasma vitamin B6 in burn victims; the second is with Dr Michael Weir of Madigan AMC, involving the analysis of plasma B_6 and amino acid profile in the rabbit model.

Immunology & Microbiology Section

Current research projects in the Immunology and Microbiology Section are focused on five areas: immunoregulatory subsets of T-cells in Bermuda grass allergy, epidermal growth factor production in peptic ulcer disease and colon carcinomas, B-cell immunodeficiencies and production of regulatory lymphokines, immunological characterization of human tracheal mucins in health and disease, and immune responses to measles virus.

In studies of immunoregulatory subsets of T cells, flow cytometric analysis has enabled us to identify specifically activated T helper cells (CD4+) in patients with Bermuda grass allergy. CD4+ cells may be functionally active as helper cells in inducing a suppressor cell population or, alternatively, as inducers of B cells which produce IgE. To date, we have been unable to demonstrate the presence of suppressor cells to Bermuda grass allergen as has been described for ragweed antigen E. We believe that the quality and/or quantity of antigen used, as well as the cellular composition of the population stimulated in vitro, are critical factors in the generation of suppressor cells. Studies are currently underway to define and optimize these factors.

Epidermal growth factor (EGF) has been shown to inhibit the production and secretion of gastric acid. Because of this latter property, reduced levels of epidermal growth factor production may be one of the contributing events in the development of peptic ulcer disease. We have established a sensitive radioimmunoassay and, more recently, an ELISA assay for measuring picogram quantities of EGF in our laboratory. Results thus far have shown that all patients with peptic ulcer disease tested have reduced levels of salivary EGF.

There are many causes for the development of immunodeficiency, including hormone imbalance (stress-related production of ACTH), malignancies of the immune system, genetically-determined insufficiencies or a congenital absence of various components of the immune system, or virus-induced deficiencies such as AIDS. Depending on the nature of the cause, immunodeficiencies may be primarily manifested in the functions of T cells or B cells or both. We have established a system for the study of B cell function which involves the activation of B cells with anti-IgM Sepharose, which cross links IgM on B cells. Once activated, the B cells undergo a process of differentiation involving immunoglobulin class switch from IgM to IgG. This switch requires the lymphokine, IL 4, which is provided exogenously to the cell culture. Following culture for several days, culture supernatants are analyzed by ELISA for the presence of secreted IgM and IgG.

There is growing concern in the communicable disease field regarding the high incidence of measles epidemics in the US. Recent outbreaks in El Paso have provided us with the opportunity to study military dependent populations of students who received immunizations during the epidemics as well as infant and adult patients who are admitted to the hospital with primary measles disease. Our laboratory has established an ELISA to measure total IgG, IgG subclasses, IgA and IgM antibodies to the measles virus. Studies of pre- and post-immunization sera from these children have established their status of immunity before and after immunization. Results of these studies will, hopefully, provide insights as to why immunity in a highly immunized population is not durable.

Our studies of tracheal mucin biosynthesis and immunochemical characterization should provide new insights into the role that mucous production plays in health and disease. Funded by a grant from the Army Medical Research and Development Command, our project seeks to define and gain a better understanding of the regulatory mechanisms that influence mucin production as well as protective mechanisms which play an essential role following exposure to toxic chemicals and environmental pollutants. Monoclonal antibodies to human mucin glycoprotein will be produced for the purpose of studying the structure, biosynthesis and function of tracheal mucin. These immunochemical reagents will also be useful in identifying, isolating and studying the gene or genes responsible for synthesis and release of mucin molecules by tracheal epithelial tissue.

TABLE OF CONTENTS

Department of Clinical Investigations

Dental Service

Headquarters

Medicine

Nursing

Obstetrics and Gynecology

Pathology

Pediatrics

Personnel Division

Primary Care and Community Medicine

Residential Treatment Facility

Social Work Service

Department of Surgery

Fort Bliss, Texas

Darnall Army Community Hospital
Fort Hood, Texas

TRADOC

PUBLICATIONS FY 90

Department of Clinical Investigation

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Maccini DM, Veit BC: Salivary epidermal growth factor in patients with and without acid peptic disease. American College of Gastroenterology, 27-31 Oct 90

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DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/17 STATUS: Ongoing

TITLE: Human Tracheal Mucin: Biochemical, Physical and Rheological Studies

START DATE: Mar 86 ESTIMATED COMPLETION DATE: Oct 91

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya Ph.D

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Brigitta Manna, John Enriquez

KEY WORDS: Tracheal mucin, Human

Study Objective: This proposal is concerned with isolation, purification and characterization of mucin glycoprotein components (mucins) from tracheal secretion of patients with asthma, chronic bronchitis and cystic fibrosis. The glycosylated and nonglycosylated peptides will be isolated, purified and sequenced (peptide portion) after subjecting the purified mucins with different proteolytic enzymes. Antibodies will be developed in rabbits against the nonglycosylated peptides which, in turn, will be used to follow the synthesis and secretion of these macromolecules in a tracheal (or bronchial) culture system. Finally, the viscoelastic properties of purified mucins will be investigated.

Technical Approach: The following proposal will be undertaken in the Department of Clinical Investigation, WBAMC, regarding respiratory mucins:

(1) Collect sputum from patients (either male or female, any age) with asthma, chronic bronchitis and cystic fibrosis.

(2) Solubilize mucins with water and buffer.

(3) Establish the homogeneity of mucin glycoproteins isolated from sputum of patients with asthma, chronic bronchitis, and cystic fibrosis by molecular sieve and ion-exchange chromatography.

(4) Isolation and characterization of peptides (or glycopeptides) derived from digestion of mucins with different proteolytic enzymes (Column and HPLC);

(5) Amino acid sequence analysis of these peptides by sequenator and cDNA cloning procedure;

(6) Raise antibodies in rabbits against these peptides (preferably against nonglycosylated peptides); and finally,

(7) Establish a tracheal (or bronchial) culture system to examine the synthesis and control in secretion of these macromolecules by ELISA or radioimmunoassay (RIA) procedures using these antibodies.

In addition to the proposals cited above, the physical properties of mucins, particularly their interaction (in terms of viscosity) with other serum proteins (such as albumin, immunoglobulin, and fibronectin) will be studied.

Progress: Partial structural characterization of the deglycosylated peptides from neutral and acidic human tracheobronchial mucins have been completed. Peptide mapping of the principal peptide from these two components resulted in identical profiles indicating that the native mucin is represented by a principal peptide backbone of similar structure (see the reference). Antibodies raised against this peptide in rabbits reacted against deglycosylated mucin preparation from colon, intestine as well as from pig and rat tracheal material. We are now using this antibody to screen human cDNA library. Also, an antisense DNA probe has been made to identify the mucin mRNA from these different sources.

Reference: Bhattacharyya, S.N.; Veit, B.C.; Manna, B.; Enriquez, J.I.; Walker, M.P.; Khorrami, A.M.; and Kaufman, B. (1990) Neutral and acidic human tracheobronchial mucin. Inflammation 14: 355-373.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/16** **STATUS: Ongoing**

TITLE: Cellular Mechanism of Mucin Secretion: Studies Involving Rat and Rabbit Tracheal Culture System

START DATE: Jan 89 **ESTIMATED COMPLETION DATE: Oct 91**

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya PhD

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: B. Manna, M. Lund, J.I. Enriquez

KEY WORDS: Mucin, animal

Study Objective: This proposal is concerned with the isolation and characterization of mucin glycoprotein components (mucin) from secretions of rat and rabbit tracheal epithelial cells in culture and establish their structural identity with those of the same components from human. The ultimate goal of this proposal is to find an animal model tracheal culture system akin to human where the control mechanism of the secretion of mucins can be studies on the gene level.

Amendment August 1989: In addition to isolation of mucin proteins in the rat and rabbit models, it has become apparent that the isolation and characterization of mucin glycoprotein components from secretions of porcine (swine) tracheal epithelial cells in culture is also necessary. Once the mucin fraction is characterized at the structural level, it can be determined if it is comparable with the same components of human tracheal mucin. The ultimate goal of this proposal is to find an animal model tracheal culture system akin to human where the control mechanism of the secretion of mucins can be studies on the gene level.

Technical Approach: Growth of epithelial cells from rat and rabbit bronchial tissues: Rats and rabbits will be euthanatized and normal appearing tracheal tissues are excised aseptically and immersed in cold, sterile L-15 culture medium containing penicillin\streptomycin and transported on ice to the laboratory. Lung tissue is sterilely trimmed away and the bronchus cut into large fragments. Cells are isolated from the human bronchus after an overnight incubation with 0.1% protease solution in minimal essential medium (MEM, Ca++free) done at 4 degrees C. The next day, incubated bronchi are flushed with MEM plus 10% Fetal Calf Serum to remove the digested cells. The cells are washed several times to remove any protease, which is toxic to epithelial cultures. The cell suspension is filtered through a sterile 100U nitrex filter and centrifuged for 10 minutes. Cell pellets are resuspended in cold MEM with 10% FCS and centrifuged again. The cold protease overnight treatment is sufficient to remove most epithelial cells lining the bronchus without much contamination of other cell types from the layer under the basement membrane. After the total cell count is taken, primary cultures are normally initiated by plating 1-2x 10 6 cells per ml per 35mm culture dish. The culture conditions are used for the human bronchial epithelial cells consist of M199 media with D-valine substituted for Dl-valine, 10% Fetal Calf Serum, L-glutamine, penicillin/streptomycin, gentamicin, insulin, transferrin, epidermal growth factor, hydrocortisone, cholera toxin, bovine hypothalamus extract, and fungizone. Primary epithelial cultures were then placed in an incubator, with conditions of 37 degrees C., 5% CO2, and 95% air, and cells allowed to adhere to the culture dish. After 3-4 days incubation, a confluent primary culture of epithelial cells is routinely observed. The cultures received media change and can be used in various studies.

Secretion of mucin and characterization: The synthesis of mucin will be followed by ^{3}H glucosamine and $^{35}SO4$ incorporation. Once the saturation curve is established, radioactive agents will not be used anymore. At the time of maximum secretion, the culture medium will be collected, lyophilized and chromatographed on Sepharose 2B and ECTEOLA column. The purified mucin will be deglycosylated by chemical procedure and the peptide portion will be partially sequenced by sequenator.

Isolation of mucin mRNA and sequencing by cDNA method: The procedure that will follow here is essentially that of Timpte et al. mRNA from tracheal culture will be isolated by guanidine isothiocyanate method followed by oligo(dt)-cellulose chromatography. Construction and screening of the cDNA library utilizing human antiapomucin will be done as described.

Control in secretion of mucin: The synthesis of mucin in epithelial culture will be followed by 3H glucosamine and 35 SO4 incorporation. The control in synthesis will be studies on transcriptional and translational levels using different inhibitory (acetylcysteine and cyclohexamide) and enhancing (pilocarpine) reagents.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Rabbit tracheal epithelial cells, cultured on collagen-coated dishes in serum-free and hormone-supplemented medium, have been found to secrete high molecular weight components in medium. The secreted material was digested with hyaluronidase and the components were purified by sepharose 2B column chromatography. The chemical analyses of these products resulted in a profile which resembled that of mucous glycoproteins (mucins). The incorporation of [^{3}H] glucosamine into mucins was inhibited by three aryl-N-acetyl-galactosamimides and a chemical carcinogen, N-nitroso-N-ethyl urea, whereas 5-azacytidine enhanced the proliferation of cells as well as the radiolabeling of mucins. Parasympathetic agent (pilocarpine), cholinergic antagonist (atropine) and β-adrenergic agonist (isoproterenol) alone have little effect on the secretion of mucins. Transmission electron microscopy exhibited mucus-secreting granules in some of the control cells, but not in the cells treated with chemical reagents (see reference).

Attempts are now being made to culture rat tracheal epithelial cells and study the mucin gene expression in these cells.

Reference: Bhattacharyya, S.N.; Ashbaugh, P.; and Manna, B. (1990) Biosynthesis of mucins by rabbit tracheal epithelial cells in culture. Communicated to Inflammation.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/63** **STATUS: Completed**

TITLE: Antibody Production Against Human Tracheal Mucin Apoprotein in the Rabbit Model

START DATE: Jun 89 **ESTIMATED COMPLETION DATE: Aug 90**

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya Ph.D

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Veit, B.C.; Manna, B.; Enriquez, J.I.; Walker, M.P.; Khorrami, A.M.; and Kaufman, B.

KEY WORDS: Mucin, animal

Study Objective: To produce antibodies against human tracheal mucin apoproteins in the rabbit model and use these antibodies to study the control in mucin production on the gene level.

Technical Approach: The animals will be injected with a small volume of mucin protein emulsified in Complete Freund's Adjuvant. After 3-4 weeks the same rabbits will receive the mucin protein, except that it will be suspended in a normal saline carrier solution and injected subcutaneously. Three to five days following the second immunization, blood will be collected 2-3 times weekly from the ear veins of the rabbits while antibody titers are elevated or for a period not to exceed two consecutive weeks. Once blood collection has ceased, the rabbits will be rested a minimum of one month. If the hematocrit is normal at this time, they may be reimmunized with the mucin protein in a normal saline carrier solution, subcutaneously and the blood will be collected as stated below.

Mucin protein will be emulsified (water-in-oil) in Complete Freund's Adjuvant. Each of the three rabbits will be inoculated with a total volume of 0.25 mls divided among 4 intramuscular injection sites in the thigh muscles. No experimental manipulations will follow for at least 3-4 weeks. During this time the rabbits will continue to be housed and cared for as stated above. Following this period, the rabbits will be re-immunized with the mucin protein solubilized in normal saline 0.1 ml, subcutaneously. After 3-5 days, 10-20 mls of blood will be collected from each rabbit 2-3 times weekly during high antibody titers. They will not be bled for a period exceeding two consecutive weeks. A hematocrit will be measured prior to each blood collection to insure that excessive blood is not taken. Blood will not be collected if the hematocrit falls below 25 % unless the rabbit is to be euthanatized. Additional vitamin and mineral supplements will be administered during the blood collection period or as long as the hematocrit is below normal. Once blood collection has ceased, the rabbits will be rested a minimum of one month. If the hematocrit is normal at this time and additional antibody is required, they will be reimmunized with the mucin protein in a normal saline carrier solution, 0.1 ml subcutaneously and the blood will be collected on the same schedule as stated above. The procedure for collecting the blood specimens is as follows: the rabbits will be placed in a restraint cage for a few minutes during the procedure. The blood will be collected by placing a small needle in an ear vein and then allowing the blood to flow into a blood collection tube. If the rabbits become distressed or if adequate blood volumes can not be obtained without causing distress the rabbits will be anesthetized and euthanatized by exsanguination as stated in para 5. b.(1), above. Antibody will then be extracted from the blood.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: The antibodies raised against HPLC-purified deglycosylated native tracheal mucin did not react with native tracheal mucin or deglycosylated pig submaxillary mucin (see table and reference). The same antibodies, however, did react strongly with deglycosylated tracheal as well as colonic mucin, indicating that the antibody was reactive with the core protein of mucin. The antibodies reacted strongly with deglycosylated human intestinal, rat and pig tracheal mucin. We are using those antibodies now for in-vitro translation as well as mucin gene expression systems.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/37** **STATUS: Ongoing**

TITLE: Tracheobronchial Mucins in Health, Disease, and Toxic Exposures

START DATE: Oct 90 **ESTIMATED COMPLETION DATE: Oct 91**

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya Ph.D

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Bruce C. Veit, Ph.D., CPT David J. Smith, Ph.D.

KEY WORDS: Bronchial mucin

Study Objective: This proposal has two objectives. One is to prepare a library of mouse monoclonal antibodies against human and rat lung mucin apoprotein to be used as probes for the study of structure and biosynthetic regulation of mucin in tracheal epithelial culture system both at the cellular and DNA level. The other objective is to study the levels and control of transcription and mucin in RNA accumulation in rat tracheal epithelial cells in cultures in response to various noxious agents, like tobacco smoke, ammonia, SO_2 and NO_2, and different drugs.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such *pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under* Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: The major components cited in this project are already in progress in our laboratory. Partial structural characterization of mucins has already been done and antibodies against these peptides have been produced in rabbits. Attempts are being made now to identify the mRNA for mucin in pigs and rats. We are starting now to culture rat tracheal epithelial cells and study the mucin gene regulation.

We have submitted a grant proposal to MRDC on the basis of this protocol. If approved, we will start working on the mucin gene expression in rats exposed to different toxic substances.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 82/60** **STATUS: Completed**

TITLE: Interactions Between Aminoglycoside Antibiotics and Vitamin B6 in Vitro and In Vivo

START DATE: Sep 82 **ESTIMATED COMPLETION DATE: Jul 90**

PRINCIPAL INVESTIGATOR: John Enriquez

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: PFC Ismael Delgado

KEY WORDS: Pathology aminoglycosides, Vitamin B6

Study Objective: To develop a method for isolating and quantitating aminoglycoside pyridoxal-5'-phosphate complexes. To isolate these complexes from the urine of patients receiving the aminoglycoside antibiotics. To determine if depletion of vitamin B6 occurs in patients receiving aminoglycoside antibiotics, and if so, how this depletion correlates with morbidity and mortality.

Technical Approach: Subjects will be patients who are to be given aminoglycoside antibiotics for clinical indications (sepsis, serious gram-negative infections, etc). These patients should also have SMAC 20 chemistry screens and monitoring of their aminoglycoside levels (procedures already routinely performed). The blood and urine samples from at least 30 patients will be examined.

Progress: It was observed that in vitro, aminoglycoside antibiotics for complexes with pyridoxal-5'-phosphate that are both isolatable and measurable. Unfortunately, we have not had, until recently, the instrumentation necessary to isolate and characterize these same complexes in vivo. This protocol has produced one prepared article for submission, one published article and one published letter to the editor.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 85/52** **STATUS: Completed**

TITLE: Pyridoxine Effect in Aminophylline Toxicity in Rabbits

START DATE: Sep 85 **ESTIMATED COMPLETION DATE: May 90**

PRINCIPAL INVESTIGATOR: John Enriquez

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC Raghave Charya, Ismael Delgado

KEY WORDS: Pyridoxine, Vitamin B6, Aminophylline toxicity

Study Objective: To determine the response of unsupplemented normal rabbits and B6 supplemented rabbits to theophylline administration.

Technical Approach: New Zealand rabbits were given single daily intraperitoneal injections of aminophylline in a dose of 17 mg/kg/day or increasing daily doses of theophylline for five days. Serum PLP levels were done every one to two days.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: The experiments proved fruitful in observing dramatic drops in plasma pyridoxal-5'-phosphate, (PLP), levels in subjects unsupplemented with pyridoxine HCl and receiving aminophylline, not only at toxic, but at therapeutic dosages as well.
Pyridoxine HCl supplemented subjects maintained higher PLP levels and exhibited varying degrees of protection from the effects of toxicity depending on their supplementation levels. This protocol has generated two articles that have been submitted for publication.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 86/28** **STATUS: Ongoing**

TITLE: Measurement of Plasma Pyridoxal 5'-Phosphate in Seriously Ill Patients and Effect of Supplementation of Pyridoxine HCL on Laboratory Tests (Monitor: COL Stephenson)

START DATE: Mar 86 **ESTIMATED COMPLETION DATE: Feb 91**

PRINCIPAL INVESTIGATOR: John Enriquez

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Stephen Carey, MC., PFC Ismael Delgado

KEY WORDS: PLP

Study Objective: Gather evidence of vitamin B6 deficiency in hospitalized patients and determine if plasma pyridoxal 5' phosphate levels can be restored easily to normal. Determine effect of PLP level changes on other measured parameters.

Technical Approach: All surgical patients will have a plasma PLP, CBC and SMAC-20 drawn on admission or, in the case of elective surgeries, as part of the pre-admission lab work. Those patients found to have a plasma PLP of greater than 20 nM will not be entered into either the B6S or the NS group. If the initial or subsequent plasma PLP goes below 20 nM, the patient will be assigned the B6S or NS group on the basis of the last digit of their social security number. Me will be given 50 mg/day or 0 mg/day of PN:HCl if his plasma PLP is between 10 and 20nM, and 100 mg/day or 50 mg/day of PN:HCl if his plasma PLP is less than 10 nM. After one week of no supplementation (for those in the NS group) or one week of supplementation (for those in the B6S group), a repeat plasma PLP, CBC and SMAC-20 will be drawn. Whenever the plasma PLP exceeds 20 nM, supplementation with PN:HCl will stop and further plasma PLP levels will be drawn weekly and at pre-discharge.

Progress: This project was successful in showing the interaction of aminoglycoside antibiotics and vitamin B6 in seriously ill patients. It was observed that aminoglycoside antibiotics can dramatically lower plasma pyridoxal-5'-phosphate levels and can also affect other parameters such as creatinine, BUN and albumin levels. Vitamin B6 supplementation seemed to significantly affect these parameters is a positive way. Also noted, was that in combination with certain other medications, the depression of plasma PLP levels and the effect on the other blood chemistries was more severe and that the effects of B6 supplementation were less dramatic.

We would like to continue this protocol as an on-going project and be able to continue receiving samples from surgery and ICU patients whenever any that meet the protocol criteria are available.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/30 STATUS: Completed

TITLE: Vitamin B6 Status of Sergeant Major Candidates: Effect of Smoking on Vitamin B6 Levels and of *Vitamin B6 Supplementation in* Vitamin B6 Deficient Individuals

START DATE: Jul 86 ESTIMATED COMPLETION DATE: Jun 90

PRINCIPAL INVESTIGATOR: John. Enriquez

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Ismael Delgado, Clent Aldridge, LTC Allister Morris, MC

KEY WORDS: Vitamin B6

Study Objective: To see if cigarette smokers are vitamin B6 deficient, and to determine if vitamin B6 supplementation of vitamin B6 deficient individuals alters serum chemistries (SMAC-20), CBC, and HDL cholesterol.

Technical Approach: Smoking-induced vitamin B6 deficiency may contribute to the altered biochemical measures. Increasing the plasma PLP of vitamin 86 deficient individuals may help to normalize these values. In particular, a relationship between plasma PLP levels and HDL cholesterol will be explored: this would have implications for the prevention and treatment of atherosclerosis. A performance measure effect of serum PLP will be explored. Subjects: All subjects will be Sergeant Major candidates, already enrolled in the Over 40-Sergeants Major Study (already scheduled to have blood drawn for a CBC, SMAC-20, and HDL cholesterol). *Controls: These will be the nonsmokers and B6 deficient patients randomized to receive a placebo instead of* vitamin B6. Design of the Experiment: (1) Initial Blood Draw - blood will be drawn for CBC, SMAC-20, HDL cholesterol, and plasma PLP. (2) Randomization and Supplementation Phase - subjects will be classified by smoking status, and assigned to vitamin B6 sufficient (B6+), intermediate vitamin B6 status (B6I), or vitamin B6 deficient (B6-) groups on the basis of the initial plasma PLP level (20 nM or greater, 10 to 20 nM, or less than 10 nM, respectively. The B6+ group will receive no PN:HCl supplementation; the B6- group will all receive 50 mg/day of PN:HCl; and the B6I group will be randomized to receive either 50 mg/day of PN:HCl or placebo. (3) Final Blood Draw - at the end of the Sergeants Major course, blood will be drawn for CBC, SMAC-20, HDL cholesterol, and plasma PLP.

Progress: This protocol resulted in a tremendous quantity of data from the 1400 subjects that were entered. The data was useful in showing that smokers have depressed levels of Vitamin B6 and that they respond to B6 supplementation in a different way than non-smokers. We also were able to enhance the standard Health Risk Assessment equation by utilizing smoking status and vitamin B6 levels. As a result of this protocol, there has been 2 poster presentations, 4 abstracts, one U.S. Army Service Conference article and one book chapter completed. Other articles and abstracts are currently being submitted for publication.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/14** **STATUS: Ongoing**

TITLE: Protective Role of Pyridoxine in Gentamicin Nephrotoxicity (in the Rabbit Model)

START DATE: Apr 1990 **ESTIMATED COMPLETION DATE: Oct 1990**

PRINCIPAL INVESTIGATOR: COL Manuel Schydlower

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC Mohammed A. Nadjem, MC; John I. Enriquez, Sr.; COL Michael Weir, MC

KEY WORDS: Pyridoxine, Gentamycin, Nephrotoxicity

Study Objective: The objective of this study is to test whether pyridoxine has a protective effect on gentamicin nephrotoxicity.

Technical Approach: Following a period of quarantine and observation, the rabbits will be brought to the operating suite in groups of seven. Each group of seven rabbits will be treated in the following manner:

rabbit #1 - 100 mg pyridoxine. (control)
rabbit #2 - 10 mg/kg gentamicin (IM), 10 mg pyridoxine.
rabbit #3 - 10 mg/kg gentamicin (IM),100 mg pyridoxine.
rabbit #4 - 10 mg/kg gentamicin (IM), saline.
rabbit #5 - 40 mg/kg gentamicin (IM), 10 mg pyridoxine.
rabbit #6 - 40 mg/kg gentamicin (IM),100 mg pyridoxine.
rabbit #7 - 40 mg/kg gentamicin (IM), saline.

These medications will be repeated every morning for five days. Blood will be drawn from an ear site for PLP, gentamicin and creatinine on days 0, (before injections begin), and two hours after injection on days 1, 3 and 5. Following the last injection and blood draw in the morning, the rabbits will be euthanized in the early afternoon and one kidney from each animal will be recovered for fixation for blinded pathologic interpretation. In each of two subsequent weeks, seven more rabbits per week will be studied similarly. This is a descriptive study that hopes to show that there is a general relationship between the renal pathology and the average fall in PLP, and/or there may be a relationship between pathology and gentamicin blood levels.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Animal phase of the study and data analysis have been completed. Report of study is in first draft form.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/55 STATUS: Terminated

TITLE: Development of a Hemophilus Influenza Anti-Idiotype Vaccine (In the Mice and Rabbit Models)

START DATE: May 87 ESTIMATED COMPLETION DATE: Apr 90

PRINCIPAL INVESTIGATOR: Bruce C. Veit Ph.D

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ George McNamee, DVM; Becky Smiley, Susan McIntyre, Cambyses Darvish

KEY WORDS: Hemophilus influenzae, vaccine

Study Objective: Prepare an immunogenic vaccine that will establish effective immunity to Hemophilus influenzae in children under two years of age. Since the polysaccharide antigen (Hib) itself is only weakly immunogenic at best, we will attempt to develop an internal image anti-idiotype vaccine which, by virtue or its protein structure, should be highly immunogenic in this patient population. Although our ultimate goal is to develop such a vaccine for human use, our initial efforts will be focused on an animal model which will be used to establish the merit of this approach.

Technical Approach: Balb/c mice and New Zealand white rabbits will be immunized with Hemophilus influenzae type B polysaccharide (PRP). Since polysaccharides are poorly immunogenic in general, a protein conjugated form of PRP, namely polysaccharide-diphtheria toxoid, will be used in order to overcome this potential pitfall. At the time of peak, antibody synthesis, rabbits will be bled via the marginal ear vein or central artery in the ear and the anti-PRP antibodies will be affinity purified on PRP-Sepharose 4B columns. Spleens from immunized mice will be single-cell suspended and fused with the MAT-sensitive myeloma cells, SP2/0. Hybridomas secreting anti-PRP antibodies will be identified using ELIZA screening techniques.

Affinity-purified rabbit anti-PRP antibodies as well as mouse monoclonal antibodies will be used to immunize Balb/c for the production of monoclonal anti-idiotypic antibodies. Appropriate hybridomas secreting the desired antibodies will be selected by ELIZA screening. Those which bind to anti-PRP but not to pooled mouse immunoglobulins or to PRP antigen, will be further characterized for their ability to elicit an antibody response to PRP in rats (heterologous species with respect to the origin of the antibodies to be used).

Upon confirmation that the anti-idiotypic antibodies elicit a specific response to PRP, infant rats (1 to 2 weeks post-partum) will be immunized with the anti-idiotype vaccine and then challenged with virulent Hemophilus influenzae intranasally. Infected animals will be housed in isolation quarters so that other animals will not become infected.

Having established the efficacy of the anti-idiotype vaccine in protecting against infection, we will then submit an additional protocol which will describe the methodologies for generating hybrid molecules of the anti-idiotype antibodies so that the "V" regions are mouse and the "C" regions are human.

In initial studies that will focus on the immunogenic aspects of the anti-idiotype vaccine (immunization of rats), we will be able to ascertain whether heterologous proteins (mouse immunoglobulins into rat) will induce anti-mouse Ig and/or immune complexes. Then the hybrid immunoglobulins will be tested by comparison for elimination of any anti-mouse Ig response that may occur.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such Pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: **A recently developed polysaccharide vaccine to H. influenza has proven to be unsatisfactory in establishing effective immunity in a large percentage of children under 2 years of age. Efforts to improve immunogenicity by conjugating the polysaccharide to a protein have met with marginal success. It is clear that a protein form of the vaccine would be most active in this age group. To this end, we have undertaken to produce such a vaccine. Our approach was to develop anti-idiotype (anti-Id) antibodies to anti-Hemophilus influenza (Hib) polysaccharide and select a particular anti-Id which bears internal image of the polysaccharide. Use of an internal image anti-Id would obviate the problem of a poorly immunogenic polysaccharide since anti-Id's are proteins which are much better immunogens in infants whose immune response systems are incompletely developed.**

Considerable time and effort were directed toward developing methodologies and optimization of procedures. Following an extensive investigation of the growth of H. influenza on various types of medium (both liquid and solid) it was determined that an accelerated loss of polysaccharide occurred during late log/stationary phase, primarily in liquid cultures. Consequently, all work was done with organisms that were grown to mid-log phase on solid medium. Confirmation that the organisms retained high levels of antigenically active type B polysaccharide was made by agglutination with type-specific antisera. Several immunization regimens were tested in order to establish optimal antibody production in mice and rabbits. Use of the soluble Hib polysaccharide vaccine proved to be less effective than formalin-treated H. influenza organisms in eliciting high antibody titers in both mice and rabbits. Rabbits were optimally immunized by daily injections i.v. whereas mice were optimally immunized by 3 to 4 weekly i.p. injections. Serum antibodies were measured by ELIZA utilizing alkaline phosphatase-conjugated anti-mouse or anti-rabbit Ig. An ELIZA technique was developed for detecting B cells which synthesize/secrete anti-Hib antibodies. This plaque-forming cell assay was utilized in determining the number of antibody-producing cells in the spleens of mice that were immunized with H. influenza. It was also utilized in screening hybridomas which were produced with the antibody-producing spleen cells. Although several stable hybridomas which synthesized and secreted antibodies were produced, none demonstrated specificity for Hib.

Because of the enormous expense of time and resources which were necessary to continue this project and because of the increased demand on technical services required for other new projects, this project was terminated without completion.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 88/04 **STATUS:** Ongoing

TITLE: Activation of T-Cell Subsets in Bermuda Grass Allergy Patients

START DATE: Nov 87 **ESTIMATED COMPLETION DATE:** Aug 92

PRINCIPAL INVESTIGATOR: Bruce C. Veit Ph.D

DEPARTMENT: DCI **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Stanislaus Ting, M.D.; LTC R.V. Charya, MC; Beck Smiley, B.S.; Susan McIntyre

KEY WORDS: Bermuda grass allergy, T-cell subsets, IL-2R, VLA, 2-color flow cytometry

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Study Objective: To determine whether there are detectable changes in numbers and functions of manifestations of Bermuda grass allergy. Since T4+ cells are associated with helper/inducer functions and T8+ cells are associated with cytotoxic/suppressor functions, alterations in the numbers of T4+ or T8+ activated T cells may correlate with changes in the immunoregulatory processes involved in controlling the allergic state. Peripheral blood samples will be obtained from patients during active allergy, immunotherapy, and disease quiescence. Samples will be analyzed by 2-color flow cytometry and by immunohistochemical staining for the distribution of T4+ and T8+ cells and the percentage of activation antigen-positive cells within each of these subsets. T cell subsets will also be analyzed for their ability to increase or suppress the synthesis and/or secretion of IgE. Serum samples from these patients will be analyzed for the presence of soluble IL-2R (circulating IL-2 receptor). These studies should improve our understanding of the immunoregulatory processes involved in the control of IgE-mediated allergic responses.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: As a continuation of our in vitro studies of suppressor cell function in allergy patients, peripheral blood lymphocytes (PBL) from Bermuda grass allergy patients (BGA-PTS) and long-term (>2 years) BGA-immunotherapy patients (IT-PTS) were activated in vitro with BGA and analyzed for levels of activation by ^{3}H-TdR incorporation. Cells from IT-PTS were unresponsive to BGA but significantly responsive to an unrelated allergen, Mulberry pollen allergen (MPA), whereas cells from BGA-PTS were highly responsive to both allergens. Cells from BGA-PTS exhibited a significantly higher level of activation than did those from IT-PTS suggesting that immunotherapy had reduced the allergenic response. Serum levels of BGA-specific IgG and IgE antibodies correlated with symptoms and levels of lymphocyte activation, i.e. BGA-PTS patients exhibited higher levels of IgE and lower levels of IgG relative to IT-PTS whom exhibited higher levels of IgG and lower levels of IgE confirming the efficacy of immunotherapy.

Although our suppressor cell studies are similar, in design, to those which have been reported for ragweed antigen in which suppressor cell activity was clearly demonstrated, we have been unable to identify functional suppressor cells in our system. In contrast, we have observed a stimulatory activity, the nature of which is currently under investigation. To generate "suppressor" cells (S), PBL were cultured with BGA for 2 days, washed, and treated with mitomycin C. PBL that had been cultured for 2 days in medium alone (I) were mixed with S cells and cultured with or without BGA for 6 days. I cells from either BGA-PTS or IT-PTS, when incubated with S cells and BGA, exhibited significantly increased responses when compared to those of I cells incubated with BGA alone. Since S cells are assumed to be non-proliferative, we have concluded that the observed enhancing activity of S cells in both BGA-PTS and IT-PTS can be attributed to the production of an enhancing factor(s) by S cells. The possibility that the enhancing factor may be antigen or modified antigen which is carried over by S cells was ruled out by the finding that insoluble antigen (antigen bound to culture

plates and therefore unable to become associated with S cells) was, nevertheless, able to activate S cells to produce their stimulatory effect when mixed with I cells and antigen.

Further studies are in progress to characterize this stimulatory activity and to determine whether this phenomenon is unique to allergic hypersensitivity or if it also occurs in other immunologic disorders.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/11 STATUS: Completed

TITLE: Antibody Production Against Human Epidermal Growth Factor (EGF) in the Rabbit Model

START DATE: Dec 89 ESTIMATED COMPLETION DATE: Apr 90

PRINCIPAL INVESTIGATOR: Bruce C. Veit Ph.D

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Antibodies, Epidermal growth factor

Study Objective: To produce antibodies against human epidermal growth factor (EGF) in the rabbit model and use these antibodies to measure salivary and serum concentrations of EGF in patients with peptic ulcers and colon carcinomas

Technical Approach: Each rabbit will be injected intramuscularly with 100ug of human EGF emulsified in Complete Freund's Adjuvant. After 3-4 weeks the same rabbits will again be injected with EGF. However, the EGF will be suspended in physiological saline and injected subcutaneously. Three to five days following the second immunization, blood will be collected 2-3 times weekly from the ear veins of the rabbits while antibody titers are elevated or for a period not to exceed two consecutive weeks. Once blood collection has ceased, the rabbits will be rested a minimum of one month. If the hematocrit is normal at this time, they may be reimmunized with EGF in physiological saline solution, subcutaneously, and the blood will be collected as stated above.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Epidermal growth factor (EGF) is a protein which has been shown to be highly active in the *stimulation of cell growth and differentiation. In patients with peptic ulcers, it is believed that the* submandibular salivary glands and Brunner's glands in the duodenum contain reduced levels of EGF and, since EGF is a known inhibitor of gastric acid secretion, deficiency in EGF may be a contributing factor in the development of peptic ulcers.

We have established a radioimmunoassay (RIA) for the quantitation of EGF in biological fluids in our laboratory. However, because of an apparent low affinity of the mouse monoclonal anti-EGF antibodies which were used in this assay, we were unable to attain nanogram level sensitivity. Since it is possible to achieve higher affinity antibodies through the immunization of rabbits with EGF, we undertook the production of such antibodies.

The goal of this project was to produce high affinity antibodies against human EGF in rabbits so that the sensitivity of our EGF RIA could be maximized.

Rabbits were injected intramuscularly with 100ug of human EGF emulsified in complete Freund's adjuvant. After 3-4 weeks the rabbits were again injected subcutaneously with EGF suspended in physiological saline. Three to 5 days following the second immunization, blood was collected from the ear veins of the rabbits and antibody titers were determined by enzyme-linked immunosorbent assay (ELISA).

Experiments are now in progress to determine the level of sensitivity of the rabbit anti-EGF antibodies in the EGF RIA.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 83/37** **STATUS: Completed**

TITLE: Cardiopulmonary Effects of Stressful Exercise at 4,000 Feet on SCT Individuals

START DATE: Jul 84 **ESTIMATED COMPLETION DATE: Jun 90**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Sickle cell trait, Stress

Study Objective: To establish baseline pulmonary function data (spirometry, helium dilution lung volumes, maximum voluntary ventilation L/min (MVV), arterial blood gas analyses (ABG), single breath diffusing capacity DLCOSB (ml/min/mmHg) and steady state diffusing capacity DLCOSS (ml/min/mmMg) (Filley technique) as well as values for the partial pressure of oxygen at 50 saturation (mmHg) (P50) in HgbAS individuals and controls and to determine percent HgbS and percent HgbF in individuals heterozygous for sickle cell trait (HbgAS) at 4000 ft.

To carefully document cardiopulmonary response of individuals identified as having hemoglobin AS during both strenuous incremental and submaximal steady-state exercise at altitude with age, race, sex, smoking, matched non-HgbAS controls.

To correlate observed abnormalities (if any) in parameters of cardiopulmonary performance with levels of HgbS in individuals with sickle cell trait (i.e. are patients with 40 percent of HgbS more likely than controls to experience abnormalities during vigorous exercise. Also, to determine whether HgbF levels may be protective as they are in patients with sickle cell disease.

To determine whether conditioning (repeat studies after six weeks) is operative in modulating cardiopulmonary performance in both SCT individuals and controls.

Conclusive data is not anticipated from this protocol, but a preliminary statement or suggestion may be offered on the important question of occupational restriction of subjects with HgbAS. This is in keeping with the National Academy of Science - National Research Council ¡s Report of 1973.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: The present study was designed to study the effect of severe inspiratory hypoxia equivalent to 4000m at rest and during acute strenuous exercise in sickle cell trait subjects. Twenty-seven SCT and 28 controls were exercised on a cycle ergometer to exhaustion breathing gas mixtures simulating sea level and 4000m. Cardiopulmonary variables, blood gases and percent sickling in arterial and peripheral venous blood were measured at rest and during exercise.

This study suggests that some individuals with SCT appear to be more susceptible to clinical problems during exposure and/or exercise at simulated 4000m compared to controls. Clinical symptoms precluded exercise at simulated 4000m in 2 individuals with SCT. The cardiopulmonary and gas exchange responses to acute strenuous exercise for individuals with SCT who were able to exercise (majority) were comparable to controls under both experimental conditions. Lower extremity exercise does not appear to significantly increase

sickling in venous blood of non-exercising limbs. One minute post exercise sickling remains elevated despite a significant increase in Sv02 which would suggest release of sickled red cells from the microcirculation of tissue not actively involved during exercise. The practical absence of sickling in arterial blood probably reflects the rapid reversibility of sickled cells as they traverse the better oxygenated pulmonary capillaries. The ready reversibility and sickling kinetics of HbAS containing sickled cells may explain why sickling does not appear to modulate exercise performance under these experimental conditions. No physiologic parameter clearly distinguishes individuals with SCT who are more likely to experience clinical symptoms than those who are asymptomatic during exercise and/or exposure to inspiratory hypoxia.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/25** **STATUS: Completed**

TITLE: Axillary Venous Sickling in Individuals with Sickle Cell Trait During Upper Extremity Exercise in a Hypoxic Environment (Monitor: Dr. Ortiz)

START DATE: Mar 87 **ESTIMATED COMPLETION DATE: Jul 89**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Dr. Jorge Zeballos

KEY WORDS: Sickling, Armcrank exercise

Study Objective: To determine the relationship between cardiopulmonary performance, blood gas and the degree of sickling in individuals with sickle cell trait during progressive armcrank exercise. To characterize the cardiopulmonary performance of individuals with sickle cell trait during progressive upper extremity exercise. To determine the effects of armcrank exercise on blood gases in individuals with sickle cell trait. To study the effects of environmental hypoxia on upper extremity exercise performance and venous blood gases at 1270 meters and during exposure to inspiratory hypoxia equivalent to 4000 meters on upper extremity exercise performance, venous blood gases and percent sickling.

Technical Approach: We anticipate using fifteen SCT individuals and a similar number of controls. Subjects will be 18 to 28 years of age and have less than a three-pack year smoking history. Volunteers will be obtained from the basic training reception station, similar to previous studies. Recruits are screened for SCT with a sickledex test and positive results are confirmed by hemoglobin electrophoresis.

Upon our request, in-processing NCOs will assemble groups of black trainees with either SCT or normal hemoglobin. We prefer to speak to the groups separately because individuals with SCT tend to have more concerns regarding their status. The trainees will be informed that a group of researchers need volunteers for an exercise study involving SCT. Previously, the reception station NCOs have vouched for our credibility, but otherwise have not encouraged the trainees to volunteer. In fact, many of the reception station NCOs would prefer the trainees did not volunteer, because of the extra administrative work it entails; i.e., transportation and personnel accounting.

After the NCO leaves, a member of our group will explain the project's purpose, risks, and benefits. After all questions have been answered, we will ask for volunteers. In the past, 10-20 of controls and 30-50 of SCTs have volunteered to participate. We will attempt to match an SCT volunteer with a control of similar body habitus for each experiment. The two volunteers will then be transported to the SCT lab.

Upon arrival, the subjects will read the volunteer agreement and ask any remaining questions. We will explain that they may withdraw from the study at any time without penalty. If the volunteer withdraws, he will be transported back to his original unit. The NCO will not be informed of the circumstances surrounding the trainee's return. Usually, within hours, the former volunteer and the rest of his unit is transferred to a training battalion and a new NCO.

After obtaining informed consent, documented in writing, we will examine each volunteer and obtain a medical history. If the subject has no contraindication to exercise, he will be accepted into the study.

A 20-gauge catheter will be inserted into a median cubital vein and advanced proximally. The insertion length will be equivalent to the distance between the subject's median epicondyle and the apex of his axilla. If an Allen's test reveals a palmar blush within five seconds, a second 20-gauge catheter will be inserted into a radial artery. Using this technique in over 100 catheter insertions, we have had no ischemic complications and all volunteers have successfully completed basic training. Approximately 50% of subjects have experienced minor wrist discomfort which typically resolved within 24 hours without sequelae. No other complications have occurred.

Exercise will be performed on a cycle ergometer, modified for armcranking and mounted on a steel frame. After the subject is familiar with the apparatus, he will perform two 35-watt incremental armcrank tests to exhaustion. Interval length will be two minutes and the anticipated duration of the test is 10 minutes. Both tests will be performed on the same day, one on room air (FI02 21%) and another on 14% FI02. The order of the tests will be varied and the subject will equilibrate, by mask, for 30 minutes on 14% FI02 prior to that test.

Exercise performance will be monitored with an ECG, mass spectrometer, and pneumotachograph interfaced with a computer system. Simultaneous blood samples will be drawn from each catheter pre- and post-exercise, and during the intervals corresponding to 0, 70, 140 watt and/or peak exercise. The following parameters will be analyzed: VD/VT and P(A-a)02, V02, VC02, VE, MR, VT, V02/kg, PO2, PC02, pH, %02 sat, % sickling, 02 content. Percent sickling will be determined on all SCT samples and on an occasional control sample.

An ACLS-qualified physician will monitor patient appearance and heart rhythm during the test. Testing will be interrupted if the patient experiences significant discomfort or if a dysrhythmia is noted. A crash cart and defibrillator will be available at all times. In over 100 prior cycle exercise tests we have had no significant complications.

We anticipate the catheters will be in place for six to eight hours. After the tests are completed, the catheters will be removed immediately and direct pressure will be placed on the wound. A vascular surgery consult will be obtained if the patient develops signs of ischemia.

Statistical analysis, using SPSS Student's t-test and ANOVA for repeated measures, will be used where appropriate.

Progress: The principal investigator concluded that exercise at 1,270 meters slightly, albeit significantly, increased sickling in blood from an exercising limb and that simulated 4,000 meters dramatically potentiated this effect. Sickling in the effluent blood of an exercising limb does not appear to measurable affect overall maximal arm crank exercise performance.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 88/05** **STATUS: Ongoing**

TITLE: IND Janssen Pharmaceutica # R51,211 Treatment of Systemic Mycoses with Itraconazole (Monitor: COL Ortiz)

START DATE: Oct 87 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Itraconazole, Systemic mycoses

Study Objective: To assess the efficacy of Itraconazole therapy in fungal dissemination disease.

Technical Approach: The details are lengthy and specified in the Pharmaceutical Companies' protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Patient is still taking Itraconazole. CSF is negative. Serology (IDCF) is still 1:4+. Patient is asymptomatic. Weight is stable. No adverse affects from Itraconazole.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 88/38** **STATUS: Ongoing**

TITLE: Comparison of Physiologic Responses to Prolonged Exercise Simulating Army Field Training in Sickle Cell Trait and Controls (Phase IVa) (Monitor: MAJ Ortiz)

START DATE: Jul 89 **ESTIMATED COMPLETION DATE: Jan 92**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: R.J. Zeballos, M.D.; COL John Little, ADA; T.W. Martin, CPT, MC

KEY WORDS: Sickle cell trait, Endurance exercise

Study Objective:

1. To determine if submaximal (50-70% VO_2 max) prolonged treadmill exercise (1 hour 30 minutes) with a final maximum exercise (5 minutes), similar to Army field training conditions, would elicit differences in exercise performance between Sickle Cell Trait (SCT) and control volunteers.

2. To evaluate changes in Percent Sickling (%S) and blood viscosity with prolonged exercise in SCT volunteers and to analyze their relationship to venous oxygen saturation, hydration status and temperature.

3. To assess biochemical and enzymatic changes in blood and urine that would suggest muscle damage (rhabdomyolysis) during prolonged exercise.

4. To compare the effect of prolonged exercise on renal function in SCT and controls.

5. To determine whether subtle pulmonary microcirculatory abnormalities not present at rest would be detected during exercise in SCT compared to controls.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Fifteen SCT/15 central patients have been entered into this protocol. Over 700 data parameters (biochemical, pulmonary, exercise, hematology) have been collected. The data is first being entered into the computer. Hematology slides have been sent for external review. We are awaiting results.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/41** **STATUS: Completed**

TITLE: Itraconazole Drug Trial, Compassionate Clearance for One Person

START DATE: Apr 89 **ESTIMATED COMPLETION DATE: Jul 90**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Dissem. cocci, Itraconazole

Study Objective:

(1) To assess the efficacy of Itraconazole therapy in fungal dissemination disease.

(2) The study is a non-blinded, non-crossover study to assess drug efficacy.

(3) Medication used will be Itraconazole.

(4) Population studied will be those with disseminated fungal disease who have failed on standard drug therapy.

Technical Approach: The details are lengthy and specified in the protocol. duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: One patient was entered into this study. He left the El Paso area and moved to San Antonio where he will be followed by Dr. Dick Grayhill, coordinator of Jansen 's Itraconazol Systemic Mycosis Group. Patient was stable throughout the year of treatment while in El Paso. No change in clinical or serologic status. GI follow-up revealed the same.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/68** **STATUS: Ongoing**

TITLE: In Vivo Sickling in Sickle Cell Trait (HbAs): Effect of Hypoxia, Exercise and Red Cell Sampling/Fixation Time

START DATE: Jul 89 **ESTIMATED COMPLETION DATE: Jul 91**

PRINCIPAL INVESTIGATOR: LTC Idelle M. Weisman

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: R. Jorge Zeballos, M.D.

KEY WORDS: Sickle cell trait

Study Objective: Recent discoveries in Hemoglobin S (HbS) polymerization kinetics make it imperative to re-examine the sickling phenomenon in vivo in order:

1. To corroborate, by using a new, specially designed blood drawing technique, that in vivo sickling is present in the blood of individuals with Sickle Cell Trait.

2. To determine the effect of hypoxia on the magnitude of sickling.

3. To compare the combined effect of hypoxia and exercise on sickling measured in effluent blood from an exercising limb and in arterial blood that has recirculated through the lungs during leg exercise.

4. To determine the effect of red cell sampling/fixation time on the measurement of percent sickling.

Technical Approach: The study will be carried out in the Human Performance/SCT Laboratory at William Beaumont Army Medical Center in El Paso, Texas at an altitude of 1270m and mean barometric pressure of 656mm Hg.

Ten individuals with SCT will be used for this study. All will be between 18 and 28 years of age and will be non-smokers. Volunteers will be obtained from the basic training reception station at Logan Heights, Ft Bliss, Texas similar to previous studies (WBAMC 83/37, WBAMC 88/38). All incoming recruits are screened for SCT with a Sickledex test; positive results will be confirmed by cellulose acetate (pH = 8.4) hemoglobin electrophoresis with % HbS determined by quantitative scanning densitometry. Individuals identified as possessing SCT (HbAS) will be asked to participate in the study after an explanation of the protocol, including its purpose, risks and benefits by one of the researchers. Based on past experience, between 30-50% of basic trainees with SCT volunteer to participate. In addition, SCT counseling will be provided by LTC Weisman. This remains important because >70-80% of basic trainees with SCT do not know that they have HbAS or what it means to be positive for HbAS. If the individual with SCT agrees to volunteer in the study, he or (they) will be transported to the SCT lab. Upon arrival, the subjects will read the volunteer agreement and ask any remaining questions. We will explain that they may withdraw from the study at anytime without penalty. If the volunteer withdraws, he will be
transported **back to his original unit. The NCO will not be informed of the circumstances surrounding the trainee's return. Usually within hours, the former volunteer and the rest of his unit is transferred to a training battalion and a new NCO.**

After obtaining informed consent, documented in writing, a physical examination will be performed on each volunteer, and a medical history will be obtained. Baseline EKG, CBC, Urinalysis and SMA-20 will be obtained/checked. If the subject has no contraindication to exercise, he will be accepted into the study. Controls are not necessary for this study.

A 20 gauge venous catheter (3.2 cm length, Quick Cath, Travenol Labs) will be inserted into one of the median antecubital veins of the exercising arm of each volunteer. If an Allen's test reveals a palmar blush within five seconds, a second 20 gauge catheter (Becton, Dickinson) will be placed in the radial artery of the non-exercising arm. Using this technique in over 150 arterial catheter insertions, we have had no ischemic complications; all volunteers have successfully completed basic training. Approximately 30-40% of subjects have experienced minor wrist discomfort which typically resolved within 24 hours without sequelae. No other complications have occurred. Previously approved WBAMC Protocol 88/38 fully discusses the risks of catheterization. The patency of the catheters will be maintained using a heparin flush solution (10 USP unit/ml) intermittently. Blood samples will be drawn anaerobically for blood gas analysis and percent sickling measurements at rest and during exercise. This is a simplified version of previously approved WBAMC protocols 83/37 ("Cardiopulmonary Effects of Stressful Exercise at Altitude (4000ft) of Individuals with Sickle Cell Trait (SCT) with modification to include altitudes of 2300m and 4000m") and WBAMC 87/25 ("Axillary Venosis Sickling in Individuals with Sickle Cell Trait During Upper Extremity Exercise in a Hypoxic Environment").

The subjects will be studied at rest breathing room air FIO2 = 21%, PIO2 = 127mmHg) and then breathing a hypoxic gas mixture (FIO2 = 14%, PIO2 = 85mmHg) equivalent to 4000m for 15 minutes at rest (before the exercise) and during the exercise tests. The hypoxic gas will be administered via a respiratory gas mask during rest and hand grip exercise and a mouth piece during leg exercise. The inspiratory port of both devices will be connected to a 120L reservoir bag continuously fed from the gas cylinder with the hypoxic gas.

Two types of exercise Formats will be Used:

a) Hand Grip Exercise: After 15 minutes of breathing the hypoxic gas mixture, the subjects will first perform a maximum rhythmic hand grip exercise at a rate of 60 grips per minute, pulling a weight of 16 pounds from an apparatus, consisting of a hand grip cable, pulley and adjustable weights. The exercise will be performed only with the arm in which the venous catheter has been placed. The duration will be approximately 3 minutes.

b) Leg Exercise: After 15 minutes of breathing the hypoxic gas mixture at rest, the subjects will be exercised on an electronically braked cycle ergometer. The exercise test will consist of two stages of steady state exercise consisting of 5 minute duration each. The first stage will be at 50%, and the second at 75% of the maximum power predicted for each individual. During the cycle exercise test, minute ventilation (VE), oxygen uptake (V02), carbon dioxide production (VC02), and respiratory exchange ratio (R) will be measured in a breath-by-breath fashion using a computerized system (Medical Graphics Corporation) that integrates flow (pneumotachometer) with the respiratory gases measured continuously in the mouthpiece with a mass spectrometer (Perkin-Elmer). Heart rate (HR) and electrocardiographic changes will be monitored continuously during the exercise tests with an Electrocardiographic System. The arterial blood gas results will be entered in the computer and the physiologic dead space-tidal volume ratio (VD/VT) and the alveolar-arterial oxygen pressure difference [P(A-a)02] will be calculated.

A short IV extension tube attached to a drawing apparatus will be connected to either the venous or the arterial catheter. The apparatus consists of the following elements: a) a 3-way stopcock connected in series with a b) one-way back pressure valve placed between the venous catheter and the port where the c) syringe with the 1% glutaraldehyde phosphate buffer solution will be connected. A 6cc plastic syringe will hold the glutaraldehyde solution. A d) plastic safety sleeve will be placed around the plunger and then marked with a e) red ring. The 1% glutaraldehyde solution is a biological fixative used for fixing blood cells. If this solution is injected into the subject, it could induce serious medical complications. To our knowledge, there is no literature available about the effect of accidental injection of glutaraldehyde into a human being.

The drawing apparatus has been tested for safety by the Clinical Pharmacist of the Hematology/Oncology Service, WBAMC (see attached report). It would appear that this apparatus/technique approaches almost complete freedom from the possibility of accidental injection of the fixative into the subject. This possibility is even less likely if used by a researcher who is familiar with the system. Another important safety feature is that during the blood sampling, all the maneuvers that are required will be that of pulling the plunger, and never that of pushing or injecting.

Arterial and Venous blood samples will be taken at rest breathing room air, at rest breathing the hypoxic gas mixture (14% FIO2), and at the end of the hand grip and leg exercises, while breathing the hypoxic gas mixture.

The blood samples will be drawn and then fixed immediately in the fixative solution (<2sec); immediately thereafter, another blood sample will be collected into a heparinized syringe. This syringe will then be removed from the drawing apparatus, and the blood fixed in glutaraldehyde solution at 30, 60, 180, and 300 second intervals, while being maintained in an anaerobic environment at 37°C. At the end of the Exercise test, the catheters will be removed.

Blood gas analysis will be performed on all samples collected including those used for the measurement of Percent sickling. Oxygen tension, carbon dioxide tension and pH will be measured in an automated blood gas analyzer (IL) and oxygen saturation in a spectrophotometric oximeter (IL CO-Oximeter).

After fixation of the blood samples, slides will be prepared from one to two drops of the glutaraldehyde-red cell suspension and examined under a phase contrast microscope. A thousand cells from random areas of the preparation will be photographed for determination of percent sickling (number of sickled cells per 100 counted). Sickling will be determined independently and in a blind fashion by two observers. A cell will be considered sickled if it is elongated with at least one or two projections or if it is irregularly shaped with an angle and one or more points (21). Ovalocytes, tear drops, echinocytes, and other poikilocytes will be excluded. These criteria for sickling morphology have been adopted and vigorously applied in our lab (22).

An ACLS-qualified physician will monitor the patient's clinical status during the test. Testing will be interrupted if the patient experiences significant discomfort (abdominal pain, muscle cramps) or if a dysrhythmia is noted. A crash cart, supplemental oxygen and defibrillator will be available at all times. In over 150 prior cycle exercise tests with hypoxia we have had no significant complications. We anticipate the catheters will be in place for no longer than two or three hours. After the tests are completed, the catheters will be removed immediately and direct pressure will be applied to the site. A stat vascular surgery consult will be obtained in the unlikely event that a subject develops signs of ischemia.

Progress: Twenty-four patients have been entered into this study. There have been no withdrawals or adverse reactions to report. Data has been entered into the computer. Hematology materials have been sent to outside clinic review. On its return, abstract for publication will be written.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/62 STATUS: Ongoing

TITLE: Armcrank and Cycle Exercise in the Evaluation of Dyspnea (Monitor: COL Ortiz)

START DATE: Jul 88 ESTIMATED COMPLETION DATE: Jul 91

PRINCIPAL INVESTIGATOR: Dr. Jorge Zeballos

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Idelle M. Weisman, MC

KEY WORDS: Armcrank, Cycle exercise

Study Objective: Compare the cardiopulmonary response to armcrank and cycle exercise in subjects with dyspnea on exertion.

Technical Approach: We will use 20 male or female patients, 18-65 years old, referred to the pulmonary department for evaluation of dyspnea on exertion. These patients routinely undergo cycle exercise testing with an arterial line in place. Subjects will be excluded if they have orthopaedic, neurologic, or vascular abnormalities which limit arm or leg exercise.

Subjects will perform both upper and lower extremity exercise on an electronically braked cycle ergometer. For the upper extremity test, the cycle will be placed on a table so that the crank shaft will be level with the seated patient's shoulders. The order of the tests will vary so that a similar number of subjects begin with either arm or leg exercise. Beginning with no added resistance or 0 watts, the work rate will increase 10-20 W/min until the subject is unable to maintain a 60 rpm crank rate. the test will also be discontinued if the subject has ventricular tachycardia, more than a 20 mm drop in systolic blood pressure, or > 3 mm ST depression.

While exercising, the subjects will breathe through a two-way valve. We will measure respiratory gases at the mouthpiece using a mass spectrometer (Perkin Elmer). Ventilation will be measured with a pneumotachometer (Hans Rudolph). An on-line computer (MGC 2001) will perform breath-by-breath calculation of 0_2 uptake (VO_2)m CO_2 production (VCO_2), minute ventilation (VE), and other measurements. We will monitor heart rhythm on an oscilloscope and measure heart rate from a rhythm strip obtained during the last five seconds of each minute.

One hour before the first exercise test, a 20 gauge catheter will be inserted in the patient's radial artery. A 25cm tube with a three-way stopcock will be attached to the catheter to permit anaerobic sampling while the subject exercises. Patency of the catheter and connecting tube will be maintained with a heparin solution (10 USP unit/ml).

We will draw blood samples with the subject at rest and every 2-4 minutes during exercise. We will measure PO_2, PCO_2, and pH with an automated blood gas analyzer (IL System 1303). Hemoglobin saturation and concentration will be measured with a spectrophotometric oximeter (IL 282 CO-Oximeter). The dead space-tidal volume ration and the alveolar-arterial oxygen difference will be calculated using standard equations.

Progress: No additional patients have been entered into this protocol since last abstract (19 patients total have been entered). There have been no withdrawals or adverse reactions to report. Data is being collected for comparison with another study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/48** **STATUS: Ongoing**

TITLE: Practical Value of Hyper-Reactive Airway Testing in the Assessment of Asthma in Army Recruits (Monitor: COL Ortiz)

START DATE: Aug 89 **ESTIMATED COMPLETION DATE: Aug 91**

PRINCIPAL INVESTIGATOR: M.D. R. Jorge Zeballos

DEPARTMENT: DCI **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC Idelle M. Weisman, MC

KEY WORDS: Asthma, AIT, Army recruits

Study Objective:

1. To determine whether a screening test for hyperreactive airways "asthma" should be established for individuals who, although having met entry requirements as specified in AR 40-501-2-24d have allergic histories and/or a history of asthma in childhood (HAC), which would appear to increase their likelihood of exercise induced asthma and other asthma related problems during basic training.

2. To determine which of the currently available methodologies, for the diagnostic evaluation of hyperreactive airways, would be most accurate (high sensitivity, high specificity), practical, and cost effective for the screening of potential Army recruits.

3. To modify standard methods for the diagnosis of airway hyperresponsiveness so as to make them more suitable to the Military Entrance Processing Service (MEPS).

4. To propose modification for AR40-501-2-24d based on the results of this study and thereby reduce the number of Existing Prior to Service (EPTS) discharges secondary to asthma.

Technical Approach: All incoming basic trainees at FT. Bliss will be asked to respond to a questionnaire which will identify the inclusion criteria: (1) history of allergic rhinitis (hay fever), and/or (2) history of allergic dermatologic disorder (i.e. eczema), and/or (3) history of asthma in childhood and (4) normal or border line pulmonary function tests. Service members responding affirmatively to any of the inclusion criteria will be asked to participate in the study.

A physical examination will be performed on each volunteer, and a medical history will be obtained. Baseline EKG, CBC, Total Eosinophil count, and SMA-20 will be obtained/checked.

The study will be conducted on 2 consecutive days in the Human Performance/Pulmonary Function Labs at WBAMC. On the first day, the exercise induced bronchoconstriction test will be performed in the morning, followed by the nebulized distilled water test in the afternoon. On the second day, the hyperventilation with cold air test will be performed in the morning, followed by the nebulized metacholine test in the afternoon. The pulmonary functions at baseline for each test should not differ by more than 5%. The volunteers will be followed during their stay at Ft. Bliss (at least 7-8 weeks) and even longer for those SM's assigned here for AIT. All admissions to a hospital for 48 hours or more, failures to pass the Army Physical Fitness Test, or discharge from the service (especially with a principal diagnosis of asthma) will be carefully documented. A relationship between positivity to hyperreactive airway tests and medical problems related to asthma will be analyzed.

An ACLS-qualified physician will monitor the patient's clinical status during all the testing. Testing will be interrupted if the patient experiences significant chest tightness, wheezing, shortness of breath, chest

pain, or if a dysrhythmia is noted. A crash cart, supplemental oxygen and defibrillator will be available at all times.

Progress: Ten subjects have been entered into the study, however, no data has been collected.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/75 STATUS: Ongoing

TITLE: Comparison of Cranial and Iliac Autologous Bone Grafts and their Effect on the Success Rates of Subsequent Osseointegrated Intra/Extraoral Implant Application in the Miniature Swine

START DATE: 2 Feb 90 ESTIMATED COMPLETION DATE: Apr 91

PRINCIPAL INVESTIGATOR: LTC Nathan C. Dickerson

DEPARTMENT: Dentac FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Michael G. Donovan, DE; Jan Faulk, MAJ, DE

KEY WORDS: Cranial bone graft, Iliac bone graft

Study Objective:

PHASE I: Design surgical techniques for harvesting bilateral iliac corticocancellous bone grafts, and cranial bone and cranial-facial flap techniques.

(1) Study will provide knowledge for surgical techniques that will minimize morbidity (pain, muscular dysfunction, nerve damage) in swine for future studies.

(2) Phase I study will be performed on one (1) domestic swine prior to bone graft studies (Phase II and Phase III) on more expensive miniature swine.

PHASE II: Compare traditional reconstruction techniques, autologous iliac bone grafts, with autologous cranial bone grafts in maxillofacial reconstruction.

Will verify if cranial bone is superior to iliac bone in maxillofacial reconstruction. Facial onlay bone grafts and continuity defect repairs are to be compared.

(a) Will compare rate of revascularization and magnitude of resorption at different time intervals for cranial and iliac bone grafts.

(b) Will evaluate need for donor bone graft to duplicate recipient site.

PHASE III: Will determine degree of osseointegration of pure titanium bone implants in cranial and iliac bone grafts in:

(1) Intraoral continuity defects

(2) Extraoral continuity defects

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Phase I of the project was completed November 1989 with evidence that the swine is a good surgical model for comparison of cranial and iliac bone grafts to the facial bones.

Phase II has been completed as of 20 August 1990. There were no difficulties with the surgical procedures, and serial necropsies have demonstrated generalized better retention of cranial bone versus iliac bone grafts. Specific measurements and analysis for histological studies, radiographic studies, and tetracycline studies are underway.

Phase III, placement of Branemark osseointegrated implants into previous cranial bone grafts, was started on 21 September 1990. Comparison of cranial and iliac autologous bone grafts and their effect on success rates of subsequent osseointegrated intra/extraoral implant application in the miniature swine is progressing as planned. Changes include no utilizing intraoral bone grafts for implants due to primary wound breakdown, and use of each animal as its own control for Branemark osseointegrated implants by placing an implant in an ungrafted area of the mandible via a percutaneous approach.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/37** **STATUS: Ongoing**

TITLE: Bone-Anchored Craniofacial Prostheses Investigation

START DATE: Oct 89 **ESTIMATED COMPLETION DATE: Dec 91**

PRINCIPAL INVESTIGATOR: COL Michael G. Donovan

DEPARTMENT: Dentac **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: John Gary, COL, MC

KEY WORDS: Craniofacial prostheses, Bone-anchored prostheses

Study Objective:

1. To evaluate the long term retention success rate for titanium implants anchoring craniofacial prostheses.
2. To evaluate the long term stability of the prostheses.

Technical Approach: Patients will be admitted to Ward 6W, and have the routine pre-surgery laboratory studies, to include blood work, x-rays and urinalysis, and any further tests required that would be dictated by their medical history. Appropriate referrals will be given to various medical specialties if indicated. The surgery to implant the prosthesis will be conducted in the operating room. Anesthetic will be given to minimize the pain that is associated with any surgical procedure. The doctor will cut the skin covering the area to be treated and then drill holes in the bones of the face, head, or both. Next, tiny titanium fixtures will be inserted into the holes, the skin will be replaced so that it covers the fixtures, and the skin stitched. The titanium fixtures will be left in place for 3-4 months to allow them to become integrated with the bone. During this time the patient will visit the doctor 2-3 more times so their condition can be monitored.

After 3-4 months, the patient will once again be admitted to the hospital, where they will undergo additional surgery. After the anesthetic is administered, the doctor will again cut the skin covering the area being treated. Some of the tissue under the skin will be removed and the skin will be stitched back together. The doctor will then puncture the skin directly over each implanted titanium fixture and will attach a small skin-penetrating abutment to each fixture. For 3-4 weeks, the treated area will be allowed to heal. During that time the patient will visit their physician 1-3 times so that their condition can be monitored.

After 3-4 weeks, a prosthesis will be made and will be attached to the anchors. After the prosthesis is in place, the patient will continue to visit their physician 3 times during the first year, then twice a year, so that their condition can be monitored, as well as their level of satisfaction.

Progress: Three patients have been completed without complication. One out of ten implants was lost.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 89/81 **STATUS:** Completed

TITLE: A Study to Assess the Training Needs of the Medical Staff for Transition to Diagnosis Related Groups

START DATE: Oct 89 **ESTIMATED COMPLETION DATE:** Jun 90

PRINCIPAL INVESTIGATOR: MAJ Henry Hernandez

DEPARTMENT: HQ **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: DRG's, Training

Study Objective: To assess the training needs of William Beaumont Army Medical Center's medical staff for transition to Diagnosis Related Groups (DRG's) and to determine a training program.

Technical Approach: Fifty physicians comprising the Department of Medicine and the Department of Surgery will be randomly selected and asked to respond to a questionnaire. The purpose of the questionnaire will be to assess the physician's current DRG knowledge level, as a method to determine transitional training requirements. The questionnaire will be a true/false type. Before the questioning begins, the respondents will be given directions and informed that their confidentiality and anonymity will be protected.

Descriptive statistics (item analysis) will be analyzed, and the alpha probability level will be established at .05 to evaluate the results of the study. A correlation matrix of all variables will be obtained. The r values for each variable will be compared to the Y sum to test for whole-part validity. Next, Randomized Blocks ANOVA will be evaluated, comparing individual test score against the domain Y (DRG knowledge). Each score will also be evaluated against each construct (general knowledge, impact issues, documentation issues, case-mix index issues, cost containment issues, and additional demographic data).

The discussion will include a detailed explanation of the observed and statistical analysis. It is expected that military physicians will not score highly on the questionnaire because as a group they have not been exposed to working conditions under a prospective payment system. Appropriate descriptive statistics which represents demographic and summary data, will be displayed graphically. A recommendation for the most practical, simple and cost effective method for training for transition to DRG's will be made.

Progress: This study hypothesized that DRG knowledge was dependent upon five constructs identified as general knowledge, impact, documentation, case-mix, and cost containment. Four additional variables were considered: age, time in service, type of provider and military rank. Two open-ended questions assessed staff input and contributed to the development of the strategic plan. The research design used parametric and nonparametric analysis to determine the relationship between the dependent and independent variables. A pilot survey was tested on 33 Army Nurse Corps Officers who indicated the survey was understandable and measured their DRG knowledge. Item analysis followed by Analysis of Variance demonstrated high levels of both construct and content validity and an acceptable reliability coefficient. It was expected that the survey will reveal similar results on the Center's medical staff. Results indicated poor item discrimination evidenced by high group means, however, staff input was useful in determining a strategic plan comprising four initiatives: strategic planning, training, assessment and restructuring (STAR). STAR is an executive strategic planning tool designed to aid the commander in implementing a DRG budget allocation system.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 86/49** **STATUS: Ongoing**

TITLE: The Natural History of HTLV-III Infection and Disease in a US Military Population

START DATE: May 86 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Charles E. Davis, Jr., MAJ Eugene Etzkorn; Ms. Renata Riley, PA-C; MAJ David Slagle, MC

KEY WORDS: HIV Natural History

Study Objective: Study the epidemiology of HTLV-III infection in active duty and retired military personnel and their dependents.

Technical Approach: Standard evaluation will be routine medical evaluation, immunological evaluation, laboratory tests, tests for opportunistic infections, HTLV-III viral cultures on body fluids and organs whenever possible. Completion of HTLV-III clinical evaluation form. HTLV-III tests. Counselling, education, and referral of contacts. Follow-up of individuals in the study. Data analysis: disease progression will be studied, as defined by Walter Reed Staging Classification. The effect of variables, including but not limited to age, sex, ethnic background, risk factors, length of infection, and simultaneous viral infections, will be studied.

Addendum: 12 Feb 90 - This protocol was amended to exclude active duty servicemembers. At the directive of the Secretary of the Army, all active duty HIV+ servicemembers are to be clinically staged periodically.

Progress: This protocol is part of an Army-wide study; all WBAMC data is submitted to a central data base at WRAIR. It is difficult to do more than evaluate the past year in terms of progression of infection in our ever increasing population (36 new patients in the last year).

Earlier this year, the IRB approved a request to exclude active duty patients from the protocol (indeed, it was required that active duty patients have the same evaluation). Excluding active duty, 15 new individuals have been entered in the protocol since last Sept 89. Three patients have died in the past year. Ten AIDS patients are currently being followed. In terms of patients currently being followed (% patients in each stage):

	WR1	WR2	WR3	WR4	WR5	WR6	WR7 (Cumulative death)
Oct 89	17%	25%	19%	7%	10%	3%	
Oct 90	21.5%	15%	29%	9%	9%	9%	6.5%

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/06 STATUS: Ongoing

TITLE: A Prospective Double-Blind Study of Retrovir in the Treatment of Patients with Early HIV-Associated Immunodeficiency

START DATE: Dec 88 ESTIMATED COMPLETION DATE: Feb 91

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Shannon M. Harrison, Chief, Inf Dis Svc, FAMC

KEY WORDS: Zidovudine in Early HIV

Study Objective:

1. To evaluate the safety and tolerance of chronic administration of RETROVIR (zidovudine) to adult patients with early manifestation of ARC, including those presenting with only HIV-associated lymphadenopathy and a CD4 cell count < 500 cells/mm3.

2. To assess the efficacy of RETROVIR therapy in the treatment of HIV disease in these patients. Therapeutic efficacy will be determined by monitoring the following variables.

a. Changes in the incidence of progression of HIV disease to more advanced disease stages.

b. Changes in clinical manifestation of HIV disease as reflected in objective signs such as weight change, lymphadenopathy, Karnofsky score and performance on tests of neurologic function.

c. Prevention of the progressive deterioration of the immune response associated with HIV disease as reflected in changes in CD'4 cell number and skin test reactivity.

d. Changes in levels of HIV viremia/antigenemia in virus-positive patients.

Technical Approach: The ability of RETROVIR to halt or delay early HIV disease progression is the critical clinical objective in the demonstration of therapeutic efficacy. clinical disease will be evaluated as described by the Centers for Disease Control classification system and the Walter Reed Staging System.

For the purpose of this study, the incidence of disease progression will be measured as follows:

1. By the development of severe ARC, characterized by a CD'4 cell count < 200 persisting for a period of at least 3 months and the new development of at least 2 of the symptoms and/or infections listed in appendix VIII. *[Protocol 27,433-15/Project 53 Burroughs Wellcome Co.]

2. By the development of AIDS characterized by the diagnosis of any of the AIDS-defining diseases or disease-related conditions listed in Appendix III.

3. By an increase in Walter Reed classification of one or more stages.

Independent interim and final analyses of disease progression will be done using both systems.

Progress: Protocol was modified as follows: Chemistries will be drawn every 3 months (instead of every month); neuropsychiatric testing discontinued (no difference found) between placebo and drug group for first nine months); unblind study began in Sep 89 and all subjects were placed on Zidovudine.

Two subjects withdrew: One due to CD4 cells <200, recurrent herpes zoster and staff folliculitis and one ETS'd and moved to Houston (may still be participating in study at Ft. Hood with LTC Harrison).

Adverse reactions included 6 megaloblastic indices, 1 nail discoloration, and 1 severe headache (resolved post continuation.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/22 STATUS: Ongoing

TITLE: Prospective Evaluation of Health Care Workers Exposed to the Blood of Human Immunodeficiency Virus (HIV)

START DATE: Mar 89 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Ms. Lynn McNicol, R.N.; Ms. Renata Riley, PA-C

KEY WORDS: HIV exposure in health care workers

Study Objective: The objectives of this prospective surveillance project are:

1) To estimate the risk of HIV infection in health care workers (HCWs) exposed via the parenteral or mucous membrane route to HIV infected blood, according to type of exposure.

2) Describe infection control precautions taken or not-taken to evaluate extent of preventable exposures.

3) To describe the clinical natural history and development of laboratory markers of HIV infection in health care workers enrolled in this project who seroconvert to HIV.

Technical Approach: The number of exposed health care workers is expected to be less than 30/year, but is dependent on the number of HIV infected individuals cared for at WBAMC, a population which is increasing in size.

Upon entry into the surveillance project, each exposed HCW will be interviewed and a questionnaire completed collecting the following data: demographic information, use of immunosuppressive drugs, circumstances of the blood exposure, type of infection control precautions used at the time of exposure, any past exposure prophylaxis and information on the source patient. The exposed HCW will be asked to complete a questionnaire concerning risk factors for HIV infection. This confidential report will be completed by the exposed HCW and mailed directly to CDC by the worker. Information collected on this form (CDC 57.42A) will not be released to personnel at WBAMC.

The exposed HCW will be prospectively followed by the investigators for one year with follow up data and specimen collection at 6 weeks, 3 months, 6 months, and one year post exposure. At each follow-up a questionnaire and 10 ml. serum will be sent to CDC. In addition to scheduled follow-ups the exposed HCW must report to the investigator any illness of at least one week duration which occurs in the 12 week period after exposure. If the symptoms are suggestive of an acute retroviral syndrome, the investigator will obtain whole blood for virus isolation + T cell subset (10 ml) and serum (10 ml) for antibody/antigen testing.

Baseline serum samples will be tested for HIV antibody, if negative, HIV antigen will also be evaluated. If a HCW seroconverts a 10 ml heparinized whole blood sample will be requested from the source patient with their informed consent. Viral isolates from the source patient and HCW will be compared using molecular techniques.

Exposed health care workers will be followed for one year post-exposure.

Progress: Five health care workers with percutaneous needlestick or cutaneous exposure to HIV infected blood were followed. No seroconversions were found.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/40** **STATUS: Ongoing**

TITLE: The Effect of Megestrol Acetate on the Cachexia of Human Immunodeficiency Virus Infection: A Randomized, Placebo-Controlled, Double-Blinded Study. (Monitor: Dr. Lundy)

START DATE: Aug 89 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CPT Daniel Loube, MC; Ms. Lynn B. McNicol, RN; 1LT Melanie Freel, RD; Ms Janet Chilton, RD; Ms. Renata Riley, PA-C

KEY WORDS: Megace in HIV cachexia

Study Objective: **Assess the efficacy of megestrol acetate in the treatment of the anorexia and weight loss associated with HIV infection. Conduct a longitudinal analysis of nutritional, biochemical, anthropomorphic and psychosocial parameters in HIV patients receiving megestrol acetate.**

Technical Approach: **The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.**

Progress: **One patient developed bilateral post subscapular cataracts after six weeks of therapy; irreversible after megace stopped. Two patients completed protocol; one gained 29 pounds in three months, and one lost three pounds in six months on protocol. One patient has just commenced protocol. No adverse effects were noted, aside from PSC cataracts in one (not reported previously with megace, although other glucocorticoid steroid effects have been).**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 89/66 **STATUS:** Ongoing

TITLE: Use of Itraconazole for Treatment of Coccidiomycosis

START DATE: Jan 89 **ESTIMATED COMPLETION DATE:** Sep 91

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ David Slagle, MC

KEY WORDS: Itraconazole, Cocci

Study Objectives: To assess the efficacy of Itraconazole therapy in fungal disease. The study is a non-blinded, non-crossover study to assess drug efficacy. Medication used will be Itraconazole. Population studies will be those with fungal disease who have failed on standard drug therapy.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Patient with chronic pulmonary cocci has had good therapeutic response with CF titers 1:256 ·1:8, negative cultures and nor further sweats, fevers, hemoptysis. Patient with renal failure and cocci osteomyelitis/arthritis improved; can ambulate without pain and has had cocci CF titers 1:64 ·1:16. Both suggestive of clinical response.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/67** **STATUS: Ongoing**

TITLE: Investigational Prophylactic Use of Zidovudine in Health Care Workers Sustaining a Deep Percutaneous Occupational Exposure to Human Immunodeficiency Virus

START DATE: Jul 89 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Ms. Lynn B. McNicol, RN; Ms. Renata Riley, PA-C; MAJ David Slagle, MC

KEY WORDS: Retrovir prophylaxis for HIV needlesticks

Study Objective: To offer a defined course of zidovudine to HIV negative health care workers within 5 days of a significant exposure to HIV. To assess the safety and tolerance of 200mg zidovudine given orally every 6 hours for 42 days in otherwise healthy persons.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no subjects enrolled in this study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/04** **STATUS: Terminated**

TITLE: Emergency Use of 2'3'-dideoxyinosine (ddI) in a Patient with AIDS Intolerant to Zidovudine

START DATE: Oct 89 **ESTIMATED COMPLETION DATE: Dec 89**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ David C. Slagle, MC; Ms. Renata Riley, PA-C; Ms. Lynn B. McNicol, RN

KEY WORDS: ddI, AIDS

Study Objective:

a. To make ddI available to persons with HIV infection who have developed intolerance to Zidovudine (AZT).

b. To evaluate the toxicity of ddI in AIDS/ARC patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: The patient died on therapy from complications of AIDS. No adverse drug reactions occurred.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/05** **STATUS: Ongoing**

TITLE: A Treatment IND Protocol for the Use of 2'3'-dideoxyinosine (ddI) in Patients with AIDS or ARC Who Are Intolerant to Zidovudine

START DATE: Dec 89 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ David C. Slagle, MC; Ms. Renata Riley, PA-C; Ms. Lynn B. McNicol, RN

KEY WORDS: DDI, HIV

Study Objective:

a. To make ddI available to persons with HIV infection who have developed intolerance to Zidovudine (AZT).

b. To evaluate the toxicity of ddI in AIDS/ARC patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Three patients have received DDI. One patient died while taking drug with disseminated CMV, PCP, not related to DDI. One patient was withdrawn due to pancreatitis. Another has diarrhea, commonly found thought to be from buffering agent. The fourth patient has just begun on protocol this week (Oct 90).

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/27** **STATUS: Terminated**

TITLE: Emergency Use of Itraconazole for Treatment of Disseminated Coccidioidomycosis

START DATE: Feb 90 **ESTIMATED COMPLETION DATE: Mar 90**

PRINCIPAL INVESTIGATOR: MAJ Naomi Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Itraconazole, Coccidioidomycosis

Study Objective: **To assess the efficacy of Itraconazole therapy in fungal disease. The study is a non-blinded, non-crossover study to assess drug efficacy. Medication used will be Itraconazole. Population studies will be those with fungal disease who have failed on standard drug therapy.**

Technical Approach: **The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.**

Progress: **One patient entered in this protocol. Emergency study was terminated and the patient was entered into protocol 89/66, "Use of Itraconazole for Treatment of Coccidiomycosis". There were no adverse reactions.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/49** **STATUS: Terminated**

TITLE: Recombinant DNA GM-CSF (rGM-CSF) in an Emergent Basis for the Treatment of a Patient with CMV Retinitis & HIV Infection

START DATE: **ESTIMATED COMPLETION DATE:**

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Recombinant DNA GM-CSF, CMV retinitis, HIV infection

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Study Objective: To offer Human rGM-CSF to patients with life threatening neutropenia (generally ANC < 500) due to an underlying disease or a therapeutic maneuver, and to assess the safety and tolerance of rGM-CSF in HIV and oncology/hematology patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients were entered into this study before it was terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 90/51 **STATUS:** Ongoing

TITLE: A Treatment IND Protocol for the Use of Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor (rGM-CSF) in Compassionate Circumstances

START DATE: Jul 90 **ESTIMATED COMPLETION DATE:** Indefinite

PRINCIPAL INVESTIGATOR: MAJ Naomi E. Aronson

DEPARTMENT: Med **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Ruben D. Sierra, MC; MAJ David C. Slagle, MC; MAJ Ricke Weickmum, RPH; Ms. Lynn B. McNicol, RN

KEY WORDS: rGM-CSF, HIV

Study Objective: To offer Human rGM-CSF to patients with life threatening neutropenia (generally ANC < 500) due to an underlying disease or a therapeutic maneuver, and to assess the safety and tolerance of rGM-CSF in HIV and oncology/hematology patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This is a newly approved study with no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/38** **STATUS: Ongoing**

TITLE: Cost-Benefit Analysis of Routine, Right-Sided Cardiac Catheterization in the Evaluation of Coronary Artery Disease by Left-Sides Catheterization

START DATE: Aug 90 **ESTIMATED COMPLETION DATE: Aug 91**

PRINCIPAL INVESTIGATOR: CPT Terry D. Bauch

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ William A. Collazo, MC; MAJ Thomas Stoughton, MC

KEY WORDS: Cardiac catheterization, Coronary artery disease

Study Objective: **This study examines the question of whether routine right-sided cardiac catheterization is justified in the evaluation of coronary artery disease by left-sided catheterization. Military beneficiaries already scheduled for left heart catheterization will be studied in a prospective fashion.**

Technical Approach: **A right-heart catheterization will be performed on 200 consenting adults of both sexes, ages 20 to 90, already scheduled for left-heart catheterization in the evaluation of known or suspected coronary artery disease. The study will not be blinded. Exclusion criteria include known or suspected pulmonary or right-heart pathology as identified by historical, physical, and non-invasive laboratory findings. The patients thus excluded will include those with congestive heart failure, myocardial disease, pericardial disease, and significant valvular heart disease. A normal right heart catheterization performed within the previous 12 months will also be an exclusion criteria. Routine right-heart hemodynamic data will be recorded to include right atrial and ventricular pressures, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, and superior vena caval and pulmonary arterial oxygen saturations. Standard left heart catheterization data will also be obtained. Given the prior practice of routine right heart catheterization in our laboratory, the patient will not be subject to additional risk by study participation. Subjects are terminated if right-heart catheterization is normal. The remainder are followed through the secondary evaluation of the abnormalities elicited. The outcome of secondary evaluation will be noted, and a cost-estimate made for the additional work. Cost-benefit will be judged by comparing the health care costs of early identification of unsuspected abnormalities versus the estimates of cost should these abnormalities have not been found.**

Progress: **To date, two patients were enrolled and completed their study participation. There were no abnormal findings and no complications.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/60** **STATUS: Terminated**

TITLE: Cholesterol and Lipid Profiles of Male Soldiers During U.S. Army Basic Training

START DATE: Sep 89 **ESTIMATED COMPLETION DATE: Dec 89**

PRINCIPAL INVESTIGATOR: MAJ Joseph Caravalho, Jr.

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CW2 Margaret A. Kinney, PA; CPT John D. MacDonald, MC; MAJ Thomas E. Martyak, MC

KEY WORDS: Cholesterol, Lipid profile, U.S. Army, Basic trainee

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Study Objective:

1. Determine the plasma total cholesterol (TC); triglyceride (TG); high density lipoprotein (HDL-C); low density lipoprotein (LDL-C); and very low density lipoprotein cholesterol (VLDL-C) levels of healthy young adult males from the general population as they enter the Army for Basic Training (BT).

2. Determine the background demographic data of these soldiers in order to assess dietary, smoking, and alcohol consumption habits, as well as previous physical activity and educational levels attained.

3. Determine the effect of eight weeks of continuous BT (i.e., without administrative or medical breaks in training) on these soldiers' serum TC, TG, HDL-C, LDL-C, and VLDL-C.

4. Determine if there is any significant change in demographic data (to include diet, physical activity and perceived level of stress) at the conclusion of BT.

5. Determine if there is any significant change in lipid profile following BT attributable to a change in diet or other factor.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This study is terminated. No scientific conclusion could be drawn from the collected data due to the preponderance of missing data (both questionnaires and serum specimen) from the conclusion of the Basic Training cycles.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/31** **STATUS: Ongoing**

TITLE: Health Status Awareness Survey

START DATE: May 90 **ESTIMATED COMPLETION DATE: Oct 91**

PRINCIPAL INVESTIGATOR: MAJ Christopher P. Cheney

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Harry E. Davis, COL, MC

KEY WORDS: Health Status Assessment Questionnaire

Study Objectives:

1. Assess patients' awareness of their medical problems.

2. Assess patients' awareness of how their current problems will impact on their future health status.

3. Identify patients' life styles and habits that impact on their health.

4. Survey the patients' insight and/or attitudes regarding care provided by the clinic.

5. Elicit suggestion as to how to improve the efficiency and operation of the Internal Medicine Clinic (IMC).

Technical Approach: The study will survey outpatients of the IMC over two calendar months. The questionnaire will be given to all patients as they sign in to our clinic and who meet our inclusion criteria. They will be encouraged to fill out the questionnaire while they are waiting for their appointment, or return it to the clinic as soon as possible via a self addressed envelope. Their responses to all questions will be encouraged. Our goal is to obtain over 500 completed questionnaires. The questionnaire evaluates a series of general medical problems seen frequently in the IMC to include tobacco abuse, alcohol abuse, hypertension, hypercholesterolemia, coronary artery disease, cancer screening and obesity. The questions address whether the patient is aware of their diagnoses, are they aware of how various life styles affect the natural history of the disease and do they know means available to lessen or eliminate the disease.

Progress: Five hundred questionnaires were handed out over a six week period in the Internal Medicine Clinic. To date, 137 completed questionnaires have been returned. Currently, a database 3 plus program has been developed to handle the analysis of approximately 200 responses on each questionnaire. Data from the questionnaires is being entered and initial evaluation of the data is expected soon. No further questionnaires are to be handed out until a thorough analysis of the data is done. However, I would expect handing out more questionnaires in an effort to increase the number of completed questionnaires to 200.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 88/46** **STATUS: Ongoing**

TITLE: Rate of Spherulin Skin Test Conversion Among Basic Trainees Exposed to Desert Training at Fort Bliss, Texas

START DATE: Sep 88 **ESTIMATED COMPLETION DATE: Nov 90**

PRINCIPAL INVESTIGATOR: MAJ Robert B. Ellis

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CPT B.L. Martin, MC

KEY WORDS: Spherulin, Skin test to C. immitis.

Study Objective: To establish the rate of spherulin skin test conversion among active duty basic trainees who are exposed to desert training at Fort Bliss, Texas. To attempt to define the morbidity associated with Coccidioides immitis in terms of time lost from basic training due to acute Coccidioidal infection.

Technical Approach: Basic trainees will be invited to participate in the study. Study participants will be briefed by the principal investigators about the study and given an opportunity to volunteer for the program. One basic training cycle will be tested in each month to determine if there is a seasonal peak to exposure. As basic training cycles are 8 weeks in length and encompass between 60-240 soldiers (average 180) and begin every week, except the 2 weeks prior to Christmas, 12 basic training cycles will be studies, giving an approximate total study base of 2,400 soldiers in 1 year. this has been coordinated with the S-3 (plans) of the Training Brigade.

Each participant will fill our a preformatted questionnaire which will identify each volunteer by name, age, sex and provide a brief history of areas where the participant has lived prior to basic training and the number of years he has lived in each area. This will enable the investigators to provide a C. immitis exposure index which will categorize each soldier as having a low, medium or high index of exposure. In a large group of people with an infinite degree of exposure this will provide relevant criteria to judge each participant's risk of prior exposure. This questionnaire will also be used to chart sensitivities and other relevant information. These will be filled in by the soldier and returned to the investigators and kept on file.

Based on the information received in this questionnaire, each participant will be assigned to a group with a low, medium, or high exposure to C. immitis. This grouping will be based on the historical data given by the patient concerning where he lived and amount of time spent in each state. The states have been divided into 3 groups and given a statistical score based on the expected rate of exposure to C. immitis based on epidemiologic studies of the regions with endemic C. immitis.

Each state is assigned a value:

a. 2 for high possibility of exposure to C. immitis
   (1) California
   (2) Arizona
   (3) New Mexico
b. 1 for moderate possibility of exposure to C. immitis
   (1) Texas
   (2) Utah
   (3) Nevada
c. 0 for low probability of exposure to C. immitis; this includes all other states.

Each participant is assigned a sum product of (State's assigned value) X(number of years lived in the state). The sum value is used to determine the life exposure index.

a. Low: 1-10
b. Moderate: 11-25
c. High: 26+

The life exposure index will then be correlated with the statistical rate of skin test positivity among our tested population.

Each participant will be skin tested to spherulin. 0.1ml of antigen will be injected intradermally after cleaning the area with 70% alcohol. Patients will be observed for 20 minutes after the test placement to record any positive immediate reactions. The reaction size will then be measured at approximately 48-72 hours after placement. Induration of 5mm or greater will be considered a positive reaction. Those who react to this first test, indicating previous sensitivity, will be included in the study for statistical purposes only. They will not be further tested. Tetanus will be used as a control antigen to ensure the patient is not anergic. The identity of those soldiers who are skin test negative to both tetanus and spherulin will be recorded for appropriate follow-up; it is estimated that as many as 40% of patients will not react to either spherulin or to tetanus.

These same soldiers (only those who did not react to spherulin on the first testing will be retested with spherulin within 1 week of graduation from basic training, using the same technique as listed above. The results will be tabulated for statistical analysis. We will ascertain the location of AIT training for all participants who remain skin test negative and if they remain in El Paso, they will be re-enrolled in an extended study and followed with repeat skin testing at the end of their 7 weeks of Advanced Individual Training (AIT), giving a total study time of 15 weeks. Also during the repeat testing, those subjects listed above who did not initially react to either tetanus or to spherulin will further receive an anergy test utilizing a battery of injections to test for skin test reactivity to tetanus, mumps, monilia and trichophyton. Those who do not react to any of these antigens will be considered anergic and will be consulted to the Allergy Clinic for any further workup required. We estimate less than 5 percent of our subjects will fall into this classification. The results of testing on any subject who meets this definition of anergy will not be included in the data base for this study.

AMENDMENT:
Each participant will be skin tested to spherulin. 0.1ml of antigen will be injected intradermally after cleaning the area with 70% alcohol. Patients will be observed for 20 minutes after the test placement to record any positive immediate reactions. The reaction size will then be measured at 24, 48 and 72 hours after placement. Induration of 5mm or greater will be considered a positive reaction. Those who react to this first test, indicating previous sensitivity will be included in the study for statistical purpose only. They will not be further tested with spherulin. Those who are skin test positive at 24 hours, but negative at 48 hours will be considered to be negative for the purposes of this study, and will be retested at the end of basic; in addition, they may have blood drawn for lymphoblast activity studies, in order to look at the possibility of false positive reactions in this group. Blood will also be drawn from representative soldiers who are skin test positive at 48 hours and who are skin test negative in order to validate and standardize the lymphoblast activity assay.

Progress: This protocol in on hold due to principal investigator participating in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/03** **STATUS: Ongoing**

TITLE: Malignancy Associated Changes in Peripheral Blood Smears

START DATE: Oct 89 **ESTIMATED COMPLETION DATE: Jun 90**

PRINCIPAL INVESTIGATOR: MAJ Robert B. Ellis

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CPT Bryan L. Martin, MC; MAJ I.L. Levey, MC

KEY WORDS: Cancer; blood cells

Study Objective: Analyze leukocytes from patients with non-hematologic cancer searching for patterns of cellular structure identifiable with the light microscope and indicative of underlying malignancy.

Technical Approach: Each individual will fill out a basic data sheet listing past medical history, past surgical history, past and present medications, and allergies. A known diagnosis of malignancy will be noted with histologic type and clinical stage if possible.

Three smears will be obtained from capillary blood of each patient along with 7cc of blood collected from the antecubital vein form which 3 smears will be made. The cytomorphological features described by Johnston et al. were noted in smears from earlobe blood and finger tip blood. To confirm their findings and determine if these features can also be found in the antecubital vein blood, both sources will be collected form patients with known malignancy. If early results indicate there is a good correlation between antecubital vein blood and fingerstick or ear lobe capillary blood, then only venous antecubital blood will be used, as this is the method of routine collection and judged less painful than fingertip collection.

Smears will be stained and examined as follows: blood will be collected four hours after meals, preferable in the morning to control possible variables in a similar method as Johnston et al. There should be nor surgery or transfusion of blood 2 months prior to the test. Fingertip and ear lobe blood will be obtained by scrubbing the area with 70% alcohol which is allowed to dry. Blood will be expressed with lancet and small drop placed on a slide. This smear will be prepared by either mechanical smear maker or manual "spreader slide" technique. The slides will be allowed to air dry for 5-10 minutes and fixed with anhydrous acetone free methanol for 30 minutes.

Smears will be stained with a modified Wright-Giemsa stain as per Johnston et al: Undiluted Wright's for 3 minutes, then Wright's diluted with equal amount of distilled water for 3 minutes. the slide will then be rinsed with water and stained with 1:10 diluted Giemsa for 13 minutes followed by water rinse and air dry.

The smears will be examined with the 100x oil immersion objective of a Zeiss photomicroscope III. A standard manual differential count will be performed on each specimen and representative photomicrographs will be taken. The leukocytes will be examined for two hematologic parameters: (1) the polymorphonuclear leukocytes will be inspected for the presence of excrescences, which are thread-like, thin, non-pedunculated projections from the nucleus, and the percent with excrescences will be calculated, (2) the cytoplasm of large mononuclear cells will be examined for the presence of small inclusion bodies surrounded by lightly stained areas or halos. One hundred mononuclear cells will be examined to estimate the percent haloed bodies.

Progress: This protocol is on hold due to principal investigator participating in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/30 STATUS: Completed

TITLE: Impact of Serum Iron from the Routine Multiphasic Biochemical Panel in the Detection of Iron Overload States

START DATE: Apr 89 ESTIMATED COMPLETION DATE: Nov 89

PRINCIPAL INVESTIGATOR: CPT Lawrence Lepler

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Jesus A. Hernandez, CPT, MC; Robert M. Miller, MAJ, MC; Edward L. Burkhalter, COL, MC

KEY WORDS: Serum iron, Screening test

Study Objective: Evaluating the yield in detecting iron overload states by prospectively evaluating chem-20 panels over a period of 6 months.

Technical Approach: All patients with abnormally elevated serum iron levels on chem-20 panels ordered at WBAMC during a 6 month period will be identified. Those individuals older than 21 years old will be invited to participate in the study. After a preliminary discussion to evaluate for the possibility of recent or repeated blood transfusions, supplemental iron therapy or known hematologic disease, the chem-20 will be repeated and at that time formal determinations of serum iron, transferrin saturation and serum ferritin will be requested. Those patients with normal studies will receive no further evaluation. However, if these test results are abnormal (elevated serum ferritin and/or transferrin saturation greater or equal than 60%) a formal interview and physical examination will be obtained to assess for hematologic or liver disease. complete blood count, prothrombin time and partial thromboplastin time will be obtained at that time. Those patients with platelet count greater or equal than 100,000 and prothrombin time not prolonged more than 2 seconds percutaneously or by laparoscopic guidance. Liver tissue will be submitted for routine histology, iron staining and quantitative iron measurement. The diagnosis of homozygous genetic hemochromatosis will be made by determination of the hepatic iron index. If genetic hemochromatosis is diagnosed, the subjects will be offered treatment with weekly phlebotomies of approximately 500cc of blood with the goal of achieving iron depletion (ferritin less than 20 mg/dl). All diagnostic and therapeutic maneuvers described in this protocol are in accordance with our routine management of patients with suspected iron overload.

Progress: Serum Iron as measured by Chem-20 was abnormally high in 260 of 3814 subjects (7%). To date 44 of the 260 with abnormal values (17%) have returned to have follow-up studies. In this group, the mean difference between simultaneously drawn Chem-20 iron and formal serum iron was 9 mg/dl (range 0-23 mg/dl). The serum iron on the formal study was less than the Chem-20 iron in 39 out of 44 measurements (88.6%). Of the 44 subjects evaluated with formal iron studies, 31 (29.5%) have abnormal values. Six (13.6%) have a transferrin saturation greater than 60% and will be considered for more definitive evaluation for an iron overload state. We conclude that evaluation of patients with an abnormal serum iron on Chem-20 may uncover a significant number of patients with iron overload.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 84/35** **STATUS: Ongoing**

TITLE: Adjuvant Chemotherapy with 5-FU, Adriamycin and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma (SWOG 7804) (Monitor: LTC L. Sanders)

START DATE: Mar 78 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Adenocarcinoma, Stomach, Adjuvant chemotherapy vs surgery

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Study Objective: To determine the efficacy of adjuvant chemotherapy with 5-Fluorouracil, Adriamycin and Mitomycin-C (FAM) on the disease-free interval and survival of patients with TNM stage-groups IB, IC, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no subjects entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 85/07 **STATUS:** Completed

TITLE: Treatment of Limited Non-Small Cell Lung Ca Radiation vs Radiation & Chemotherapy (SWOG 8300) (Monitor: LTC L. Sanders)

START DATE: Jul 84 **ESTIMATED COMPLETION DATE:** 1990

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Lung Carcinoma

Study Objective: To compare combination chemotherapy (FOMi/CAP: 5-Fluorouracil, Vincristine and Mitomycin-C alternating with Cyclophosphamide, Adriamycin and Cis-platinum) plus radiotherapy to radiotherapy alone for patients with limited, non-small *cell lung cancer (NSCLC) in a randomized study with stratification for known important prognostic factors with regard to response rate, response duration and survival duration. To determine the toxicity of radiotherapy plus FOMI/CAP relative to radiotherapy alone for patients with limited NSCLC. To evaluate the responsiveness of smaller tumor burdens to FOMI/CAP (i.e., less than metastatic disease). To determine the pattern of relapsing disease in each treatment arm and in subgroups of patients determined by histology and response to FOMI/CAP. To determine if prophylactic brain irradiation will decrease the chances for brain metastases and influence toxicity of survival.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no subjects entered into this study at WBAMC. This study was completed by SWOG.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 85/10** **STATUS: Completed**

TITLE: Evaluation of Tamoxifen in Unresectable and Refractory Meningioma (SWOG 8415) (Monitor: LTC L. Sanders).

START DATE: Jul 84 **ESTIMATED COMPLETION DATE: 1990**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Meningioma

Study Objective: To determine the antitumor activity of Tamoxifen in meningiomas not amenable to surgery or radiotherapy. To estimate the response rate and response duration experienced by these patients.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no subjects entered into this study at WBAMC. This study was completed by SWOG.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/32** **STATUS: Completed**

TITLE: SWOG 8313 Multiple Drug Adjuvant Chemotherapy for Patients with ER Negative Carcinoma of the Breast (Monitor: LTC L. Sanders)

START DATE: Apr 84 **ESTIMATED COMPLETION DATE: Jun 90**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Breast carcinoma

Study Objective: **To compare the quality of life of patients with operable breast cancer randomized to receive one year of CMFVP or a short intensive regimen of FAC-M x 4 courses. To compare a multiple item questionnaire to a single item questionnaire for assessing quality of life.**

Technical Approach: **The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.**

Progress: **There have been no subjects entered into this study at WBAMC. This study was closed on 15 Jun 90 by SWOG.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/40** **STATUS: Completed**

TITLE: SWOG 8590 Effect of combining chemotherapy with Surgery and Radiotherapy for Resectable Squamous Cell Carcinoma of Head and Neck (Monitor: LTC L. Sanders)

START DATE: Feb 85 **ESTIMATED COMPLETION DATE: Jan 90**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Squamous Cell Carcinoma

Study Objective: Case identification and data collection.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC. The study was completed by SWOG.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/41** **STATUS: Ongoing**

TITLE: SWOG 8600 Randomized Investigation of High Dose vs Standard Dose Cytosine Arabinoside with Daunorubicin in Patients with Acute Nonlymphocyte Leukemia (Monitor: LTC L. Sanders)

START DATE: Nov 86 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Nonlymphocyte leukemia

Study Objective: To compare, among patients with acute nonlymphocytic leukemia, the rate of complete remission produced by induction regimens of either standard dose cytosine arabinoside and daunorubicin or high dose cytosine arabinoside and daunorubicin. To compare the duration of complete remission and of disease-free survival among patients who each receive one of three combinations of induction and consolidation regimens: Standard dose cytosine arabinoside and daunorubicin for both induction and consolidation. Standard dose cytosine arabinoside and daunorubicin for induction followed by high dose cytosine arabinoside and daunorubicin for consolidation. High dose cytosine arabinoside and daunorubicin for both induction and consolidation.

To determine the comparative toxicities of these three programs of induction and consolidation.

To determine the feasibility of implementing a predetermined approach to supportive care within a multi-institutional cooperative group setting for patients receiving intensive chemotherapy for acute nonlymphocytic leukemia.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/47** **STATUS: Ongoing**

TITLE: SWOG 8598 Prospective Trial for Localized Cancer of the Esophagus (Monitor: LTC L. Sanders)

START DATE: Oct 86 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: *Cancer, esophagus*

Study Objective: Determine the role of chemotherapy for a potentially curable subset of patients with squamous cell cancer of the esophagus. Specifically to determine if the combination of chemotherapy and radiation will add to the overall survival and cure of patients treated with the combination when compared to patients treated by radiation alone. Determine if the patterns of recurrence for patients treated with the combination of chemotherapy and radiation differs from those patients treated with radiation alone.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/48** **STATUS: Completed**

TITLE: SWOG 8691 A Randomized Comparison of Deoxycoformycin vs Alpha Interferon in Previously Treated Patients with Hairy Cell Leukemia (Monitor: LTC L. Sanders)

START DATE: Dec 86 **ESTIMATED COMPLETION DATE: Oct 89**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Leukemia

Study Objective: Compare deoxycoformycin and alpha-interferon with respect to frequency of response, time to response, and duration of relapse-free survival among unsplenectomized patients with hairy cell leukemia.

Compare deoxycoformycin and alpha-interferon with respect to improvement in specific patient characteristics including hematologic parameters, size of the spleen, performance status, frequency of documented infections, and number of red blood cell and platelet transfusions.

Estimate the rate of response for each treatment when used among patients who have failed to respond to or had unresolvable toxicity from the other treatment.

Determine the impact of a complete versus a partial remission on remission duration and survival.

Compare toxicities of administration of interferon versus deoxycoformycin to patients with hairy cell leukemia.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC. The study was completed by SWOG.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/74** **STATUS: Completed**

TITLE: SWOG 8693 Adjuvant Therapy of Primary Osteosarcoma: A Phase III Randomized Intergroup Study (Monitor: LTC L. Sanders)

START DATE: Mar 87 **ESTIMATED COMPLETION DATE: Jun 90**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Osteosarcoma

Study Objective: Determine whether the intensity of adjuvant chemotherapy affects its success in terms of local recurrence, disease-free survival and overall survival in patients who have primary osteosarcoma of the extremities and who are randomized to either surgery followed by adjuvant chemotherapy with three drugs or surgery followed by adjuvant chemotherapy with six drugs. Determine the influence of clinical prognostic variables on disease outcome. Determine the influence of histopathology on disease outcome. Determine the influence of clinical prognostic variables on disease-free survival and survival after resection of pulmonary metastases in patients who relapse after being treated as above.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC. The study was completed by SWOG.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/75** **STATUS: Ongoing**

TITLE: SWOG 8694 A Comparison of Pentostatin (NSC-218321) and Alpha-Interferon (NSC-377523) in Splenectomized Patients with Active Hairy Cell Leukemia (Monitor: LTC L. Sanders)

START DATE: Feb 87 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Hairy Cell Leukemia

Study Objective: To compare the frequency of response between pentostatin and a-IFN treatment in patients with hairy cell leukemia who following splenectomy manifest active or progressive disease. To compare time to response between these two treatments. To compare the response duration of these two treatments.

To determine whether pentostatin salvages nonresponders to a-IFN treatment and whether a-IFN salvages nonresponders to pentostatin treatment. To compare the toxicity of the two treatments.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 87/77** **STATUS: Ongoing**

TITLE: SWOG 8792 Phase III Study of Alfa-nl (Wellferon) as Adjuvant Treatment for Resectable Renal Cell Carcinoma (Monitor: LTC L. Sanders)

START DATE: Jun 87 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Renal Cell Carcinoma

Study Objective: To assess in a controlled fashion the effectiveness of interferon alfa-nl (Wellferon) as a surgical adjuvant in patients with renal cell carcinoma. Study endpoints will consist of patient survival and time to recurrence.

Technical Approach: The details are lengthy and specified in the SWOG protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/26** **STATUS: Terminated**

TITLE: A Randomized, Double-Blind, Placebo-Controlled Dose Range Evaluation of Oral GR 38032F in the Prevention of Nausea and Vomiting Associated with Non-Cisplatin Chemotherapy

START DATE: Feb 89 **ESTIMATED COMPLETION DATE: 1989**

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Irwin L. Levey, MC; MAJ Ruben D. Sierra, MC; LTC Marcia L. Carle, AN; Karlyn K. Pearl, RN; CPT Ricke J. Weickum, MS

KEY WORDS: Nausea and vomiting

Study Objective: To determine the antiemetic efficacy of three different doses of oral GR 38032F in patients receiving a cyclophosphamide based regimen of chemotherapy.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in Department of Clinical Investigation and are available upon request.

Progress: The sponsoring company, Glaxo, Inc., has completed patient accrual and has closed this study. There have been no eligible patients to enroll in this study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 89/29 **STATUS:** Ongoing

TITLE: SWOG 8624: A Phase III Randomized Trial of Combination Therapy for Multiple Myeloma. Comparison of (1) VMCP/VBAP to VAD or VMCPP/VBAPP for Induction; (2) Alpha-2b Interferon or No Therapy for Maintenance; and (3) Alpha-2b Interferon + Dexamethasone for Incomplete or Non-Responders

START DATE: 1986 **ESTIMATED COMPLETION DATE:** Indefinite

PRINCIPAL INVESTIGATOR: COL Ray O. Lundy

DEPARTMENT: Med **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Multiple myeloma, Chemotherapy, Interferon

Study Objective: To compare the effectiveness of three chemotherapy induction schedules for the induction of remission in previously untreated patients with multiple myeloma. The three schedules are:

1) VMCP/VBAP;
2) VAD (a four day infusion schedule);
3) VMCPP/VBAPP,

To compare the value of Intron-A (alpha-2b interferon) maintenance versus no maintenance for patients proven to achieve remission (at least 75% tumor regression after induction).

For patients who achieve only improvement (50-74% tumor regression) or are non-responders with chemotherapy induction, to determine whether dexamethasone plus alpha-2b Interferon (INTRON-A) will increase the remission rate and survival duration.

D. To determine prognostic applicability to multiple myeloma of serum beta-2 microglobulin level, plasma cell LI%, using the BU-1 monoclonal antibody, bone marrow plasma cell morphologic characteristics, and histochemical staining for acid phosphatase and beta-glucuronidasecontent.

E. Nationwide, the study group desires to accrue 450 evaluable patients in the induction phase of approximately 3.3 years, and expects to have 130 patients in the maintenance phase, and 230 patients in the dexamethasone plus interferon trial. We expect no more than 20 patients will be enrolled at WBAMC.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study at WBAMC.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/04** **STATUS: Completed**

TITLE: Salivary Immunoreactive Human Epidermal Growth Factor (IR-hEGF) and Bicarbonate in Patients with Peptic Ulcers

START DATE: Feb 89 **ESTIMATED COMPLETION DATE: Feb 90**

PRINCIPAL INVESTIGATOR: MAJ David Maccini

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC Allan L. Parker, MC

KEY WORDS: Epidermal growth factor; peptic ulcers

Study Objective: To determine if there exists a significant difference between the levels of salivary and serum *Ir-hEGF and bicarbonate found in patients with documented peptic ulcer disease and a control group* without peptic ulcers.

Technical Approach: Serum and salivary samples will be collected from patients prior to their undergoing esophagogastroduodenoscopy (EGD). Patients who are found to have active peptic ulcers will serve as the study group. Patients with no ulcers by EGD or past history of PUD will serve as the control group. All patients (male and female) over the age of eighteen will be eligible to participate in the study. Levels of IR-hEGF will be tested in both saliva and serum, while HCO3 will be measured in saliva, of study patients and controls.

Salivary samples will be collected by spit technique. Approximately 3.0cc of saliva will be obtained by having the patient spit into a sterile container. The samples will be frozen and stored until the assay is performed in the Department of Clinical Investigations. Using a one-way analysis of variance, the salivary and serum IR-hEGF activity in each group will be compared. A p value of <0.05 will be considered to be statistically significant. Twenty patients will be studies in each group. Statistical support will be obtained from the Department of Clinical Investigations following collection of all the data.

Progress: Epidermal growth factor inhibits gastric acid secretion and has a cytoprotective effect on the upper gastrointestinal tract. This study was undertaken to determine whether patients *with endoscopically proven* active peptic ulcer disease have a salivary deficiency of human epidermal growth factor (hEGF) when compared *to patients with a normal esophagogastroduodenoscopy* (EGD). Saliva was collected from fasting subjects prior to EGD. The levels of EGF were measured by radioimmunoassay. Statistical evaluation was performed by analysis of variant followed by Student's t-test. The concentrations of the peptide were lower in patients with active peptic ulcer disease (3.1 ± .54ng/ml.mean ± SE. n= 25) compared with normal subjects (4.9 ± .56ng/ml. n=58. $p<0.03$). No significant differences in salivary hEGF were noted between patients with normal EGD and patients with gastritis 3.85 ± .86ng/ml, n=13), esophagitis (4.5 ± 1.3ng/ml, n=7), or Barrett's esophagus (5.3 ± 1.5ng/ml, n=6). There were no differences in the salivary levels of hEGF between males and females, or between smokers and nonsmokers. There was no correlation of hEGF levels with age. The pathophysiologic significance of this finding is uncertain. Lower salivary hEGF may reduce one of the *defensive mechanism responsible for protecting* the gastroduodenal mucosa from injury by physicochemical agents, thus contributing to ulcer development.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/71 STATUS: Terminated

TITLE: Iron Levels in Hair of Patients With Anemia of Chronic Inflammatory Disease, Iron Deficiency Anemia and Normals

START DATE: Sep 89 ESTIMATED COMPLETION DATE: Aug 90

PRINCIPAL INVESTIGATOR: MAJ David Maccini

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Allan L. Parker, MC; MAJ James M. Baunchalk, MC

KEY WORDS: Iron, hair

Study Objective: This study is to determine if measurement of iron levels in the hair of patients with anemia and chronic inflammatory disease can be used to exclude iron deficiency as a cause of their anemia.

Technical Approach: Twenty patients will be studied in each of three groups. Group one will be patients with anemia and chronic inflammatory disease. These patients will be recruited from the Rheumatology Clinic. Group two will be patients with iron deficiency anemia and no evidence of any inflammatory disease. These patients will be selected from patients evaluated by the Gastroenterology, Hematology and Gynecology Services for iron deficiency anemia and also from screening results of complete blood counts (CBC) performed in the laboratory. Group three will consist of normal volunteers who have no evidence of anemia or chronic inflammatory condition. These patients will consist of hospital staff and patients seen in the GI Clinic.

After obtaining informed consent, 14 milliliters of blood will be drawn for the following studies: CBC, reticulocyte count, sedimentation rate, serum iron and ferritin levels. Additionally, three scalp hairs will be plucked and submitted for measurement of iron content. Levels of iron in hair and blood will be compared between the three groups.

Progress: This study was terminated due to lack of interest and the associate investigator PCS'd.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/73** **STATUS: Ongoing**

TITLE: Serum Gastrin and Epidermal Growth Factor Levels in Patients with Adenomatous Polyps and Carcinoma of the Colon

START DATE: Sep 89 **ESTIMATED COMPLETION DATE: Aug 91**

PRINCIPAL INVESTIGATOR: MAJ David M. Maccini

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: COL Edward L. Burkhalter, MC

KEY WORDS: Epidermal growth factor; colon cancer; adenomatous

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Study Objective: **The purpose of this study is to determine if there is a significant elevation of the serum levels of gastrin and EGF in patients with colon carcinoma and colonic adenomatous polyps when compared to a control population (patients with a normal colonoscopy).**

Technical Approach: **Measurement of serum gastrin and epidermal growth factor will be performed in three groups of patients. Group one will be patients who are found to have polyps (adenomatous or hyperplastic) at colonoscopy. Group two will consist of patients who are found to have colorectal carcinoma at colonoscopy or surgery. And group three will include patients who have undergone colonoscopy and had a normal examination (no prior history of colonic polyps or cancer). patients will be between the ages of 18 and 99 (male and female) and have no history of other malignancies or peptic ulcer disease. It is expected that most patients will be recruited prior to or after undergoing colonoscopy in the GI Clinic at WBAMC. Indications for colonoscopy will be independent of this study. Twenty patients will be included in each group.**

Patients will have ten milliliters of blood drawn at the time their IV is being started for colonoscopy. **This will end the patient's participation in the study. Findings at colonoscopy will be noted on the usual endoscopic record used by the clinic (WBAMC form 524). Blood will be take to Clinical Investigation where it will be centrifuged and the serum frozen. Measurement of epidermal growth factor levels will be performed by RIA by an assay previously set up in Clinical Investigations. Gastrin levels will be processed through the Nuclear Medicine Service. Statistical analysis of the data in each group will be performed and compared. A p value <0.05 will be considered statistically significant.**

Progress: **Samples have been obtained from 45 patients with normal colonoscopies; 28 patients with polyps, and 11 patients with colonic carcinoma. Continuing to collect samples from patients with newly diagnosed cancer of the colon as they become known. Major factor delaying completion of this study is the set up of assay by Clinical Investigation.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/46 STATUS: Ongoing

TITLE: Rate of Spherulin Skin Test Conversion Among Basic Trainees Exposed to Desert Training at Fort Bliss, Texas

START DATE: Sep 88 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: MAJ Bryan Martin

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Robert B. Ellis, MC

KEY WORDS: Spherulin, Skin test to C. immitis.

Study Objective: To establish the rate of spherulin skin test conversion among active duty basic trainees who are exposed to desert training at Fort Bliss, Texas. To attempt to define the morbidity associated with Coccidioides immitis in terms of time lost from basic training due to acute Coccidioidal infection.

Technical Approach: Basic trainees will be invited to participate in the study. Study participants will be briefed by the principal investigators about the study and given an opportunity to volunteer for the program. One basic training cycle will be tested in each month to determine if there is a seasonal peak to exposure. As basic training cycles are 8 weeks in length and encompass between 60-240 soldiers (average 180) and begin every week, except the 2 weeks prior to Christmas, 12 basic training cycles will be studies, giving an approximate total study base of 2,400 soldiers in 1 year. this has been coordinated with the S-3 (plans) of the Training Brigade.

Each participant will fill our a preformatted questionnaire which will identify each volunteer by name, age, sex and provide a brief history of areas where the participant has lived prior to basic training and the number of years he has lived in each area. This will enable the investigators to provide a C. immitis exposure index which will categorize each soldier as having a low, medium or high index of exposure. In a large group of people with an infinite degree of exposure this will provide relevant criteria to judge each participant's risk of prior exposure. This questionnaire will also be used to chart sensitivities and other relevant information. These will be filled in by the soldier and returned to the investigators and kept on file.

Based on the information received in this questionnaire, each participant will be assigned to a group with a low, medium, or high exposure to C. immitis. This grouping will be based on the historical data given by the patient concerning where he lived and amount of time spent in each state. The states have been divided into 3 groups and given a statistical score based on the expected rate of exposure to C. immitis based on epidemiologic studies of the regions with endemic C. immitis.

Each state is assigned a value:

a. 2 for high possibility of exposure to C. immitis
   (1) California
   (2) Arizona
   (3) New Mexico

b. 1 for moderate possibility of exposure to C. immitis
   (1) Texas
   (2) Utah
   (3) Nevada

c. 0 for low probability of exposure to C. immitis; this includes all other states.

Each participant is assigned a sum product of (State's assigned value) X(number of years lived in the state). The sum value is used to determine the life exposure index.

a. Low: 1-10
b. Moderate: 11-25
c. High: 26+

The life exposure index will then be correlated with the statistical rate of skin test positivity among our tested population.

Each participant will be skin tested to spherulin. 0.1ml of antigen will be injected intradermally after cleaning the area with 70% alcohol. Patients will be observed for 20 minutes after the test placement to record any positive immediate reactions. The reaction size will then be measured at approximately 48-72 hours after placement. Induration of 5mm or greater will be considered a positive reaction. Those who react to this first test, indicating previous sensitivity, will be included in the study for statistical purposes only. They will not be further tested. Tetanus will be used as a control antigen to ensure the patient is not anergic. The identity of those soldiers who are skin test negative to both tetanus and spherulin will be recorded for appropriate follow-up; it is estimated that as many as 40% of patients will not react to either spherulin or to tetanus.

These same soldiers (only those who did not react to spherulin on the first testing will be retested with spherulin within 1 week of graduation from basic training, using the same technique as listed above. The results will be tabulated for statistical analysis. We will ascertain the location of AIT training for all participants who remain skin test negative and if they remain in El Paso, they will be re-enrolled in an extended study and followed with repeat skin testing at the end of their 7 weeks of Advanced Individual Training (AIT), giving a total study time of 15 weeks. Also during the repeat testing, those subjects listed above who did not initially react to either tetanus or to spherulin will further receive an anergy test utilizing a battery of injections to test for skin test reactivity to tetanus, mumps, monilia and trichophyton. Those who do not react to any of these antigens will be considered anergic and will be consulted to the Allergy Clinic for any further workup required. We estimate less than 5 percent of our subjects will fall into this classification. The results of testing on any subject who meets this definition of anergy will not be included in the data base for this study.

AMENDMENT:
Each participant will be skin tested to spherulin. 0.1ml of antigen will be injected intradermally after cleaning the area with 70% alcohol. Patients will be observed for 20 minutes after the test placement to record any positive immediate reactions. The reaction size will then be measured at 24, 48 and 72 hours after placement. Induration of 5mm or greater will be considered a positive reaction. Those who react to this first test, indicating previous sensitivity will be included in the study for statistical purpose only. They will not be further tested with spherulin. Those who are skin test positive at 24 hours, but negative at 48 hours will be considered to be negative for the purposes of this study, and will be retested at the end of basic; in addition, they may have blood drawn for lymphoblast activity studies, in order to look at the possibility of false positive reactions in this group. Blood will also be drawn from representative soldiers who are skin test positive at 48 hours and who are skin test negative in order to validate and standardize the lymphoblast activity assay.

Progress: This project is on hold due to principal investigator participation in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/03 STATUS: Ongoing

TITLE: Malignancy Associated Changes in Peripheral Blood Smears

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: MAJ Bryan Martin

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Robert B. Ellis, MC; MAJ I.L. Levey, MC

KEY WORDS: Cancer; blood cells

Study Objective: Analyze leukocytes from patients with non-hematologic cancer searching for patterns of cellular structure identifiable with the light microscope and indicative of underlying malignancy.

Technical Approach: Each individual will fill out a basic data sheet listing past medical history, past surgical history, past and present medications, and allergies. A known diagnosis of malignancy will be noted with histologic type and clinical stage if possible.

Three smears will be obtained from capillary blood of each patient along with 7cc of blood collected from the antecubital vein form which 3 smears will be made. The cytomorphological features described by Johnston et al. were noted in smears from earlobe blood and finger tip blood. To confirm their findings and determine if these features can also be found in the antecubital vein blood, both sources will be collected form patients with known malignancy. If early results indicate there is a good correlation between antecubital vein blood and fingerstick or ear lobe capillary blood, then only venous antecubital blood will be used, as this is the method of routine collection and judged less painful than fingertip collection.

Smears will be stained and examined as follows: blood will be collected four hours after meals, preferable in the morning to control possible variables in a similar method as Johnston et al. There should be nor surgery or transfusion of blood 2 months prior to the test. Fingertip and ear lobe blood will be obtained by scrubbing the area with 70% alcohol which is allowed to dry. Blood will be expressed with lancet and small drop placed on a slide. This smear will be prepared by either mechanical smear maker or manual "spreader slide" technique. The slides will be allowed to air dry for 5-10 minutes and fixed with anhydrous acetone free methanol for 30 minutes.

Smears will be stained with a modified Wright-Giemsa stain as per Johnston et al: Undiluted Wright's for 3 minutes, then Wright's diluted with equal amount of distilled water for 3 minutes. the slide will then be rinsed with water and stained with 1:10 diluted Giemsa for 13 minutes followed by water rinse and air dry.

The smears will be examined with the 100x oil immersion objective of a Zeiss photomicroscope III. A standard manual differential count will be performed on each specimen and representative photomicrographs will be taken. The leukocytes will be examined for two hematologic parameters: (1) the polymorphonuclear leukocytes will be inspected for the presence of excrescences, which are thread-like, thin, non-pedunculated projections from the nucleus, and the percent with excrescences will be calculated, (2) the cytoplasm of large mononuclear cells will be examined for the presence of small inclusion bodies surrounded by lightly stained areas or halos. One hundred mononuclear cells will be examined to estimate the percent haloed bodies.

Progress: This project is on hold due to principal investigator participating in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/77 STATUS: Completed

TITLE: In Vitro Qualitative ELISA Testing as a Screening Tool for Significant Allergy

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Jan 90

PRINCIPAL INVESTIGATOR: LTC David L. Michaels

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Allergy diagnosis, In Vitro test

Study Objective: Evaluate the sensitivity and specificity of the new flipSCREEN™ in vitro diagnostic test for allergy.

Technical Approach: Forty out-patients referred for allergy evaluation to WBAMC Allergy Clinic will be recruited for the study. These patients will have a medical history and physical examination compatible with a diagnosis of probable allergic rhinoconjunctivitis.

After obtaining informed consent, a serum sample will be obtained (20cc), then routine skin prick tests with allergens normally employed at WBAMC Allergy Clinic will be performed. Skin tests will include, but not be limited to, all antigens present on the flipSCREEN test sticks as listed:

a. Perennial allergens: cat, dog, mite, alternaria, cladosporium, penicillium, and mucor.

b. Regional pollens: June grass, Bermuda, short ragweed, Russian thistle, English plantain, cottonwood, and ash.

Prick skin tests will be read at 15 minutes and the diameter in millimeters of measured wheal and erythema will be recorded. further prick testing will be subsequently performed at another site using serial 1:5 dilutions of the antigens showing 3mm or greater wheal on initial testing. The highest antigen dilution showing a positive test will be recorded. All antigens for skin testing will be those available through the Central Allergy Laboratory at Walter Reed Army Medical Center (manufacturer is Hollister-Stier). These antigens may differ somewhat from those available on the flipSCREEN assay, but it is not possible to perform skin test and in vitro test with the same antigen lot and batch from the same manufacturer. This also would not be the case in a clinical practice situation where in vitro test might be done at a site distant from the allergist's office.

A serum total IgE (PRST) will also be performed on the blood sample collected from each patient. Additional serum will be saved for possible subsequent analysis for IgG_4 antibody or for specific IgE antibody as measured by the quantitative ELISA technique. These results would be the subject of a separate study.

The results of skin prick test titration and flipSCREEN qualitative assay will be compared with each individual antigen. Sensitivity and specificity of the in vitro assay will be calculated:

$$\text{Sensitivity} = \frac{\text{true positive tests}}{\text{true positives + false negatives}} \times 100$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{true negative + false positives}} \times 100$$

A "true positive" is a patient with positive flipSCREEN and positive prick skin test. A "false negative" is a patient with negative flipSCREEN and a positive prick skin test. A "true negative" is a patient with both negative flipSCREEN and skin test, while a "false positive" patient has a negative skin test, but a positive flipSCREEN.

All skin testing is done on patients who have been off antihistamines for a minimum of 5 days. Appropriate positive (histamine) and negative (saline) controls are done to insure reliability of testing.

In addition to determining sensitivity and specificity of the in vitro test, results will be compared with degree of skin test reactivity as measured by skin prick test to dilutions of antigen. The weakest dilution showing skin test positivity will be employed as an expression of skin test reactivity. This compares with other studies which attempt to quantify degree of reactivity based on area of skin whealing and erythema or on an arbitrary scoring system.

No special risks to the patient are associated with this study. The only additional inconveniences are the venipuncture for serum studies and the increased skin test time (approximately 30 minutes) needed to carry out serial dilution prick testing. Following the allergy appointment, the subject's participation is terminated and appropriate medical treatment for allergy is prescribed with whatever follow-up plans as appropriate.

Progress: The sensitivity and specificity of a new in vitro test (flipSCREEN) for the detection of specific IgE antibody were measured in 40 patients referred for allergy evaluation. Prick skin tests using 1:20 w/v antigen were positive if measured wheal diameter was 4mm or greater. Further testing was done with 1:100 and 1:500 antigen concentration. These skin test results were compared with the graded reaction measured by the qualitative ELISA procedure. Eight pollens and 6 perennial allergens were tested in each patient. Thirty-four of the 40 patients had 2 or more positive prick tests; 28 of these patients (82%) had 2 or more positive qualitative ELISA tests. Sensitivity of the ELISA was 66% for pollens and 52% for perennial antigens. Higher ELISA results were seen with pollens and correlated better with the skin prick test titration results. Specificity was 87% for pollens for perennial antigens.

The qualitative ELISA using appropriate local antigens may be useful in screening patients who would benefit from thorough allergy evaluation.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/78 STATUS: Ongoing

TITLE: **Food Sensitivity and Inhalant Allergy: Effect of Immunotherapy**

START DATE: Sep 89 ESTIMATED COMPLETION DATE: Aug 90

PRINCIPAL INVESTIGATOR: LTC David L. Michaels

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Allergy, food sensitivity, immunotherapy

Study Objective: This project will investigate the incidence of allergy to various foods in patients being treated for inhalant allergy. Change in reported food allergy symptoms following inhalant immunotherapy will be investigated to determine whether the food symptoms represent cross reactivity with IgE antibody to inhalant allergens.

Technical Approach: The first phase of this study will employ a questionnaire to evaluate the frequency of adverse reactions to various ingestants including foods, preservatives, food colors, alcohol, and aspirin. This questionnaire will be distributed to all patients currently being treated with immunotherapy at WBAMC Allergy Clinic. Patients who agree to participate in the study will also be queried whether any of the ingestant symptoms have changed following inhalant immunotherapy. responses will be correlated with skin test results, antigens contained in immunotherapy mix, and duration of immunotherapy.

Where possible correlations between food and inhalant allergen are found, repeat skin testing with both antigens will be performed using the skin prick test titration method to measure degree of sensitivity. RAST assays will also be performed to highly reactive foods to determine correlation with skin prick test results. Selected patients may also be asked to participate in double blind food challenges to confirm the relationship of food ingestion to symptoms. A second phase of this study will use information obtained from the questionnaire. New patients being evaluated for inhalant allergy at WBAMC Allergy Clinic will be questioned about possible food sensitivities. Skin prick tests to the most commonly implicated foods will routinely be done in patients having positive skin tests to inhalant allergens. The food skin test results will be compared with the pattern of inhalant skin test reactivity and the presence of symptoms recorded on the history form. Testing of 200 patients in this manner should determine whether a particular positive food skin test in an inhalant sensitive person is of any clinical significance or merely represents antibody cross reactivity.

Progress: Questionnaire responses have been collected and data have been surveyed. No patients have been tested yet for presumed food allergy. Effects of immunotherapy or food allergy symptoms have not been solicited from patients.

DETAIL SUMMARY SHEET

DATE: 1 October 96 **PROTOCOL #: 90/03** **STATUS: Ongoing**

TITLE: Learning and Behavior Disorders in Children Referred for Allergy Evaluation

START DATE: Nov 89 **ESTIMATED COMPLETION DATE: Mar 91**

PRINCIPAL INVESTIGATOR: LTC David L. Michaels

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: A.W. Atkinson, LtC, MC

KEY WORDS: Attention-deficit disorder, Behavior, Allergy

Study Objective: This project will use a questionnaire to assess the frequency and type of learning and/or behavior disorders in children age 5-12 who are referred to the Allergy Clinic for evaluation of presumed allergic respiratory symptoms (rhinitis, asthma).

Technical Approach: Parents of 100 successive children from age 5-12 being referred for allergy evaluation will be asked to complete the Yale Children's Inventory Questionnaire. These will be reviewed and scored by staff of the Developmental Pediatric Service. If significant abnormalities are identified, parents will be contacted and appropriate interventions will be instituted if deemed necessary by the Developmental Pediatrician.

All children with diagnosed allergy will be prescribed customary allergy treatment to include medications, allergen avoidance, and possibly immunotherapy.

One year after the initial evaluation, each child will be recalled for allergy follow-up. The Yale Inventory will be repeated and scores will be compared with those before allergy treatment. Patterns of significant change in specific areas of learning or behavior may indicate beneficial effects from allergy treatment in children with specific problems.

There are no additional risks to subjects who participate in this study. The usual allergy testing and treatment will be carried out as for patients not in the study. The only additional procedure is the completion of the questionnaire.

Progress: Case reports have described children with "allergic irritability syndrome" improving after allergy treatment. The present study employed a partial Yale Children's Inventory Questionnaire consisting of 60 scorable questions. Forty-five consecutive children, age 5-12, referred for allergy evaluation were compared with a group of 435 age matched controls seen for routine school physicals. Higher scores were seen in the group of allergic children, especially those age 5.5 to 8.5, in the categories measuring attention, adaptability, manageability, impulsivity, and behavior. This indicates significant learning and behavior disorders may be more frequent in allergic children. More meaningful data may come from a larger sample which also measures survey results after allergy treatment.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 86/34** **STATUS: Ongoing**

TITLE: The Effects of Verapamil and Diltiazem on Gastric Emptying

START DATE: Dec 87 **ESTIMATED COMPLETION DATE: Jun 91**

PRINCIPAL INVESTIGATOR: MAJ Albert J. Moreno

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC Morakinyo A. Oyewole Toney

KEY WORDS: Gastric Emptying

Study Objective: Calcium channel blockers are currently indicated in the treatment of several medical problems. Data on the effects of calcium channel blockers on gastric emptying currently is sparse, but potentially important. This study is to determine the effects of verapamil and diltiazem on gastric emptying in normal human volunteers.

Technical Approach: Selection of patients: Twenty healthy (10 male, 10 female) nonpregnant volunteers with an age range of 21-40 will be studied. Patients with any underlying medical problem, on any medication, with a known allergy history to verapamil or diltiazem, or with an abnormal gastric emptying study will be excluded from the study. Patients will also need a normal physical examination, vital signs, EKG, and SMA-20 prior to entering the study. A BHCG will be drawn on all female patients.

Radiation doses: Each patient will have three studies. Each stu· consists of 1 mCi Tc-99m SCOI and 250 uCi of In-111 DTPA. The target organs for the Tc-99m SCO' and the In-111 DTPA will be the stomach and colon. The stomach may receive approximately 340 m/rad from Tc-99m SC0L. The distal bowel may receive up to 650 m/rads from the In-111 DTPA. These are acceptable levels of radiation exposure.

Patients presenting to the Gastroenterology Service, WBAMC, will be invited to participate in the study. They will be assigned a number for identification purposes. Each subject will undergo study with each drug. A daily history and physical exam will be accomplished.

Gastric emptying: A modification of the technique prepared by Heading et al. will be used. Both solid and liquid phases will be studied. The solid phase will be a standard meal of beef stew impregnated with 1 mCi of 99mTechnetium labeled sulfur colloid. The liquid phase will be 150cc of water combined with 250 uCi of 111Indium labeled diethylene-triamine-pentaacetic acid 111In-DTPA). The time of ingestion of the meal is defined as the midpoint in the period of ingestion. Initial scanning is done every 15 minutes (60 sec images) for a total of three hours. During scanning the patient will be supine, but at all other times they will be seated in a chair.

Methods: Baseline scan: Day 1. If this is abnormal (40% retention at three hours), the patient will be excluded.

Scan 2: Patients on verapamil for three days or diltiazem for one dose. Last dose of the medication will be 30 minutes prior to scanning. The patient will have nothing by mouth after midnight except for medications. The patients will be randomized to receive verapamil or diltiazem first. There will be a one-week minimum of time off the initial medication prior to starting the second medication. A plasma concentration of the drug will be drawn prior to the gastric emptying study.

Scan 3: The patient will receive the second drug in the same format. The patient will be examined daily by an associate investigator during the investigational period.

Statistical analysis: Student t-test

Medications: Verapamil: Dosage schedule will be 80mg by mouth every six hours. The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. After continuous dosing (every six hours for ten doses) the half life increases to 4.5 to 12.0 hours. Therefore, the drug will be administered for three days prior to testing. The last dose will be 30 minutes prior to testing.

Potential side effects: Cardiovascular: Hypotension - 2.9%, peripheral edema - 1.7%, AV block - 0.8%, bradycardia - 1.1%, CHF or pulmonary edema - 0.9%.

Central nervous system: Dizziness - 3.6%, headache - 1.8%, fatigue - 1.1%.

Gastrointestinal: Constipation - 6.3%, nausea - 1.6%.

Side-effects with less than 0.5% incidence and where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions and spotty menstruation.

Diltiazem: Dosage schedule will be 60mg by mouth 30 minutes prior to the test. The plasma elimination half life is 3.5 hours whether single or multiple administrations are used; therefore, a single dose is sufficient.

Progress: Continued slow acquisition of patient data due to equipment problems and staff shortage. Five subjects have been entered in this study with no withdrawals or adverse reactions to report.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/23** **STATUS: Ongoing**

TITLE: Evaluation of HBV Immunization Using a Series of Two Heptavax and One Recombivax

START DATE: Mar 90 **ESTIMATED COMPLETION DATE: Jun 91**

PRINCIPAL INVESTIGATOR: COL Ana A. Ortiz

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CPT Carl Gibson, MC; Mrs. Karlyn Pearl, R.N.

KEY WORDS: HBV Immunization

Study Objective: To evaluate if completing the immunization process of active duty personnel with Recombivax after they have received their first two doses with Heptavax will increase their hepatitis surface antibody titers to levels similar to those receiving the conventional three doses of Heptavax. *In addition, will like to find out* if their titers are similar a year later.

Technical Approach:

Group A - Control: Fifty patients who have received two doses of Heptavax and are ready to receive the third dose (6 months since their first vaccine, and 5 months post the second vaccine) will be studies. Blood for hepatitis surface antibodies will be obtained at the time of their third immunization, three weeks later, and a year later.

Group B - Study Group: *Fifty patients who had received the second dose of* Heptavax and are ready to receive their third dose (Recombivax) will be studied.

Blood for Hepatitis-S antibodies will be obtained at the time the third vaccine is due, three weeks later, and a year later.

These patients will be receiving Recombivax.

Patients will be selected to participate in the study group as follows. As patients present to receive *either the Heptavax or the* Recombivax, every other one will be asked to participate in the study.

Progress: One hundred patients were enrolled in this study. Blood was obtained previous to the Heptavax or Recombivax and 3-4 weeks post immunization. Hepatitis B titers are pending. Blood will be obtained a year from now to follow the Hepatitis B titers.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/74 STATUS: Ongoing

TITLE: Echocardiographic Standards for Adolescents Based on Tanner Staging

START DATE: Aug 88 ESTIMATED COMPLETION DATE: Jun 91

PRINCIPAL INVESTIGATOR: COL William Pearl

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Dr. Maatinko and Dr. Stafford, Dept of Pediatrics

KEY WORDS: Echocardiography

Study Objective: To establish echocardiographic standard for healthy adolescents based on Tanner staging, which measures biologic age rather than chronologic age. The new standards will allow a more narrow definition of normal.

Technical Approach: We propose to obtain an echocardiogram on consenting patients presenting to the Pediatric and Adolescent Clinic for school or sport physicals, between 10 and 17 years of age. Tanner staging will be assessed by examiners, which is part of the normal physical examination. Complete physical examinations will be performed and subjects with evidence of chronic illness or heart or lung disease will be excluded. Furthermore, a questionnaire is to be completed by each subject which elicits additional information on athletic activities and health. The patient will be sent to the Cardiology Clinic upon completion of the physical examination for an echocardiogram to be performed by a trained technician.

Echocardiographic data will be measured by computer analysis and reviewed by a pediatric cardiologist. Measurements will include the thickness of the right free ventricular wall, interventricular septum, left ventricular free wall, aortic root, left atrium, aortic valve opening, and each of the identifiable portions of the mitral valve motion. From the data collected, mean values and standard deviations will be determined for males and females in each of the five Tanner stages. Additional data to be collected on each subject will include height, weight, race, and body surface area.

Progress: The study is nearing completion. Data has been accumulated on approximately 240 subjects and is currently being analyzed. A few more subjects may be required, depending on the results of the preliminary analysis. Two abstracts have been published, and there have been no complications or complaints.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/12 STATUS: Terminated

TITLE: Use of the Investigational Drug Levamisole on an Emergent Basis for the Treatment of a Patient with Duke's C Adenocarcinoma of the Colon

START DATE: Dec 89 ESTIMATED COMPLETION DATE: Jul 90

PRINCIPAL INVESTIGATOR: MAJ Ruben D. Sierra

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Levamisole

Study Objective: To provide an investigational agent, levamisole (in combination with 5-FU), to physicians for the management of individual patients with Dukes C colon cancer who are not eligible or are unwilling to participate in clinical trials.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: The subject is a 65-year-old male with Astler-Coller C2 adenocarcinoma of the sigmoid colon, resected last November 1989. Because of the poor prognosis for recurrence, the patient was started on adjuvant 5-fluorouracil/levamisole. The levamisole was provided by the National Cancer Institute on a "compassionate" basis. The patient was to receive treatment for 12 months. At the present time, the patient has received 28 weeks of adjuvant chemotherapy without any significant side effects seen.

Further therapy will continue with 5-FU and levamisole as planned. The levamisole will be obtained commercially by the WBAMC pharmacy.

Levamisole, which was recently approved by the Food and Drug Administration, will be available commercially as of 20 Jul 90. Therefore, the National Cancer Institute will no longer provide the drug free of charge.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/18** **STATUS: Terminated**

TITLE: Levamisole Plus 5-FU as an Adjuvant to Surgery for Resectable Adenocarcinoma of the Colon

START DATE: Dec 89 **ESTIMATED COMPLETION DATE: Jul 90**

PRINCIPAL INVESTIGATOR: MAJ Ruben D. Sierra

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: *Levamisole*

Study Objective: To provide an investigational agent, levamisole (in combination with 5-FU), to physicians for the management of individual patients with Dukes C colon cancer who are not eligible or are unwilling to participate in clinical trials.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Levamisole, which was recently approved by the Food and Drug Administration, will be available commercially as of 20 Jul 90. Therefore, the National Cancer Institute will no longer provide the drug free of charge.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/48 STATUS: Terminated

TITLE: Emergency Treatment with Recombinant DNA GM-CSF (rGM-CSF) in Compassionate Circumstances

START DATE: Dec 90 ESTIMATED COMPLETION DATE: Jul 90

PRINCIPAL INVESTIGATOR: MAJ Ruben D. Sierra

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Recombinant DNA GM-CSF (rGM-CSF)

Study Objective: To offer Human rGM-CSF to patients with life threatening neutropenia (generally ANC < 500) due to an underlying disease or a therapeutic maneuver, and to assess the safety and tolerance of rGM-CSF in HIV and oncology/hematology patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: One patient with an Astler Coller C2 adenocarcinoma of the sigmoid colon was entered in this protocol. Because of the poor prognosis for recurrence, the patient was started on adjuvant 5-fluorouracil/levamisole. The levamisole was proved by the National Cancer Institute on a "compassionate" basis. The patient was to receive treatment for 12 months. At the present time, the patient has received 28 weeks of adjuvant chemotherapy without any significant side effects seen. Levamisole was recently approved by the Food and Drug Administration and will be available commercial; therefore, the drug will be obtained commercially by the WBAMC pharmacy and it will not longer be provided free by the National Cancer Institute.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/84 STATUS: Ongoing

TITLE: Induction of Tumor Necrosis Factor Alpha (TNF-alpha) in Human Infection with Coccidioides immitis

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Oct 91

PRINCIPAL INVESTIGATOR: MAJ David C. Slagle

DEPARTMENT: Med FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Matthew J. Dolan, MC, USAF; Rebecca A. Cox, Ph.D.; MAJ J. William Kelly, MC; MAJ Robert A. Zajac, MC, USAF; MAJ Gregory P. Melcher, MC, USAF

KEY WORDS: Coccidioides immitis, Tumor necrosis factor alpha

Study Objective: To determine if human infection with the dimorphic fungus Coccidioides immitis induces the production of cytokine TNF-alpha/cachectin as part of the overall host immunologic response to infection.

Technical Approach: Patients and controls (staff volunteers) from each facility will be phlebotomized on one occasion; approximately 50 ml of blood by peripheral venipuncture will be required. Antigen stimulation will be performed at WBAMC by MAJ Slagle, using the facilities of the Department of Clinical Investigation. Supernatants from this portion of the assay will be frozen at -70°C, batched and transported at a future date to the San Antonio State Chest Hospital (SASCH). The TNF-alpha RIA will be performed by the Research Immunology Laboratory at SASCH.

Patients suitable for inclusion in this study include individuals 18 years of age or old or older having documented active infection with C. immitis, as evidenced by:

1. Acute pneumonitis with positive sputum culture.

2. Disseminated disease within the thorax, with pulmonary parenchymal involvement as shown by biopsy stain or culture.

3. Extrathoracic disseminated disease, with demonstration of C. immitis on biopsy stain or culture of involved tissue or biologic fluid.

Exclusion criteria for patients and controls include the presence of concurrent infection or underlying malignancy. Patient controls will be matched for age (± 10 years), sex, and race.

Risks to patients and controls are limited to those risks associated with phlebotomy (bruising, infection, or thrombophlebitis at the venipuncture site). The study is designed to begin in October 1989 upon IRB approval, with an anticipated duration of two years. It is anticipated that 5-10 patients from WBAMC will be eligible for enrollment in each year of the study.

PBM from each patient and control will be stimulated in vivo with Formalin-killed spherules (test antigen), lipopolysaccharide (LPS) from E. coli serotype 055:B5 (positive control), and tissue culture media (negative control). thus, TNF-alpha levels will be analyzed using two-factor analysis of variance (factors of infected/not infected and stimulated/not stimulated).

Progress: Given time constraints, The principal investigator has been unable to enroll patients in this study. He has set up the required equipment in the lab and run normal serum as initial controls. There are some

methodological problems which need to be worked out. Unfortunately, the San Antonio State Chest Hospital Research Immunology Lab has had personnel turnovers and is not actively pursuing this protocol at present. Principal investigator will consider terminating this project if he is unable to devote any time to it over the next year.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/54** **STATUS: Ongoing**

TITLE: Efficacy of Passive Immunization in the Prevention of Infection Due to Klebsiella pneumoniae and Pseudomonas aeroginosa

START DATE: Oct 90 **ESTIMATED COMPLETION DATE: Dec 92**

PRINCIPAL INVESTIGATOR: MAJ David C. Slagle

DEPARTMENT: Med **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Naomi E. Aronson, MC

KEY WORDS: Immunization, Klebsiella pneumoniae, Pseudomonas aeroginosa

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Study Objective: (1) To determine the efficacy of intravenous immunoglobin (IVIG) compared with albumin in reducing the incidence of infection caused by Klebsiella and Pseudomonas bacterial serotypes contained in the two vaccines. (2) To determine whether IVIG delays onset or lessens severity of serotype-specific infection.

Technical Approach: In a double blind, randomized fashion, study participants will receive a one time IV infusion of K-P IVIG (5gms, 7gms, 9gms, or 11gms depending on weight of $\leq$ 50Kg, 51-70Kg, or $\geq$ 91Kg, respectively) and multivitamins or albumin and multivitamins. All patients will be followed daily for signs of infection while in the hospital for a maximum of 6 weeks. Patients who are discharged prior to this time will be telephoned to ascertain 6-week survival status.

Progress: This is a newly approved study with no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/55 STATUS: Completed

TITLE: Nursing Implications for Determining the Differences in Paternal-Infant Attachment Behaviors Exhibited in the Intensive Care Nursery and the Term Nursery

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Dec 89

PRINCIPAL INVESTIGATOR: MAJ Lorna Chatmon

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Carol Fox, AN

KEY WORDS: Paternal and infant bonding

Study Objective: The purpose of this observational study is to determine if paternal-infant attachment behaviors differ between father's experiencing a normal term infant delivery and those experiencing a preterm infant delivery. The following questions will be addressed: 1) Does the altered ability of the preterm infant to interact with the father effect the attachment behaviors exhibited by the father? 2) Do the variables of infant gender, father's presence at delivery, father's early contact with infant, pleasure or pain value placed on the pregnancy by the father, and whether the pregnancy was planned or unplanned predict attachment behaviors?

Technical Approach: Subjects for the study would be recruited during initial obstetrical orientation or during preadmission to the labor and delivery unit. Couples would be approached and if the selection criteria met, would be asked to participate in a study of "how first-time fathers get to know their infants". A sample of 20 fathers, 10 of which have experienced a preterm delivery and 10 which have experienced a term delivery would be selected. The sample size is felt adequate to pilot test the use of the assessment inventory tool with fathers of preterm infants as well as term infants. Randomization of study participants is not possible due to the differentiation of participants into groups experiencing preterm deliveries versus term deliveries. Four criteria for sample selection exist; 1) This is the fathers' first child, 2) Study participants are married, 3) Fathers are present at delivery, 4) The infant is born alive, whether term or preterm. A term infant is defined as any infant greater than 36 weeks gestation and 2500 grams. A preterm infant is defined as less than 36 weeks gestation and 1500-2500. The exclusion of preterm infants less than 1500 grams is felt to be necessary due to their often precarious initial medical course and the inability of this study to adequately research them at this time.

The inventory is used during 3 observational periods of father-infant interaction. Each observational period is 10 minutes long. during that time the nurse observer would check each item or behavior on the inventory with a plus (+) if the behavior was observed; if a behavior was not observed it would be indicated with a minus (-). The paternal behaviors are scored on an item-by-item basis and analyzed individually. Observation periods occur during father-infant interaction in delivery, recovery, nursery and neonatal-intensive care unit, as well as when the fathers are visiting in the room with their infants. The first observational period would occur during delivery if the infant is handed to the father and/or in recovery. The second and third observational periods would then occur during subsequent visit and interaction between the father and his infant.

Progress: Ten subjects were entered into the study with no subjects withdrawing and no adverse reactions. The project was completed December 1989 and data analysis is pending.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/53** **STATUS: Ongoing**

TITLE: Relationship of Childbirth Preparation Classes on Anxiety Levels of Primiparas: A Pilot Study

START DATE: Sep 90 **ESTIMATED COMPLETION DATE: Dec 90**

PRINCIPAL INVESTIGATOR: LTC Lorna Chatmon

DEPARTMENT: Nsg **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: CPT Karen R. Kurth, AN

KEY WORDS: Anxiety, Pregnancy

Study Objective: **To determine the relationship between childbirth preparation classes and anxiety levels in primiparous women.**

Technical Approach: **The study design is non-experimental. Subjects will be placed in one of two groups. The first group will be those first time mothers who have attended formal, structured prenatal classes and the second group will be mothers who have not attended these classes. Because it could be ethically questionable to determine who can and cannot attend prenatal classes, the study is non-experimental, lacks randomization and uses a non-probability sample.**

A biographical data-sheet will be completed prior to the administration of the State-Trait Anxiety Inventory. The questionnaires are self-administered and require minimal explanation. The biographical data sheet consists of general information. The STAI consists of 20 questions referring to state anxiety and 20 questions on trait anxiety. The questionnaires take approximately 20-30 minutes to complete. Data analysis will be done using nonparametric statistics to test significance at $p < .05$.

Progress: **To date, approximately one-quarter of the projected participants have completed the study. No problems have been encountered. Confidentiality has been maintained and the completed forms are stored to assure privacy. No data analysis of the questionnaires has been done to this point. There has been no difficulty in recruiting participants to the study and no problems are identified.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/09** **STATUS: Ongoing**

TITLE: Effects of a Relaxation Technique on Postoperative Pain and Ventilatory Effort

START DATE: Feb 90 **ESTIMATED COMPLETION DATE: Aug 90**

PRINCIPAL INVESTIGATOR: MAJ Barbara Culp

DEPARTMENT: Nsg **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Rosalinda Kellner, RN

KEY WORDS: Relaxation, Nursing, Postoperative pain, Ventilation

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Study Objective: To perform a pilot study which will examine the effects of a relaxation technique on postoperative pain and ventilatory effort in cholecystectomy patients.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Protocol terminated due to retirement of principal investigator. There is no data to report at this time.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/34 STATUS: Terminated

TITLE: A Study on the Correlation of Arterial Carbon Dioxide Level with End-Tidal Carbon Dioxide Level as Measured by Mass Spectrometry

START DATE: Sep 90 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: CPT William Glasscock

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Laura Murphy, AN; CPT Michael Phillips, AN; 1LT Mark Schierenbeck, AN

KEY WORDS: Arterial carbon dioxide

Study Objective: Investigate the accuracy and correlation, if any, between a mass spec obtained PetCo2 value and the arterial blood gas drawn PaCo2 value.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Unable to obtain progress report from the principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/56 STATUS: Completed

TITLE: Follow-up Support for Breastfeeding Mothers: Mothers' Perceptions of and Outcome of the Breastfeeding Experience

START DATE: Jun 89 ESTIMATED COMPLETION DATE: Nov 89

PRINCIPAL INVESTIGATOR: LTC Marcia L. Kossman

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Elizabeth E. Cook, RN

KEY WORDS: Follow-up support, Breastfeeding mothers

Study Objective: The purpose of this study is to evaluate the effectiveness of extending nursing care for breastfeeding mothers past the post-partal discharge. This study will determine what, if any, differences occur over a three month period in the breastfeeding experience of mothers who receive follow-up support in addition to routine breastfeeding education, versus mothers who receive only routine breastfeeding education. The following questions will be addressed:

1. What, if any, relationship exists between the length of time mothers continue to breastfeed and the availability of follow-up support?
2. What, if any, relationship exists between the number and type of breastfeeding problems experienced and the availability of follow-up support?
3. What, if any, relationship exists between the ability of mothers to resolve breastfeeding problems and the availability of follow-up support?
4. What, if any, relationship exists between mother's feelings of satisfaction with the breastfeeding experience and the availability of follow-up care?

Technical Approach: The proposed research design for this study is quasi-experimental, utilizing a 2 group, nonprobability sample. Mothers will be randomly assigned, a priori, to either the experimental or the control group. The experimental group will consist of mothers who will receive follow-up support, over a 3 month period, in addition to routine post-partum breastfeeding education. The control group will consist of mothers who receive only routine post-partum breastfeeding education.

The population to be studies includes those mothers who have planned to breastfeed their infant. For the purpose of this study, the sample will be comprised of primiparas who have verbalized intent to breastfeed, and who have given birth to healthy, full-term infants. Both control and experimental groups will consist of 5-15 randomly assigned participants. A random numbers table will be used a priori to assign numbers from 1 to 30 to either the control group (routine post-partum education only) or the experimental group (follow-up support in addition to routine post-partum education).

Mothers in both the experimental and control groups will be contacted within 24 hours after delivery by the researcher to request permission to participate in the study. Mothers will be randomly assigned to either control or experimental groups as previously stated.

Mothers in the control group will be asked to complete a brief demographic questionnaire when they agree to participate in the study. These mothers will then be contacted by telephone at 1, 2, 4, 6, 8, and 12 weeks post-partum. The purpose of these calls will be to establish the duration of breastfeeding, reasons for weaning (if applicable), problems that have occurred, and successful problem solving strategies. At 12 weeks the Maternal Perceptions Questionnaire will be completed to measure mothers' feelings of success and satisfaction with the breastfeeding experience (sooner in the event that breastfeeding is discontinued). No advice or teaching will take place during these calls, and there will be no effort to problem solve. The

researcher will refer mothers only to their discharge instructions for resource numbers, or to the clinic/doctor if questions arise.

Mothers in the experimental group will be requested to complete the demographic questionnaire when they agree to participate in the study. The mothers will be contacted by telephone at 1, 2, 4, 6, 8, and 12 weeks post-partum. Mothers in this group will have an opportunity to discuss breastfeeding, and any concerns they may have, with the researcher. The purpose of these calls will be to establish the duration of breastfeeding and reasons for weaning (if applicable). Problems with breastfeeding will be evaluated, and the researcher will assist the mother to problem-solve and identify solutions. Mothers will be given a phone number where they can call the researcher if additional assistance is needed. At 12 weeks the Maternal Perceptions Questionnaire will be completed to evaluate mothers' feelings of success and satisfaction with the breastfeeding experience (sooner in the event that breastfeeding is discontinued).

Progress: This pilot study suggests that mothers who were provided with resource numbers for continued support and actively sought help, were able to improve their ability to problem solve and continue breastfeeding in the first 3 months post-partum.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/08 STATUS: Ongoing

TITLE: Relationships Among Selected Pre and Post-natal Factors and Perception of Birth

START DATE: Jun 90 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: LTC Kathleen B. Mauro

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Deborah Oakley, Ph.D.

KEY WORDS: Pregnancy, Stress

Study Objective: To examine the birth experiences of civilian women who are married to active duty soldiers. The immediate and short range study aims will be to:

1. Identify perinatal factors which significantly influence and predict women's perceptions of their birthing experiences.

2. Explore relationships between the selected prenatal factors.

3. Communicate results to the military nursing community, military health care providers, and military leaders.

Technical Approach: A non-probability sample of 250 expectant mothers, planning to deliver and receive 6 week postpartum care at WBAMC will be obtained. Subjects will meet the following selection criteria: civilian, married to an active duty Army soldier, able to read and understand English, 32-38 weeks pregnant, experiencing an uncomplicated pregnancy, and anticipating her first delivery.

All prenatal clinic charts at WBAMC will be screened to determine subject eligibility. Data will be obtained prenatally and postnatally using mailed questionnaires and chart audits. An introductory mailing containing a cover letter, a stamped postcard, a stamped envelope, two copies of the informed consent, and questionnaire #1 will be sent to all eligible women. Questionnaire #2 will be sent to each subject approximately six weeks after her delivery as determined by either a returned postcard or a documented delivery. Hospital records of participating mothers and their infants will be reviewed in order to determine the presence of selected complications. Mothers may withdraw from the study at any time by indicating their desire to due so on the postcard provided and returning the postcard to the researcher. No additional data will be requested from subjects who choose to withdraw.

Progress: No subjects have been entered in this study, and no progress has been made to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 90/43 **STATUS:** Ongoing

TITLE: Job Satisfaction in Clinical Head Nurses

START DATE: Jul 90 **ESTIMATED COMPLETION DATE:** Sep 90

PRINCIPAL INVESTIGATOR: LTC Kathy Mauro

DEPARTMENT: Nsg **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Jerilyn A. Wadford, AN

KEY WORDS: Headnurse, Nurse, Job satisfaction

Study Objective: To describe the relationship between selected factors and overall job satisfaction in the Army Nurse Corps Clinical Head Nurse.

Technical Approach: A convenience sample of Army Head Nurses at William Beaumont Army Medical Center will be surveyed. The survey will be distributed to all ANC Head Nurses within the facility. An envelope will be provided and participants will be encouraged to complete the survey within 2 days. One week after initial distribution of the survey, each participant will receive a reminder encouraging them to return the survey if they have not already done so or thanking them if they have. Frequency distributions will be computed for all variables. Scores will be summed and divided by the number of items to attain a mean for each subscale. An overall means for the global scale will be attained as a general measure of nursing satisfaction. The data will be further analyzed using the demographics to assess differences in years of active federal service, specialty, sex, months as a head nurse, marital status, dependents, and work hours. Because of the use of a small sample, results may not be generalized to the Army Nurse Corps. The instrument to be utilized is recently developed. Personal variables cannot be controlled or documented because of subjectiveness of the survey.

Progress: Subjects still being actively recruited. No preliminary results are available.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/07 STATUS: Terminated

TITLE: The Actual Role of the Army Emergency Nurse

START DATE: Unknown ESTIMATED COMPLETION DATE: Unknown

PRINCIPAL INVESTIGATOR: LTC Carol Pieniadz

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Army emergency nurse

Study Objective: To examine the actual role functions as performed by Army Emergency Nurses using a work sampling technique and to compare observed actual role functions to perceived actual role functions from a previous study. This study is based on two previous studies. The first is a *nonexperimental descriptive* study of Emergency Nurse role functions, using a work sampling methodology (Marsh, 1987). The second study is also a nonexperimental descriptive study that examines the perceived actual and ideal practice role functions of emergency nurses.

Technical Approach: The sample the investigator will utilize will be role function observations made on Army Emergency Department nurses working in one of two level II Emergency Departments. The sampling procedure has three stages: Level II Emergency Departments will be selected since approximately 80% of the Emergency Centers in the Army are designated Level II. These Level II Emergency Centers are found in both Medical Department Activities (MEDDAC's) and Medical Centers (MEDCEN's) within the Army; thus, one MEDDAC Level II Emergency Center and one MEDCEN Level II Emergency Center will be chosen. The nurses to be observed will be selected by shift availability and amount of experience as a nurse in the emergency care setting. Nurses must have a minimum of 5 months emergency care experience to be included. Role functions performed by the nurse will then be sampled at 5 minute intervals. The observation is an instantaneous one, i.e., whatever the nurse is doing at that instant is the behavior observed and recorded. Observations will be made for 4 days at each facility. both day shift and evening shift will be included. Observations will be collected for 8 hours each day, for a total sample of 384 observations at each institution.

Progress: No progress report was received from the principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/62 STATUS: Ongoing

TITLE: The Effects of Psychodrama, Large Groups and Small Groups, on Head Nurses' Burnout, Anxiety, and Work Satisfaction

START DATE: Jun 89 ESTIMATED COMPLETION DATE: Dec 90

PRINCIPAL INVESTIGATOR: CPT B.J. Thomas

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Conrad Silvani, AN; CPT Danny Davison, AN; Mariva Barajas, DAC

KEY WORDS: Burnout, Anxiety, Work satisfaction

Study Objective: To empirically validate the use of the psychiatric techniques of using psychodrama, small group, and large group interventions by measuring the changes in burnout, anxiety, and work satisfaction.

Technical Approach: The subjects for this study will be the convenience sample of all the head nurses that attend the work shop "Stress and Burnout for Head Nurses".

Three instruments will be used in this study: The Tedium Measure, Spielberger's State-Trait Anxiety Self Evaluation Questionnaire, and Stamps-Piedmonte Index of Work Satisfaction.

Data will be collected using all three instruments at the beginning of the work shop after a brief welcome, introduction, and signing of the consent form. Demographic data will also be collected at this time. Only the Tedium Measure and STAI will be self-scored at this time. The results of these scores will be discussed in a large group atmosphere for the rest of the first hour.

The second hour will consist of psychodrama vignettes that all of the participants will have the opportunity to participate in using scripts that have been developed to portray typical difficulties on the nursing units. The scripts have been designed to demonstrate different leadership styles and attitudes that may be encountered on nursing units.

The third hour of the work shop will be small groups that will focus on the feelings and attitudes that the participants had when they were placed in the roles of the vignettes in positions other than the head nurse such as ward clerk, LPN, staff nurse, patient, etc.

The fourth hour will be a large group problem-solving discussion on how to improve attitudes, and decrease burnout and stressors by the inclusion of positive attitudes and conditions in the work place. All three of the instruments will then be re-administered at the end of the fourth hour.

Two weeks after the work shop each of the head nurses will again be administered each of the three instruments by the primary investigator.

The control group, which will consist of the head nurses that do not participate in the workshop , will be contacted on an individual basis and be administered the three instruments after signing a consent form and filling in the demographic data. The second administration of the instruments will take place approximately four hours after the first administration. The third administration of the instruments will take place approximately two weeks after the first two. No intervention will take place between the administration of the instruments.

All data sheets will be coded to protect the privacy of the participant. Only the primary investigator will have a master list of participant names and codes that will be secured at all times.

Progress: A four hour workshop was presented to 15 head nurses two different times. Data was collected before the workshop, after the workshop and at two weeks after the workshop. The data is currently being analyzed.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/24 STATUS: Ongoing

TITLE: The Effect of Relaxation Therapy on Patients with Asthma

START DATE: Jan 87 ESTIMATED COMPLETION DATE: Aug 91

PRINCIPAL INVESTIGATOR: Helen Villegas RN

DEPARTMENT: Nsg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Raghava Charya, MC

KEY WORDS: Asthma

Study Objective: To measure the effects of relaxation therapy on asthma symptoms, frequency of prn medications, and emergency medical care.

Technical Approach: Fifty intrinsic asthma patients, 20-40 years of age, followed daily in the Allergy clinic, will be involved in participating in this pilot study for 6 weeks. History and biographical data will confirm the diagnosis of intrinsic asthma. Pulmonary function tests (PFT) will be measured on the first visit. PFT will also be recorded on the second and last visit. Patients will keep an asthma diary which will document daily peak expiratory flow rate, asthma symptoms, assessment of mood and use of prn medications and medical care. After 3 weeks, subjects will return to the Allergy Clinic with their completed diaries. Their PFT will be recorded. They will be instructed in the use of a relaxation tape to use each morning upon awakening and each night after retiring. This relaxation tape will include facial muscle exercises and positive thoughts and imaging. Medical news in the Journal of the Medical Association reported in 1983 that the imagination can be used to relieve asthma symptoms while Connors has concluded that tension changes in the facial musculature reliably influences the PEFR. The patient will be given a new asthma diary to record the next 3 weeks. The hypothesis is that the relaxation therapy component of the patient's multifactorial therapy will improved asthma symptoms and decrease medication intake and the need for emergency medical care.

Progress: The control group for the study will begin keeping their asthma diary in February 1991, the same time of the year that the research subjects documented theirs.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/46 STATUS: Completed

TITLE: The Effect of Intraperitoneal Administration of Tissue Plasminogen Activator on Adhesion Formation in a New Zealand Rabbit Model

START DATE: Aug 89 ESTIMATED COMPLETION DATE: Mar 90

PRINCIPAL INVESTIGATOR: CPT Dan Gehlback

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Cesar Rosa, MC

KEY WORDS: Adhesions, Tissue plasminogen activator

Study Objective: To investigate whether the intraperitoneal administration of tissue plasminogen activator can prevent adhesion formation following an abdominal operation for lysis of pelvic adhesions.

Technical Approach: 60 New Zealand white rabbits will be randomly assigned to 4 treatment groups. All animals will undergo laparotomy and standardized peritoneal injury to induce adhesion formation. Three weeks later the rabbits will undergo a second laparotomy with lysis of adhesions, using the operating microscope and microsurgical technique, with intraperitoneal adjunctive treatment as follows: Group 1 will serve as controls with no further treatment; Group 2 will have 20 ml of 2% sodium carboxymethylcellulose added; Group 3 will have 20 mg rt-PA combined with 20 ml 2% sodium carboxymethylcellulose added; and Group 4 will have 20 ml of 32% dextran 70 added. All animals will have a hematocrit drawn intraoperatively and one day after surgery. Three weeks later the animals, blinded to the surgeons, will be sacrificed and undergo adhesion scoring individually by each author, using two separate scoring systems. system 1: the summation of adhesion location (0 = no adhesions, 1 = adhesions on 25% of traumatized area, 2 = adhesions on 50% of traumatized area, and 3 = total adhesion involvement) and tenacity (0 = no resistance to separation, 0.5 = some resistance required, and 1 = sharp dissection required), with range 0-4. system 2: 0 = no adhesions; 1 = localized, filmy adhesions; 2 = localized, dense adhesions; 3 = widespread, filmy adhesions; and 4 = widespread, dense adhesions.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Recombinant tissue plasminogen activator (rt-PA) has been investigated as an adjunct in the prevention of post-surgical adhesion formation. Forty-five mature New Zealand rabbits underwent laparotomy and bilateral uterine horn abrasion using a scalpel for scarification. Adhesions were scored according to the extent of uterine horn involvement and quality of the adhesions. Three weeks later, after the adhesions were scored and lysed using microsurgical technique, the animals were randomized to receive 20 ml of one of four adjunctive treatments: (1) Ringer's lactate; (2) 2% sodium carboxymethylcellulose, (3) 10 mg rt-PA mixed in 2% sodium carboxymethylcellulose; or (4) 32% dextran 70. The adhesions were scored again 3 weeks later at necropsy. Adhesion scores decreased (mean ± standard deviation) in Group 1 (n=10) from 3.50 ± 1.43 to 3.35 ± 1.45; in Group 2 (n=9) from 3.83 ± 1.19 to 3.61 ± 1.32; in Group 3 (n=8) from 3.50 ± 1.58 to 2.81 ± 1.46; and in Group 4 (n=10) from 3.75 ± 1.57 to 3.50 ± 1.35. There was no statistically significant difference in adhesion reformation between the four groups. Four rabbits died of intra-abdominal hemorrhage following lysis of adhesions, of which three had been treated with rt-PA and one with carboxylmethyl- cellulose. In contrast to previous reports the use of intraperitoneal rt-PA did not reduce post-surgical adhesion

formation and was associated with hemorrhagic complications.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/08 STATUS: Ongoing

TITLE: OBGYN Bowel Training Utilizing the Pig Model

START DATE: Jul 86 ESTIMATED COMPLETION DATE: Open-ended

PRINCIPAL INVESTIGATOR: MAJ Carla G. Hawley-Bowland

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Surgical training in residency - GI

Study Objective: This training is designed to teach physicians the basic knowledge and operative skills required to perform basic small and large bowel surgery.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing bowel injuries, resecting and anastomosing small bowel, and large bowel exteriorization. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery consists of small bowel resection and re-anastomosis. The surgical site is then closed and the animal awaken from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of resecting the colon and creating a colostomy. Afterward, the surgical site will be closed and euthanasia administer while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Six pigs were utilized with 12 operative episodes. One procedure was complicated by a superficial wound abscess discovered at time of second procedure. Eight residents were training in bowel surgical techniques.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/33 STATUS: Ongoing

TITLE: OB/GYN Microsurgical Tubal Re-Anastomosis Training Utilizing A Rabbit Model

START DATE: Mar 86 ESTIMATED COMPLETION DATE: Open-ended

PRINCIPAL INVESTIGATOR: MAJ Carla G. Hawley-Bowland

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Cesar Rosa, MC

KEY WORDS: Tubal Re-anastomosis

Study Objective: This training is designed to teach resident physicians the basic knowledge and operative skills required to perform microscopic tubal surgery.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeon's confidence in utilizing the operating microscope and microsurgical instruments as well as planning and accomplishing the operative procedures. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery consists of unilateral uterine cornua resection and re-anastomosis. The surgical site is then closed and the animal awaken from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted. The first microsurgical anastomosis site will be re-explored for patency and the training procedure will be repeated on the contralateral cornua. After completion of the procedure euthanasia will be administered as described below.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Seven rabbits were utilized with seven operative episodes. There was one anesthetic death. Seven residents were trained in microsurgical tubal reanastomosis.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/64 STATUS: Ongoing

TITLE: Genitourinary Tract Surgery Training Utilizing a Pig Model and Comparing Stenting Technique

START DATE: Aug 86 ESTIMATED COMPLETION DATE: Open-ended

PRINCIPAL INVESTIGATOR: MAJ Carla G. Hawley-Bowland

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Surgical Training

Study Objective: This training is designed to teach resident physicians the basic knowledge and operative skills required to perform genitourinary surgery while simultaneously evaluating the need for ureteral stenting following the operative procedures.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing GU injuries, resecting and anastomosing ureters, and reimplanting ureters into the urinary bladder. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery will consists of unilateral ureter resection and re-anastomosis. Upon completion of this procedure, the laparotomy incision will be closed and the animal awaken from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of transecting the contralateral ureter at the point of entry into the urinary bladder and reimplanting the ureter through the bladder wall. Afterward, the laparotomy incision will be closed and euthanasia administer while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Seven pigs were utilized with 13 operative episodes. There was one postoperative death secondary to pericardial tamponade. Eight residents in genitourinary surgical techniques.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/24 STATUS: Completed

TITLE: An Evaluation of Core Temperatures Using the CORTEMP Ingestible Telemetry Monitoring System (ITMS) in Pregnant Patients Undergoing Physical Training

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Dec 89

PRINCIPAL INVESTIGATOR: COL Kevin C. Kiley

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL Larry L. Morgenstern, Chief, Dept of OB-GYN, WBAMC

KEY WORDS: Cortemp

Study Objective: To evaluate core body temperatures in pregnant women during exercise by use of the ingestible CORTEMP system (ITMS).

Technical Approach: Over a six month period women volunteers 18 years of age and older in three groups will be asked to participate in the study.

a. PHASE I: Female soldiers, preferably in the same unit, who are not pregnant will be interviewed and examined after volunteering. They will then be instructed on the use of the CORTEMP. These non-pregnant women soldiers will participate in their unit's designated routine physical training program. Data on their core temperatures will be correlated with their specific PT (i.e. running vs calisthenics) and weather conditions. I anticipate 10-15 soldiers participating.

b. PHASE II: Female soldiers recently diagnosed as pregnant through the Department of OB-GYN, WBAMC will be asked to volunteer for the CORTEMP study if they are cleared to continue unit PT or are transferred into the low impact aerobic class at Ft Bliss. I anticipate 5-10 soldiers participating. Similar instruction, observations and data recording will be performed.

c. PHASE III: Dependent wives cared for by the Department of OB-GYN who are participating in the low impact aerobics program at Ft Bliss will be asked to participate in the study. Women at all gestational ages will be included to document possible differences by gestational age. I anticipate 10-15 women participating in this group.

The primary investigator will supervise all phases or the study to include counselling and observation or PT and low impact aerobics.

Progress: Hyperthermia nas been associated with teratogenic effects in animal studies and concern remains for potential damage to the human fetus when exposed to elevated maternal core temperatures. The CORETEMP® capsule is a new device that transmits a near magnetic resonance signal reflecting internal temperature when swallowed. We studied seven healthy, nonpregnant soldiers performing routine unit level physical training and noted a 1°C rise in core temperature associated with running in formation, but not while performing calisthenics. Seven pregnant soldiers were then studied during varying gestational ages while performing supervised low impact aerobics. There was no significant change in core temperature during or after the 45 minute exercise period. This investigation supports the safety of low impact aerobics in pregnancy as it relates to potential hyperthermia.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/23** **STATUS: Terminated**

TITLE: An Evaluation of the Hollister Female Urinary Incontinence Systems (FUIS) for Women Soldiers in a Field Environment

START DATE: **ESTIMATED COMPLETION DATE:**

PRINCIPAL INVESTIGATOR: COL Kevin C. Kiley

DEPARTMENT: OBGYN **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: COL Larry L. Morgenstern, Chief, OB-GYN

KEY WORDS: Female urinary device

Study Objective: To evaluate the possibility of extended continuous use of the Female Urinary Incontinence System (FUIS) to assist women soldiers in voiding under field and combat conditions.

Technical Approach: Over a three to six month period, selected volunteer units at Ft. Bliss will be offered inclusion in the study. After counselling and a complete gynecologic examination by the principle investigator, the volunteer soldiers will be instructed on wear and care of the system and then will wear the device under field conditions of up to 14 days. After completion of the field training exercise the volunteers will again undergo an examination and will fill out a questionnaire. These soldiers will be 18 years or older. I expect a total of approximately 25 soldiers to participate.

Exclusion criteria include soldiers who have/are:

1) **Active urinary tract disease under treatment.**
2) **Active gynecologic disease processes (to include "staph" cultures).**
3) **Anatomic abnormalities (imperforate hymen, double vagina)**
4) **Pregnancy**
5) **Active menses**

Data to be collected on the soldiers includes:

1) **Age, gravidity, parity, race, birth control history**
2) **Prior obstetric or gynecologic disease**
3) **Results of a gynecologic exam**
4) **Pre and post use cultures of urine, and cervix**
5) **MOS, duty description**
6) **Level of physical exertion during the FTT.**

Progress: Project is on hold due to principal investigator participating in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/13 STATUS: Ongoing

TITLE: Accuracy of Transvaginal Ultrasound in the Diagnosis of Ectopic Pregnancy

START DATE: Jan 88 ESTIMATED COMPLETION DATE: Jul 89

PRINCIPAL INVESTIGATOR: CPT Vincent Lyons

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Andrew W. Robertson; MAJ George G. SanMiguel; CPT Philip Bayliss; LTC Marcia Kossman; LTC James Brown

KEY WORDS: Ectopic pregnancy, transvaginal ultrasonography

Study Objective: To compare the predictive accuracy of transvaginal sonography to transabdominal sonography in the diagnostic evaluation of patients with suspected ectopic pregnancies.

Technical Approach: One hundred unselected stable patients undergoing diagnostic work-up for a suspected ectopic pregnancy will be recruited to voluntarily participate in the study. Once enlisted in the study, they will receive a transvaginal sonogram utilizing a technique described by Brown, et al. in the antepartum diagnostic center. All transvaginal sonography will be performed by the attending or resident staff using an ultramark four ultrasound machine. A 3.5 MHZ end fire sector transducer covered with an aquasonic gel filled glove will be used. The information obtained will be retained in the ADC and blinded to the physicians who will then perform the standard diagnostic work-up. Once the patient's care is completed, her hospital chart will be reviewed for the information listed on the attached data collection record.

A Fisher extract test with a P of .05 will be used to compare the accuracy of the T/V to the T/A technique for predicting the presence or absence of an ectopic pregnancy.

Progress: Data collection on 50 patients was completed and no further subjects will be entered in the study. No adverse effects were noted, however, details of conclusions are not available due to deployment of principle investigator in support of Operation Desert Storm. The protocol will remain active pending final results.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/19 STATUS: Completed

TITLE: The Effect of Ultrasound Training on the Ability of Obstetric Residents to Accurately Predict Fetal Weight

START DATE: Sep 89 ESTIMATED COMPLETION DATE: Mar 90

PRINCIPAL INVESTIGATOR: CPT Thomas E. Page

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Dan Gehlbach, MC; MAJ Andrew Robertson, MC

KEY WORDS: Fetal weight; Ultrasound

Study Objective: To assess the accuracy in predicting fetal weight by the residents during their rotation in the Antepartum Diagnostic Center, by comparing actual birth weights to those predicted by ultrasound within a week of delivery.

Technical Approach: The Antepartum Diagnostic Center records will be reviewed from the past 18 months and those ultrasounds which were performed within one week of delivery will be identified. The patient identification and ultrasound measurements will be entered into a database file, and the percent absolute error in predicted birth weight will be recorded. The data will be stratified according to the resident performing the ultrasound and broken down by week of the rotation. We anticipate approximately 400 deliveries will meet our criteria of delivering within one week of their last ultrasound. The accuracy of the resident's ultrasounds will be compared to those done by the staff perinatologist during the same time period.

Progress: Management decisions of complicated pregnancies rely upon accurate estimate of fetal weight (EFW) by sonography. Formal resident instruction in ultrasonography should thus be an integral part of residency training. This formal training is accomplished during the PGY 3 year at WBAMC through a scheduled rotation with staff perinatologists. To evaluate the effectiveness of instruction of EFW, a prospective investigation was performed comparing the accuracy of EFW by PGY 3 residents during their ultrasound rotation compared to EFW by perinatologists during the same period of time. During the 6 month study period, 72 sonographic EFW performed by residents were compared to 76 EFW by perinatologists. There were no significant differences between the two groups (7.13% versus 7.89% error). We conclude that a formal course of instruction in sonographic EFW appears to be effective.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/56** **STATUS: Ongoing**

TITLE: Comparison of Glucola v. Karo Syrup in the Performance of the One-Hour Glucose Screening Test

START DATE: Oct 90 **ESTIMATED COMPLETION DATE: Jan 91**

PRINCIPAL INVESTIGATOR: CPT Thomas E. Page

DEPARTMENT: OBGYN **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Frederick Harlass, MC

KEY WORDS: Glucola, Karo syrup, Glucose screening test

Study Objective: Devise a less expensive and more palatable way of performing the one hour glucose tolerance test.

Technical Approach: Approximately 50-60 patients will be investigated in a prospective manner. The study patients will be entered into the investigation in a random manner (method to be determined). The patients will serve as their own control. The patients will initially be tested with either the standard solution or the Karo syrup. The patients will then be retested during the following week with the comparative solution. The investigation will not be blinded. Statistical analysis will be performed by Student's T-test and any other applicable method. Exclusion: insulin dependant diabetes mellitus. Ages will range from 18 to 45. All subjects will undergo thorough physicals as part of their routine obstetrical care as well as routine baseline CBC, Pap smear, RPR, Type and Rh, Cervical cultures, and rubella titers.

Progress: This is a newly approved study with no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 84/76 STATUS: Terminated

TITLE: Improved Pregnancy Rates After Using Oil-Soluble Contrast Media (OSCM) for Hysterosalpingography (HSG)

START DATE: Dec 84 ESTIMATED COMPLETION DATE: Aug 90

PRINCIPAL INVESTIGATOR: MAJ Cesar Rosa

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: HSG, Pregnancy Rates, Contrast Media

Study Objective: To determine whether OSCM used for HSG improves pregnancy rates in patients with patent fallopian tubes and no other major cause for infertility.

Technical Approach: Patients from the Gynecology Infertility Clinic will be invited to participate. After a complete initial evaluation which includes history, physical exam, semen analysis, documentation of adequate ovulatory function by BBT and serum progesterone, and postcoital test; patients will be scheduled for HSG to evaluate tubal patency as is routine in the evaluation of these infertility cases. All HSGs will be done using water soluble contrast media (WSCM) in order to establish tubal patency and to evaluate presence or absence of rugal marks. Those individuals with a normal study as evidenced by unilateral or bilateral spillage, without evidence of distal obstruction in either tube, will then be randomized to receive 5 ml of OSCM injected through the HSG cannula or no OSCM at all. For this purpose a table of random numbers will be used assigning each group to odd or even numbers. No effort will be made to blind the study as far as the follow-up will be similar in both groups and the measured parameter will be an objective, all or none end result "pregnancy. Patients with normal studies will be followed expectantly for a minimum of four menstrual cycles during which they will be encouraged to maintain BBT charts and to time intercourse with ovulation. After this period of time, those patients with persistent infertility will be progressed through their infertility evaluation as otherwise indicated. Participation in this study will not change in any way the couple's infertility evaluation. The proposed waiting period after a HSG is presently the norm after any normal study; so no unnecessary or extra delay is being introduced into these patient ¡s evaluation. The HSG will be performed by residents from the Dept Obstetrics and Gynecology, under the direct supervision of one of the principal investigators, as is the norm for all HSGs performed presently. Generally, whether OSCM or WSCM are used for HSG is a matter of personal choice by the operator. Both contrast media to be used WSCM (Renografin-Squidd Pharmaceuticals, Princeton NJ) and OSCM (Ethiodol-Savage Co, Missouri City, TX) have been in common use for a number of years and are accepted as safe. Patients allergic to iodine, seafood, or x-ray contrast material will be excluded from the study. Statistical Methods: Contingency tables, using chi-square analysis, comparing OSCM vs no OSCM; pregnancy rates in one group vs the other. The subjects to be considered will be healthy females in their reproductive years, attending the Gynecology Infertility Clinic due to involuntary infertility of more than one year duration. This group is heterogenous in terms of military status and age range 18-36. Facilities to be used will be the same fluoroscopy room in the x-ray department which presently is allotted to the Gynecology Department for HSGs one afternoon a week. The maximum number of studies per day will be six, as is the norm presently. We do not anticipate the use of any additional facilities or resources other than the one routinely used for HSGs.

Progress: This project is being terminated due to the difficulty in recruiting patients and the lack of clerical support.

During the existence of this protocol, seven patients were enrolled. Six withdrew or were excluded by the investigator due to persisting vaginal bleeding while on the continuous estrogen/progesterone replacement. Presently, there is one patient that is continuing her continuous regime and experiencing no side effects. My plan is to continue her on the same regime, one that is clinically acceptable. There were no complications or adverse effects in any of the patients that participated in the study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/47 STATUS: Terminated

TITLE: Continuous Estrogen/Progesterone Replacement Therapy (Monitor: Dr. Svec)

START DATE: Nov 88 ESTIMATED COMPLETION DATE: Apr 90

PRINCIPAL INVESTIGATOR: LTC Cesar Rosa

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT W.T. McGrail, Jr., MC; CPT Mitchell Silver, MC; CPT Rebecca Cavazos, MC; CPT M.D. Wood, MC; COL Ana Rodriguez, MC;

KEY WORDS: Estrogen, Progesterone, Hormone replacement

Study Objective: Assess the effect of the continuous administration of estrogen/progesterone as replacement therapy on the endometrium, bone, and lipid profile of postmenopausal women.

Technical Approach: In this study, we intent to offer continuous estrogen-progesterone replacement to suitable candidates. In so far as this is a relatively new method of estrogen administration, data will be obtained to evaluate the effect of this replacement regimen on bleeding patterns, endometrial stimulation, effect on bone mineral content, and effect on serum lipids.

In this study, no control group will be used. We understand that when given the possibility of not having a monthly bleeding episode, it would be extremely difficult to have the patients agree to submit themselves to randomization (cyclic vs continuous). In addition blinding such a study would be extremely difficult due to the almost certain withdrawal bleeds associated with cyclic therapy. Our goal is to accumulate data on the effects of this type of replacement.

Females presenting to the Gynecology Clinic with symptoms or evidence of estrogen deficiency (hot flashes, genital atrophy, premenopausal syndrome) will be offered inclusion in the study. Criteria for exclusion will be: undiagnosed abnormal uterine bleeding, estrogen dependent malignancies (endometrium or breast), and known pregnancy. Relative contraindications: uterine fibroids, previous thromboembolic disorders. The previous use of estrogens will not be considered a contraindication. Postmenopausal state will be documented with an elevated FSH (over 40 MIU/ML).

a. Conjugated estrogens (Premarin) 0.625mg and medroxyprogesterone acetate 2.5mg daily will be offered as standard replacement.

b. For those patients requiring a higher estrogen dose, conjugated estrogens 1.25mg, and medroxyprogesterone acetate 5mg will be offered. This will be evaluated according to patient's symptoms.

* 0.625mg of CE has been shown to be the minimal effective dose for protection against osteoporosis.

Progress: Principal investigator requested termination of this project due to the difficulty in recruiting patients and the lack of clerical support in continuing the study.

During the existence of this protocol, seven patients were enrolled. Six withdrew or were excluded by the investigator due to persisting vaginal bleeding while on the continuous estrogen/progesterone replacement.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/58** **STATUS: Ongoing**

TITLE: Gonadal Function After Vasectomy

START DATE: Nov 89 **ESTIMATED COMPLETION DATE: May 91**

PRINCIPAL INVESTIGATOR: LTC Cesar Rosa

DEPARTMENT: OB/GYN **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Neal Dunn, MC

KEY WORDS: Vasectomy

Study Objective: To evaluate whether there is any clinical or subclinical evidence of testicular function after vasectomy.

Technical Approach: Approximately 30 active duty males (or others) between the ages 25-40, having vasectomies performed by the Urology Service will be considered suitable candidates. There will be no blinding or randomization necessary. All subjects will receive the same tests. Each patient will serve as his own control. The following tests will be performed:

***Prior to vasectomy -**

1. **Blood for Testosterone, FSH, LH, PRL, Estradiol. Serum to be frozen for future reference.**

2. **GnRH test: After the above is collected at - 0 min; similar samples will be obtained at 15, 30, 45, 60, 90 and 120 min after injection of 100 mcg of LHRH (Factrel, Ayerst Labs, New York) at 0 minutes.**

3. **Serum for antisperm antibodies. To document the incidence of antisperm antibodies following vasectomy. There is evidence of an increased incidence of antisperm antibodies in the circulation after vasectomies.**

4. **A total of 110ml of blood will be obtained per session (at time of vasectomy, then 6 and 12 months afterwards).**

5. **Testicular ultrasound to objectively measure size of the testicles.**

6. **Physical examination (as usual prior to surgery) and testicular size determination with orchidometers (particular attention to testicular tenderness or granuloma formation).**

***The same tests will be administered at 6 and 12 months after the vasectomy.**

Progress: In accordance with a modification of protocol which was submitted to DCI,

10 patients with vasectomy) have undergone 1st GNRH infection
3 continue)

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/08 STATUS: Completed

TITLE: Comparison of Two Endometrial Biopsy Instruments: Novak's Curette vs Pipelle (Monitor: MAJ Andrew Robertson)

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Apr 90

PRINCIPAL INVESTIGATOR: CPT M. Mitchell Silver

DEPARTMENT: OBGYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Philip Miles, M.D.; LTC Cesar Rosa, MC

KEY WORDS: Endometrial biopsy instruments

Study Objective: To assess the correlation between the Novak's curette and the Pipelle endometrial biopsy instrument, in terms of amount of tissue and ability to yield a histologic diagnosis. In addition, the relative degree of pain or discomfort associated with endometrial sampling utilizing each instrument will be assessed.

Technical Approach: Patients requiring endometrial sampling due to diverse conditions (postmenopausal bleeding, abnormal uterine bleeding, infertility evaluation, preoperative evaluation) will be invited to participate. No patients (18-60 years of age) will be excluded from the study.

The participants will be randomly divided into 2 groups. One group will have the endometrial biopsy with the Novak's instrument, followed by the procedure with the Pipelle. The second group will have the procedures in the reverse sequence. Whether each procedure has the 1st or 2nd sequence will be determined at random, utilizing a list of random numbers.

Those patients whose biopsies will be performed for evaluation of infertility, will have a single stroke lateral wall sampling, using each instrument on one side of the uterus. The common precautions to avoid inadvertent sampling of an early pregnancy will be observed, i.e., barrier contraceptions during the biopsy cycle, and a sensitive RIA pregnancy test the day prior to the biopsy.

Normally, only one biopsy method would be done. This project would entail a second biopsy procedure done to each patient.

All tissues will be submitted as two separate specimens to the Pathology Department. Patient management decisions will be based on the findings of either or both specimens. At the completion of the study, the histology slides will be coded and reassessed in a blinded, random fashion by one of the investigators (PM). The amount of tissue and its quality will be assessed. A diagnosis will be assigned to each specimen. At completion, the two specimens from the same patient will be compared. To facilitate the review of the slides, at the time of processing the tissues - 2 slides will be prepared from each specimen. One will go to the laboratory files, the other slide will be included in a "study file" for later review.

The two groups receiving the endometrial biopsies will be given a questionnaire immediately following the procedure. This questionnaire will rate the discomfort associated with the procedure and will ask which of the two procedures they would rather have.

Progress: A randomized prospective study was carried out to compare the Novak's and Pipelle endometrial biopsy instruments. Two parameters were evaluated: 1) quality of the biopsy obtained, and 2) pain related to the procedure. Fifty-five patients were randomized to one of two groups. Group I (N-26) patients had a Pipelle followed immediately by a Novak's biopsy. Group II (N=29) patients had the procedures performed in a reverse sequence. After the procedure, each patient completed a pain questionnaire. In a blinded fashion, individual histology slides were reviewed by one of the authors; paired, then reviewed again, and preference indicated. Both instruments yielded biopsies of similar quality (Z= -.1811, p= .8563). Pain scores were less for the Pipelle (Z= -3.3991, p= .000). The pathologist showed no preference when choosing Noval's or Pipelle

slides ($x2 = 2.083$, $p = 0.149$). In our patient population, the Pipelle instrument was comparable to the Novak's instrument in obtaining adequate tissue and was less painful.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/30 STATUS: Ongoing

TITLE: Accupressure Bracelets: An Effective Treatment for First Trimester Nausea and Vomiting of Pregnancy

START DATE: ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: CPT Gary Wharton

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Dan L. Gehlbach, MAJ, MC

KEY WORDS: Accupressure bracelets, Vomiting of pregnancy

Study Objective: To investigate whether the use of an acupressure bracelet can effectively treat nausea and vomiting associated with first trimester gestation.

Technical Approach: Pregnant women who complain of significant nausea and/or vomiting for at least one week's duration will be eligible for this study (dependent daughter's under the age of 18 will be excluded from the study as minors). Patients with other identifiable causes of nausea/vomiting, such as viral syndrome, molar pregnancy, thyroid disease, or preexisting gastrointestinal disease, will be excluded. Patients who are unmarried and less than 18 years of age will be excluded, as will those who require hospitalization on their initial presentation to the clinic. Entry to the study will be offered to all eligible patients at their New OB physical, and to patients presenting to the OB Walk-in Clinic who complain of morning sickness. 75 patients will be randomized by card flip into 3 study 75 patients will be randomized by card flip into 3 study groups of 25 patients each. Group 1 will consist of dietary instruction alone; Group 2 will receive dietary instruction and the accupressure bracelet; and Group 3 will receive dietary instruction and the placebo bracelet. Specific oral and written instructions will be given by the authors on correct wear of the bracelets: the accupressure bracelet is to be worn snugly against the arm at 3 fingerbreadths above the wrist flexor crease with the bead against the flexor tendons; the placebo bracelet is to be worn at the level of the wrist flexor crease and loosely enough that a finger may be easily slid beneath the band.

On initial presentation and at each of two weekly visits the patient will be weighed on the same scale in the OB-GYN Clinic, and a questionnaire (Figure 1) administered by an independent observer. The authors will review treatment aspects and record routine obstetrical data at each visit. Patients will be given handouts with specific dietary/treatment instructions and will be asked to record prospectively the number of episodes of emesis. Each patient will be followed for 2 weeks.

Additional support will be required by the Brace Shop in preparation of the placebo bracelets.

Progress: Unable to obtain report from principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 87/83 **STATUS:** Ongoing

TITLE: Analysis of Hospital Bacterial Pathogens - Chromosomal and/or DNA Fingerprinting

START DATE: Oct 87 **ESTIMATED COMPLETION DATE:** Jul 91

PRINCIPAL INVESTIGATOR: CPT R.R. Gomez

DEPARTMENT: Path **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Michael Lieberman,MS; CPT David Smith, MS

KEY WORDS: DNA, Pathogens, Epidemiology, Nosocomial Infection

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Study Objective: Identification of bacterial strains by subjecting plasmid DNA or chromosomal DNA to restriction endonuclease digestion and then agar gel electrophoresis.

Technical Approach: Plasmid DNA fingerprinting. Methods for plasmid DNA fingerprinting have been described in the literature. A typical method involves isolation of plasmid DNA by lysis and centrifugation. The plasmid DNA is digested with restriction endonuclease. The resultant DNA fragments are analyzed by agarose gel electrophoresis and the pattern obtained from different isolates and compared. Electrophoresis patterns obtained will be compared by visual inspection; thus, statistical analysis is not required.

Progress: Isolates of Pseudomonas aeruginosa were obtained from patients suspected of having nosocomial infections with this organism. Chromosomal DNA was extracted from these isolates using a technique for cell lysis employing detergent treatment and enzymatic digestion. The DNA was then purified by anion exchange chromatography. The DNA prepared by this method was of sufficient quality (purity) and quantity for further analysis by restriction endonuclease digestion and agarose gel electrophoresis. However, no further work has been done. The principal investigator has PCS'd and a new one must be appointed.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/90 STATUS: Terminated

TITLE: Survey of Patients' Serum for Anti-Pseudomonas aeruginosa Ribosomal Antibodies

START DATE: Nov 87 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: MAJ Michael M. Lieberman

DEPARTMENT: Path FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Pseudomonas aeruginosa ribosomal antibodies

Study Objective: Determine if patients with confirmed Pseudomonas aeruginosa infections have antibodies to ribosomes from these bacteria.

Technical Approach: Patients identified in the clinical microbiology laboratory with Pseudomonas aeruginosa infection will have bacteria isolated and serotyped using a commercially obtained kit. A blood specimen will be drawn from these patients at the time of identification and, if possible, at a later time. Antibodies to ribosomes in the patients' serum will be determined by an enzyme-linked immunosorbent assay that has previously been developed. Test serum ribosomal antibody titers are determined as the reciprocal of the highest serum dilution yielding a specified photometric absorbance. The procedure involves ultrasonic disruption of the bacterial cells and isolation and purification of the ribosomes by ammonium sulphate fractionation, differential ultracentrifugation, and molecular sieve chromatography. ELISA analyses on individual serum dilutions will be performed in triplicate and the mean values and standard deviations calculated. Differences greater than two standard deviations between test serum and control serum values at equivalent dilutions are considered significant.

Progress: No progress has been made on this protocol during the past year. It has proven difficult to obtain patients' blood specimens some time after identification of Pseudomonas aeruginosa isolates from other specimens of these patients. In the few cases where this was done, the isolates were of a different serotype than the serotypes from which ribosomal vaccine preparations are presently on hand. In those cases new vaccine preparations would have to be made, which requires more time than is presently available to the investigator. Thus, this protocol is being terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/63 STATUS: Terminiated

TITLE: Analysis of Cellular Immunity Against Pseudomonas Aeruginosa Engendered by Immunization of Mice with Ribosomal Vaccine From P. Aeruginosa

START DATE: Jul 88 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: MAJ Michael M. Lieberman

DEPARTMENT: Path FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Dennis A. Stewart, MS; Bruce Veit, Ph.D;

KEY WORDS: Pseudomonas aeruginosa, ribosomal vaccine, cellular immunity

Study Objective: To determine if the cellular immunity (i.e., the adoptive transfer of protection with splenocytes from immune to non-immune mice) engendered by immunization of mice with ribosomal vaccines from P. aeruginosa is mediated by T lymphocytes or B lymphocytes.

Technical Approach: Vaccination of mice and preparation of immune spleen cells. P. aeruginosa ribosomal vaccine (previously prepared as described [1-3] and available for use) is used to immunize a group of about 100 mice. After an appropriate interval post-vaccination and booster vaccination, the vaccinees are killed and their spleens excised aseptically. Spleen cell suspensions are prepared by mincing the spleens in a liquid medium and passing the resulting material through a sterile nylon gauze filter. (Suspensions of spleen cells from normal mice are also prepared as controls.)

Separation of splenocytes into T and B cell fractions. Plastic petri plates are coated with rabbit anti-mouse immunoglobulin antibodies (obtained commercially). The spleen cell suspensions are allowed to incubate on the anti-mouse Ig coated plates and then removed. The B cells (which have Ig molecules on the exterior of their cell membrane) should adsorb to the surface of the anti-mouse Ig coated plates. The T cells should be removed with the supernatant medium. The adsorbed cells can then be recovered by gentle agitation of the plates in fresh medium. Both the T and B cell fractions can be further purified by a second cycle of adsorption to anti-mouse Ig coated petri plates.

Analysis of T and B lymphocytes. To confirm the separation of the spleen cell suspensions into T and B cell fractions, these fractions will be analyzed by specific mitogen stimulation and by flow cytometry.

(1) T and B lymphocytes are specifically stimulated by particular mitogens. Concanavalin A and phytohemagglutinin A stimulate certain populations of T cells but do not affect B cells, whereas bacterial lipopolysaccharide (LPS) stimulates B cells but not T cells. Thus, these mitogens will be used in lymphocyte stimulation assays (involving uptake of radio-labeled thymidine by stimulated cells in culture) with the T and B cell fractions of the splenocyte suspensions. (Similar assays are currently being performed in the Clinical Investigation Laboratory under other protocols.)

(2) Using the capabilities of the cytoflourograf in the Department of Clinical Investigation, the T and B cell suspensions will be analyzed for the presence of specific surface antigens. Fluorescein (or other florescent molecule) conjugated monoclonal antibodies to surface antigens of murine T or B lymphocytes are available for use. These reagents will be mixed with the cell suspensions and the resulting florescent-labeled cells will be analyzed by flow cytometry. This type of analysis should be able to determine the relative purity of the T and B cell fractions. D. Adoptive transfer of immunity. Isolated T and B lymphocytes (as well as whole spleen cells from both immune and non-immune mice) will be injected (intraperitoneal) into normal (non-immune) mice (10^8 cells per mouse). One day later all of these mice (as well as mice that did not receive any cells) will be directly challenged by inoculation with a live culture of P. aeruginosa. Mice will be scored for survival on a daily basis after challenge.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: No progress was made on this protocol during the past year due to lack of time available to the principal investigator to pursue these extensive animal experiments.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/76 STATUS: Ongoing

TITLE: In vitro Studies of Bactericidal Activity Associated with Specific Antibody to Pseudomonas aeruginosa Ribosomal Vaccine and Bactericidal Protein(s) Extracted from Live P. aeruginosa

START DATE: Nov 88 ESTIMATED COMPLETION DATE: Jul 91

PRINCIPAL INVESTIGATOR: LTC Michael M. Lieberman

DEPARTMENT: Path FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Pseudomonas aeruginosa, Bactericidal protein

Study Objective: (1) To determine the extent of bactericidal activity associated with specific antibodies directed against P. aeruginosa ribosomal vaccines. (2) To characterize the bactericidal "blocking" or inhibiting activities observed in specific antiserum to such vaccines. (3) To further characterize the nature and effects of bactericidal proteins extracted from live P. aeruginosa, and their interaction with bactericidal antibodies.

Technical Approach: In vitro bactericidal and opsonophagocytic assays. Murine antisera to ribosomal vaccines have been prepared previously and are available for use. The bactericidal and opsonophagocytic assays have been described in detail. Briefly, the assays involve mixing combinations of bacteria, antiserum (or IgG purified from antiserum by commercially available Protein A affinity chromatography or ion exchange chromatography methods), complement, and phagocytic cells (for opsonophagocytosis). (Phagocytes, i.e., polymorphonuclear leukocytes are prepared at the time of the experiment from a normal human volunteer.) After incubation of the mixtures, aliquots are spread on agar plates to determine the number of viable bacteria (colony forming units) remaining in the reaction mixtures. This number is compared with the initial inoculum in the mixture to determine the relative bactericidal or opsonic capability of the antiserum or IgG being tested.

"Blocking" activity is observed when the addition of more antiserum or purified IgG to a reaction mixture results in less (or no) bactericidal activity than is obtained without the additional antiserum or IgG. Thus, if experiments are performed in which bactericidal or opsonic activity is determined as a function of the concentration of antiserum or purified IgG, in some cases a "prozone" is obtained, i.e., maximal bactericidal activity is found at intermediate concentrations of antiserum or IgG, with significantly less activity at both higher and lower concentrations. Furthermore, it may be shown that IgG purified by one method from an antiserum which exhibits this "prozone" effect also demonstrates the same effect, whereas IgG purified by a different method from the same antiserum no longer exhibits a "prozone" at the same concentrations of IgG.

Interaction of protein extracts of P. aeruginosa with antiserum and purified IgG. Bactericidal and opsonic reaction mixtures will be set up including the proteinaceous, aqueous extracts in addition to antiserum or IgG. In these cases, the extract by itself has no bactericidal activity against the particular strain of P. aeruginosa used, and the antiserum or IgG by itself also demonstrates no such activity. However, when mixed together, bactericidal activity may appear.

Progress: In vitro bactericidal and opsonophagocytic assays with specific antisera and purified IgG to ribosomal vaccines were performed with two different strains of P. aeruginosa. Strain 12-4-4 was found to be highly susceptible to direct bacterial killing with immune serum or IgG and complement. Phagocytes (PMNL) enhanced bacterial killing about two-fold, but were not required for bactericidal activity. the results of analogous experiments with strain VA 134 were remarkably different. Immune serum or IgG plus complement without phagocytes did not yield bactericidal activity. The addition of PMNL at a high ratio of phagocytes to bacteria (2 to 1) did result in bacterial killing, but PMNL with normal IgG plus complement was also bactericidal. Despite this apparent lack of in vitro bactericidal activity, however, the immune serum or purified

IgG from antiserum to ribosomal vaccine from this strain did provide in vivo protection by passive immunization against homologous challenge.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/90** **STATUS: Terminated**

TITLE: Cystic Fibrosis: Antibodies to Mucoid and Non-Mucoid Pseudomonas aeruginosa

START DATE: -- **ESTIMATED COMPLETION DATE: Aug 90**

PRINCIPAL INVESTIGATOR: LTC Michael M. Lieberman

DEPARTMENT: Path **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: MAJ Robert Wittler, MC; Prof. Marvin Salin, Ph.D.

KEY WORDS: Cystic fibrosis, Pseudomonas aeruginosa

Study Objective: The objectives of this project are to determine the specificity of antibodies against mucoid and non-mucoid Pseudomonas aeruginosa in sera from cystic fibrosis patients and to localize their binding sites on the surface of the bacterium by direct visualization using immuno-gold electron microscopy.

Technical Approach: The bacteriology of sputum specimens from cystic fibrosis patients would be monitored as part of routine clinical procedures. Upon identification of (non-mucoid) P. aeruginosa in the sputum, a serum specimen would be obtained from the patient. Routine bacteriological monitoring would be continued until mucoid organisms are recovered. Subsequent to this conversion to a mucoid phenotype, another serum specimen would be taken. Preliminary ELISA analysis of both sera would be performed using the mucoid and non-mucoid organisms isolated from the patient (autologous strains) as well as a heterologous strain. Specificity of the antibodies will be determined by inhibition studies with purified antigens such as LPS, MEP, and OMP. Localization by immuno-electron microscopy will be performed (at Mississippi State University) using a commercially obtained anti-human IgG conjugated with colloidal gold in an indirect (sandwich) technique.

Extraction and purification of antigens, ELISA and immuno-electron microscopy will be performed by standard, published techniques and have all been utilized previously by either the investigator at WBAMC or the investigator at Mississippi State University.

Progress: This protocol was submitted contingent on obtaining an NIH research grant. The grant request was not approved by NIH. Thus, this protocol is being terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/45 STATUS: Ongoing

TITLE: Comparison of Two Techniques of Estrogen Receptor Assay in Breast Cancer

START DATE: Nov 89 ESTIMATED COMPLETION DATE: Jun 91

PRINCIPAL INVESTIGATOR: CPT Ann R. Price

DEPARTMENT: Path FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Tu Huu Nguyen, MC; CPT Gordon Bell, MC; LTC Steven Arny, MC

KEY WORDS: Estrogen receptor assay, breast cancer

Study Objective: To confirm that the immunohistochemical assay is as reliable as the biochemical assay in determining estrogen receptor content in human breast cancer and to determine whether the immunohistochemical assay would be a more efficient method to perform at William Beaumont Army Medical Center than shipping specimens to another laboratory for biochemical assay.

Technical Approach: The study will consist of two phases which can be performed simultaneously.

Phase I: Phase I will be a retrospective evaluation of the estrogen receptor content of the paraffin embedded tissue blocks of the 50 most recently diagnosed breast cancers at WBAMC. The paraffin imbedded tissue will be pre-processed with the Trypsin and Dnase and the immunohistochemical assay will be performed by a single technician. The slides will then be scored in a qualitative and semiquantitative manner as outlined by Cudahy, et.al., and Pertshuk, et.al. Tumors found to contain more than 10% estimated positive cancer cells will be considered estrogen receptor positive. An ocular grid on the microscope will aid in accurately assessing tumor cellularity. The semiquanitative evaluation will be calculated by estimating the intensity of the nuclear staining as 1+, 2+, or 3+ of 200 cells and then multiplying 1, 2, or 3 by the percentage of cells estimated at each intensity. This figure will then be adjusted by multiplication with the previously estimated cellularity values less than 5 will be "zero-trace", 5-18 will be "low-intermediate", and greater than 18 will be "high". The biochemical assay results are expressed in fentomoles (FMOL) of receptor per microgram of DNA. Tumors with values less than 0.10 FMOL will be considered "negative", 0.10-0.30 FMOL will be "low-intermediate", and greater that 0.30 FMOL will be "positive". The results of the two techniques will be compared to determine concordance. All statistical analyses will be performed by means of the chi-squared test.

Phase II: Phase II will be a prospective, blinded evaluation of the estrogen receptor content of breast carcinomas by two methods - the immunohistochemical technique using the Abbot Kit (ERICA) and the biochemical assay done by PathLab. Each breast biopsy specimen is received in the fresh state in the Pathology Department at WBAMC. Standard operating procedure will be followed and a frozen section will be performed if the specimen is grossly suspect for cancer. Once a diagnosis of cancer is made histologically, additional frozen sections will be cut for immunohistochemical processing for evaluation of estrogen receptors. If the specimen contains sufficient tissue for biochemical assay (at least one cubic centimeter of tumor), a specimen will be sent to PathLab for evaluation as per usual procedure. The remaining specimen will be processed as usual into paraffin embedded blocks for histochemical viewing. Additional sections will again be made for immunohistochemical evaluation also. One histochemical technician will process the special staining as is standard operation in the WBAMC Pathology Department. The slides processed on frozen and paraffin embedded tissue will be read by all pathologists in the department, depending upon the rotational schedule assigned. The evaluators of the slides will be blinded to the results from the PathLab assay. The frozen and paraffin embedded immunohistochemical slides will be evaluated on different days, thus allowing different evaluators to be blinded to the previous result. The results will be reported as previously outlined

in phase I. results of the immunohistochemical assays on both fresh frozen and paraffin imbedded tissue will be compared to each other as well as to the results of the biochemical assay to determine concordance. The cost and time involved to obtain a report of the results will also be compared in order to determine the efficiency of the immunohistochemical assay. As stated previously, this study may eventually be expanded through screening of medical records to determine if the immunohistochemical assay is as effective in predicting the response to hormonal therapy as the biochemical assay since this is the ultimate goal of any estrogen receptor assay.

Progress: Initially, difficulty was encountered in obtaining needed supplies to begin the protocol. Then the kit requested was not kept refrigerated during shipping and, therefore was useless. The kit was reordered and on processing, the procedure did not work. Principal investigator is currently evaluating whether this is due to technique or another bad kit.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/59** **STATUS: Completed**

TITLE: Yale Children's Inventory-Normative Data

START DATE: Aug 89 **ESTIMATED COMPLETION DATE: Sep 90**

PRINCIPAL INVESTIGATOR: LTC A.W. Atkinson

DEPARTMENT: Ped **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Yale Children's Inventory

Study Objective: **To obtain a normative data for Yale Children's Inventory for Routine Use in the Developmental Pediatric Clinic.**

Technical Approach: **Subjects would be approximately 350 military dependent children between the ages of 5 to 18 years, presenting to School Physicals Clinic whose parent consents to completing the questionnaire. The 2 page, 33 item questionnaire will be given out with volunteer agreements as parents enter the clinic and collected as they exit the clinic. Data will be analyzed by descriptive statistics and by age and sex primarily. If total numbers allow, data will also be analyzed by ethnic grouping. A normative table will be developed for use in assessing the scores obtained on the Yale Children's Inventory for those patients referred to the Developmental Pediatrics Clinic for evaluation of school related problems.**

Progress: **The Yale Children's Inventory was named on 435 parent reports during two school physical days in August 1989. The data were analyzed by descriptive statistics methods to produce a normative chart for comparing individual reports during developmental evaluations. This chart describes percentiles for each of 13 behavioral/developmental areas of importance when assessing past school/social performance. The chart is currently being "desk-top published" by Mrs. LaMonde in DCI and will be used in the Developmental Pediatrics/EFMP Service and made available to all staff. This narrative data may be worthwhile for publication in a national journal.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 88/29** **STATUS: Ongoing**

TITLE: Ceftriaxone for Outpatient Management of Suspected Occult Bacteremia (Monitor: COL Popejoy)

START DATE: Apr 88 **ESTIMATED COMPLETION DATE: Sep 91**

PRINCIPAL INVESTIGATOR: CPT Valerie A. Bell

DEPARTMENT: Ped **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Suzanne Cuda, M.D., Robert Goldbach, M.C.

KEY WORDS: Ceftriaxone, occult bacteremia, pediatrics

Study Objective: To compare the effectiveness of ceftriaxone versus augmentin in the treatment of children with a possible blood infection.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Study is ongoing as per protocol. Principal investigator is waiting to enroll an adequate number of patients with bacteremia to be statistically significant. This is a multicentered study. There are currently 71 patients enrolled, 8 of which were bacteremic with streptococcus pneumoniae. The entire study has enrolled 464 patients with 52 positive blood cultures (based on last report). There are 14 participating hospitals in the study. Of these, WBAMC is second from the top in number of patients enrolled.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/91 STATUS: Ongoing

TITLE: Protocol for Determining the Prevalence of Drug Affected Babies in the Military Population

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Mar 89

PRINCIPAL INVESTIGATOR: CPT Valerie A. Bell

DEPARTMENT: Peds FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Howard Oaks, MC; CPT Anna Heisser, MC; CPT Bill McGrail, MC; MAJ Frank Galin, AN; CPT Gordon Bell, MC

KEY WORDS: Drugs, Babies, Military

Study Objective: To determine the prevalence of the use of illicit drugs during pregnancy in a military population.

Technical Approach: This study is to include all pregnant women who present in labor at WBAMC over a 4 month period or 400 patients, and the infants they deliver.

There will be 400 subjects. Two study groups; mothers and infants. A urine drug screen for marijuana, PCP, cocaine and heroin will be done on all subjects. The drug screen is an enzyme immunoassay. This is a test that is not normally done on these type patients. Urine will be collected from all mothers upon admission to labor and delivery, and frozen. All newborn's first void will be collected with a urine bag and frozen. Biweekly both sets of specimens will be sent to toxicology and assigned study identification numbers. The assay will then be performed.

Data will be collected weekly from the toxicology section of the laboratory and analyzed to determine the prevalence of positive drug screens in the mothers and the infants.

Progress: There have been no patients enrolled and no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/83** **STATUS: Terminated**

TITLE: Very Early Developmental Intervention - A Comparative Study

START DATE: Oct 89 **ESTIMATED COMPLETION DATE: Sep 90**

PRINCIPAL INVESTIGATOR: LTC Pilarita Cortez

DEPARTMENT: Peds **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: Shirley Cliff, LPT

KEY WORDS: Developmental intervention

Study Objective: To determine if very early developmental intervention programs for Neonatal Intensive Care Unit (NICU) graduates positively influence the child's developmental outcome at 15 mos. And, to determine if training parents to carry out a home intervention program is an effective, less expensive alternative to direct physical or occupational therapy (PT/OT).

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Protocol was terminated due to loss of key individuals assisting the principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/29 STATUS: Completed

TITLE: Serum Hormone Levels Over an Eight Week Period of Submaximal Exercise in Untrained Young Med (Basic Trainees)

START DATE: Apr 90 ESTIMATED COMPLETION DATE: Aug 90

PRINCIPAL INVESTIGATOR: CPT Suzanne E. Cuda

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Rita L. Svec, MAJ, MC

KEY WORDS: Serum hormone levels

Study Objective: To determine whether a prolonged period of submaximal exercise causes suppression of serum testosterone with corresponding increase in serum cortisol, and if this effect is more pronounced in individuals who lose weight.

Technical Approach: Basic trainees 21 and below with no known medical problems and taking no medications will be eligible to volunteer. Basic trainees placed in the Fitness Training Unit(FTU) will be a subpopulation. Each cycle ten men from the FTU and 40 men from a randomly selected platoon will be asked to participate. There will be five cycles for a total of 250 men. During the first week of training, or the first week in the FTU, a 15ml sample of blood will be drawn from each man. This will be repeated during the 7th week of Basic training, regardless of whether the subject was in the FTU or not. Free testosterone, cortisol, and Hemoglobin will be measured. Samples will be drawn between 0700-0900. In addition, a questionnaire regarding age, race, physical activity and family history will be filled out by each volunteer during the first blood draw. A select number of volunteers will be tape tested to assess body mass index. Also, we will review PT cards on each subject for assessment of physical conditioning at the end of each cycle. The study will be complete at the end of Jul 90 if started in Mar 90.

Data Analysis: Results from the FTU will be compared to the control group, and each subject will be compared to himself. Statistical correlation using Analysis of Covariance and Linear Regression will be used.

Progress: Two hundred subjects entered in study and four withdrew due to not finishing basic training. No adverse reactions to report. Principal investigator is currently processing and interpreting data. Conclusions are pending.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/69 STATUS: Completed

TITLE: Anabolic Steroid Use Among Adolescents

START DATE: Aug 89 ESTIMATED COMPLETION DATE: Dec 89

PRINCIPAL INVESTIGATOR: COL John D. Foley, MC Ret

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Walter K. Imai, LTC, MC

KEY WORDS: Anabolic steroids, Ergogenic aids

Study Objective: To discover adolescent knowledge of anabolic steroids, their sources of knowledge, their sources of knowledge, their personal beliefs of steroid effects and their own usage or thoughts of potential usage.

Technical Approach: An anonymous survey is proposed to inquire into adolescent beliefs about anabolic steroids, their sources of information, their personal usage and reasons for usage. Perceived need for more factual information about steroids will be asked as well as limited demographic data. A copy of the proposed questionnaire is attached.

Subjects included will be adolescent dependents over age 12 years who come to the WBAMC Adolescent Clinic for preparticipation sports physicals. Sample size will be as large as possible, ideally over 200 adolescents. The survey will begin in August and continued into the fall with completion by December at the latest. Subject participation in the project will terminate with completion of the questionnaire. Adolescents will be asked to complete the survey after their examination by the physician. They will be asked to fold it once and place it in a provided receptacle in each exam room. A "Fact Sheet" about anabolic steroids will be left for each subject to take home and read after completing the survey. This study will entail no risk to the patient and will provide educational benefit.

Progress: Three-hundred-ninety-six subjects were entered into the project. All data has been collected and submitted for statistical analysis. The principal investigator is presently in process of formulating conclusions based on data printouts prior to abstract formulation.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 90/06 **STATUS:** Ongoing

TITLE: Perceived Susceptibility to Harm During Adolescence

START DATE: Oct 89 **ESTIMATED COMPLETION DATE:** Dec 91

PRINCIPAL INVESTIGATOR: LTC Walter Imai

DEPARTMENT: Peds **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Lawrence D. Cohn, Ph.D.

KEY WORDS: Risk taking behavior

Study Objective: The aim of the proposed research is to determine if teenagers hold exaggerated beliefs about their ability to avoid injury and illness. Such unrealistic optimism has been found to characterize the judgments of adults, and the proposed research seeks to determine its developmental course during early-, middle-, and late-adolescence. Although established procedures exist for assessing unrealistic optimism, these procedures have not been employed with adolescents. The proposed research will fill this gap. In so doing, the research will test the frequent assertion that teenagers overestimate their own invincibility.

A second objective of the research is to determine if unrealistic optimism contributes to the initiation of adolescent substance use, reckless driving, and other health threatening activities. The association between risk-taking and unrealistic optimism will be examined in adolescents in the general population, as well as adolescents who have been hospitalized due to injuries arising from their own risk behaviors. The goal of this comparison is to determine if teenagers who are *unsuccessful at avoiding harm* (i.e., hospitalized teens) display the greatest degree of optimistic bias.

A third objective of the research is to determine if unrealistic optimism diminishes when adolescents evaluate dangers for which they are at unique risk. In particular, the study seeks to determine if Hispanic, Black, and White youth show diminished optimism when evaluating the health threats associated with their respective ethnic background (e.g., increased threat of diabetes among Hispanics).

The final objective of the research is to determine if two developmental variables, age and ego development, influence the magnitude of unrealistic optimism displayed by adolescents.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Awaiting funding for collaborative support functions and personnel.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/61 STATUS: Ongoing

TITLE: Neonate Emergency Procedure Training in the Rabbit and Guinea Pig Model

START DATE: Jul 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Steven W. Jesse

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Emergency procedures, Pediatric training

Study Objective: To train physicians who have not been previously trained in emergency management of neonates, but who will be called upon to perform this function in the Neonatal Intensive Care Unit. The rabbit model will simulate the full term human neonate; the guinea pig model will simulate the preterm human neonate.

ADDENDUM #1: Additionally, the rabbit model will be utilized to demonstrate the procedure for instituting and maintaining an infant on an Infrasonic's Infant Star high frequency ventilator.

Technical Approach: This training is designed for junior house staff who are inexperienced in the management and emergency care of sick infants. Demonstration by a staff neonatologist of the various procedures to be learned will be performed before any hands-on attempts by the interns and residents. The housestaff will then rotate through practical skill stations to perform the assigned tasks. The skill stations and animal lab allow the student to observe and practice to proficiency those life-saving skills necessary in the management and stabilization of the neonatal patient. The animal lab will be held on two separate days with a staff neonatologist and staff veterinarian present on both days.

ADDENDUM:

If HFV training is to be provided, then following the administration of anesthesia the staff veterinarian or neonatologist will place a carotid artery catheter as follows: A 3 cm ventral longitudinal skin incision will be made in the mid-cervical region. The 2 cm segment of carotid artery will be isolated by sharp and blunt surgical technique. A proximal and a distal 3-0 silk tie will be passed around the carotid artery. After the distal tie is ligated, a 20 ga catheter will be placed into the carotid artery and directed proximally. The proximal tie will then be secured and the catheter will be sutured to the skin. The skin incision will be closed and the patency of the catheter will be maintained with a heparin lock to enable periodic arterial blood collection for blood gas analysis.

High frequency ventilation: While anesthetized, an intubated rabbit will be placed on an Infrasonic's Infant Star HFV, initially on a conventional IMV mode. Monitoring will be done by chest auscultation and arterial blood gas analysis in the Biological Research facility. HFV will be instituted following the Infrasonic's lab outline. The animal will remain in this mode while the ventilation strategy is thoroughly explained and demonstrated to the participating personnel.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, analgesics, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Semiannual use of rabbits, guinea pigs to train pediatric housestaff in emergency life saving (and invasive) procedures has been expanded to include selected obstetrics housestaff and senior NICU nursing personnel. Training procedures have strictly followed existing protocol and has been well received by trainees. Will continue with annual review for all selected incoming personnel.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/65 STATUS: Ongoing

TITLE: Pediatric Intubation Training Utilizing the Feline Model

START DATE: Jul 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Steven W. Jesse

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Intubation, pediatric training

Study Objective: This training is designed to teach physicians and other health care professionals basic knowledge and endotracheal intubation skills required to resuscitate a neonate (newborn) or infant.

Technical Approach: The laboratory exercise described below will concentrate on developing the health professional's confidence in establishing an airway. Each new house officer will be required to intubate 2 cats employing a laryngoscope and endotracheal tube.

Animals will be anesthetized with ketamine HCL (22 mg/kg, given intramuscularly), with atropine (0.04 mg/kg, subcutaneously). Up to 2 additional half-doses (11 mg/kg) of ketamine may be given if needed. Pre-anesthesia with tranquilizer (Acepromazine, 0.2 mg/kg, subcutaneously) may be given to allow easier intubation for first-time trainees. Administration and monitoring of anesthesia will be directly supervised or performed by the attending veterinarian. The veterinarian will be present at all times to assist, modify, or terminate the procedure. Butorphanol tartrate (0.2 mg/kg SC every 8 hours) will be administered after the procedure to alleviate any possible pain.

At the discretion of the instructor, the stages and planes of anesthesia may be defined and assessed by the students. The animal will be placed in dorsal recumbency. Each trainee will visualize the larynx, noting the similarity of the feline larynx to that of the human infant; palpate the larynx externally; and perform visual intubation using the laryngoscope and endotracheal tube.

Two animals will be intubated by each first-time trainee in each laboratory session. Previously trained individuals will use one animal.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Semiannual use of felines to train pediatric housestaff in emergency life saving (and invasive) procedures has been expanded to include selected obstetrics housestaff and senior NICU nursing personnel. Felines are used solely for intubation training. Training procedures have strictly followed existing protocol and has been well received by trainees. Will continue with annual review for all selected incoming personnel.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/92 STATUS: Ongoing

TITLE: **The Effect of Breastfeeding on the Enteral Absorption of Human IgG *in the Neonatal Hartley Guinea* Pig**

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Nov 90

PRINCIPAL INVESTIGATOR: MAJ Steven W. Jesse

DEPARTMENT: Peds FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Breastfeeding, Enteral Absorption of Human IgG, Human IgG

Study Objectives: To assess the influence of breastfeeding on the enteral absorption of immunoglobulin in the neonatal guinea pig. And to assess whether such enterally absorbed immunoglobulin retains function in the form of opsonic activity against Type III Group B Streptococcus.

Technical Approach: Multiparous, untimed-pregnant Hartley guinea pigs will be obtained from a commercial source. Dams will be allowed to deliver pups vaginally at term. Pups will be randomly assigned to receive all nutrition via either suckling, (Group A), or via a commercially available animal formula, (Group B). Appropriate nutritional additives (vitamin C, etc.) will be added to the formula by the veterinary staff. Pups in each group will be gavaged shortly after birth with a single dose, 3g/kg(3cc/100g) 10% Human IgG obtained through a commercial pharmaceutical company. This unit dose has been demonstrated in past investigations to result in consistent enteral absorption of enough *Human IgG to be easily detected* by current methods of analysis.

Serum samples will be collected at 1, 2, 3, 7 and 14 days following the administration of the IgG. Sera will be separated and stored at -4 degrees C until analysis.

Positive controls will consist of values from sera obtained from animals from prior investigations who were injected with lg/kg 10% HIgG intraperitoneally. Negative controls will be derived from sera pooled from dams and stillbirths during this current investigation.

Lab analyses:

Serum total Human IgG: Competitive Inhibition
Enzyme Immunoassay (25)
IgG Opsonic Activity: Opsonophagocytic Assay (26)

Volume required:

30 uL sera (60 uL blood) per assay
2 assays/sample = 120 uL (0.12 ml)/sample
5 samples/animal over 14 days = 0.6ml total
Estimated blood volume of newborn guinea pig =
7cc. Blood requirements are thus minimal.

Addendum: 16 Mar 90 - Added Objective: to better define the timing of gut closure for the enteral absorption of human IgG in the neonatal guinea pig.

Method: Newborn Hartley guinea pig pups will be randomized to receive human IgG orally at the following times: birth, 24 hours of age or at 48 hours of age. Pups will also be randomized to be either exclusively breast or formula fed (as per the current protocol).

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: All animal procedures were completed on schedule and all animals have been euthanatized. Current status is awaiting lab time by principal investigator to analyze serum samples for human IgG. Estimated completion is November 1990; at which time an abstract will be prepared. No direct adverse reactions were noted; death of some pups occurred, primarily in those separated from their dam to be exclusively "bottle fed"; etiology of this is not directly known, but probably represents absence of intritional +/- trophic effects of colostrum in breast milk.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/89 STATUS: Ongoing

TITLE: Prevalence of Primary Measles Vaccine Failures in a Dependent Military Population and the Effect of MMR Revaccination on Antibody Response

START DATE: Nov 89 ESTIMATED COMPLETION DATE: Jan 91

PRINCIPAL INVESTIGATOR: COL Lou A. Popejoy

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Bruce C. Veit, Ph.D.; MAJ Robert R. Wittler, MC; COL Manuel Schydlower, MC; LTC Robert Martig, MS

KEY WORDS: Measles vaccine, MMR Revaccination, Antibody response

Study Objective:

a. Determine the prevalence of primary vaccine failures.

b. Assess risk factors in identifying primary vaccine failures.

c. Determine the antibody response of measles seropositive and measles seronegative subjects to revaccination with MMR.

Technical Approach: All patients 6-20 years of age who wish to receive revaccination with MMR are eligible for the study. These individuals, and if applicable, their guardians will receive a printed explanation of the study. Informed consent concerning the collection of demographic and vaccination data and the risk of venipuncture will be obtained.

A data sheet with the date, subject's name, SSN, phone number, date of birth, date of prior MMR vaccination(s), ethnicity, and gender will be completed. Prior to being revaccinated, a venipuncture will be performed and a 5-7 ml of blood will be collected. The subject will then receive his/her MMR. A second venipuncture will be performed 2-3 weeks following MMR revaccination and 5-7 ml of blood will be collected. Specific measles IgG, IgM, and IgA will be determined by ELISA on each serum specimen. Subjects who are seronegative 2-3 weeks following revaccination will be asked to submit another specimen for antibody determination 6-8 weeks following revaccination.

There will be 500-700 subjects included in this study, and the duration of the study will be 4 months.

Relationships between prevalence of seropositivity, age, age of initial vaccination, interval between vaccinations, and mean DOD will be evaluated using stratified risk ratios, regression analysis and ANOVA.

Progress: Study is complete except for serologic analysis. Once analysis is complete, abstract can be prepared. Two-hundred-eighty subjects had initial sera, and one-hundred subjects withdrew after choosing not to return for repeat sera. There were no adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/88 STATUS: Ongoing

TITLE: Incidence of Corynebacterium Hemolyticum Pharyngitis in an Adolescent Clinic

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Martinko

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Robert Wittler, MC

KEY WORDS: Corynebacterium Hemolyticum Pharyngitis, Adolescents

Study Objective: The incidence and seasonal variation of corynebacterium hemolyticum pharyngitis will be determined over a one year period in the Adolescent Clinic at WBAMC.

Technical Approach: All patients (13-20 years of age) presenting to the Adolescent Clinic at WBAMC with a complaint of "sore throat" who receive a throat culture will automatically be included in the study., It will be conducted over a one year period. A checklist of associated signs and symptoms will be used to standardize the information charted on each patient. No additional tests are needed. The throat culturette which would be obtained anyway will be sufficient. In the lab, the culturette will be plated out on the usual blood agar plates, but those from the Adolescent will be marked to be held for 72 hours. Group A beta hemolytic strep can be read at 24 hours (or less), but corynebacterium hemolyticum takes 48-72 hours for adequate growth. those plates with growth suspicious for Corynebacterium hemolyticum will be verified using sugar fermentation techniques.

Patients with a positive culture will be contacted and prescribed a ten day course of erythromycin. (The lab will do sensitivity tests periodically on cultures to determine alternate therapies.) The patients will also be requested to return after treatment for a follow-up throat culture to ascertain eradication of infection. Those who have not responded will be tested for co-incident infectious mononucleosis. Household contacts under age 22 will be requested to also have a throat culture (due to the high incidence of positive results in this population shown in Miller's study).

Those patients identified as having corynebacterium hemolyticum will benefit by treatment which should decrease duration of illness, recurrence of infection, and propagation to others in the household. Risks are minimal. No invasive tests are being done. Erythromycin (250mg four times a day for ten days) is among the safest of antibiotics. (Its main side effect is nausea, which can be minimized by taking it with food.)

Progress: Over 300 subjects have been entered into this study and no adverse reactions nor withdrawals are reported. The principal investigator (PI) has PCS'd and a new PI is being considered.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/43** **STATUS: Terminated**

TITLE: The Treatment of Children with Learning Disorders using Neuro-Linguistic Programming (NLP) Strategies

START DATE: **ESTIMATED COMPLETION DATE:**

PRINCIPAL INVESTIGATOR: Richard L. Riley MD

DEPARTMENT: Ped **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: LTC A.W. Atkinson, MC; Stephen L. Grouell, Ph.D.

KEY WORDS: Neuro-linguistic programming, Learning disorders

Study Objective: To determine whether Neuro-Linguistic Programming strategies, which can be taught to children and their parents, can help a certain subgroup of learning disordered children, overcome their handicap as compared to the use of more conventional strategies.

Technical Approach: A population of 20 children, ages 8 to 12, who have demonstrated delays of one year or more in reading and spelling will be selected from: (1) current Developmental Pediatrics files; (2) the Developmental Pediatrics referrals; and from referrals generated by a request to Ft Bliss elementary school principals.

These children: (1) will be of average or above intelligence; (2) will have demonstrated difficulty in at least 4 of the following characteristics as reported on a standardized school report questionnaire, the ANSER *system, routinely used in the* Developmental Pediatric's Clinic: comprehension of verbal instructions (1.27); retaining recent instructions (1.36); retaining yesterday's lesson (1.37); remembering classroom routines (1.40); following multi-step instructions (1.41); performing tasks in correct order (1.42); poor planning or organizing (2.8); poor listener (2.19); and (3) exhibit difficulty in at least 8 of the following characteristics as reported on the parent's ANSER system *questionnaire*: understanding spoken directions (7.7); remembering where to find things (7.11); remembering telephone numbers (7.12); telling the left from right (7.14) understanding what he/she reads (7.16); *figuring out new reading words* (7.18); spelling accurately (7.22); remembering assignments (7.27); knowing what and how to study (7.28); learning new words (7.29); memorizing things for school (7.30) difficulty staying with tasks when expected to do so (8.4); planning or organizing before doing things (8.8); learning a new skill and retaining the ability (8.11); listening (8.19).

Children selected for the study will be tested by the Slosson Oral Reading test (SORT) and the Boder Test of Reading and Spelling Patterns (Boder) to determine their baseline level of reading and spelling ability.

These children will then be distributed into a boy and girl group. Children will then be randomly selected from these groups and placed in a test group or a contrast group.

The test group will be evaluated by one investigator to determine the child's strategies for spelling and reading. The child will then be taught NLP strategies for spelling and reading. The child will then be taught NLP strategies for spelling and reading. A parent will be included in these sessions. The test group will be seen weekly for a total of three sessions. during each session, a group of 20 spelling words from the Boder will be given using NLP methods and a reading assignment will be given. These lists will begin with the list just below the child's reading level. At the next appointment, the misspelled words will be given again and new words from the next highest list will be added to total 20 words. The parent and child will be instructed to repeat the process two times during the ensuing week, and following each review with the parent, the child will be given the words orally and asked to spell them in writing, at home. These will be brought in at the following session to be used to compile the next list and to verify that the words were given twice during the week. One week following the last treatment session, the child will again be given the Boder and the SORT.

The contrast group will be evaluated by the 2nd investigator, but they will not be introduced to NLP techniques. This investigator will coordinate a typical "rote memory" approach to the spelling words, and will give a reading assignment, without any special strategies being suggested. The spelling list will be given during the session, with the parent present, and the parent and child will be asked to review the list twice during the week, followed by writing the words after the parent has given them orally. These lists will also progress in the same manner as the test group, and a week after the last treatment session, the child will again be given the Boder and SORT. The groups will then be switched with the contrast group becoming test group #2 and test group #1 becoming a control group. The NLP investigator and the contrast investigator will maintain their respective roles. However, the new contrast group will be allowed to continue to use NLP strategies. Each group will be given word lists beginning with the level of achievement indicated by their most recent test results. These lists will also progress in the same manner as before. The child will be asked to review the lists twice during the week and bring in the two test results the following week.

Test group #2 will be taught NLP strategies for spelling and reading as was test group #1. The word lists will progress as they did in the first phase, and written test results will be brought in the following week.

During the 8th session, the groups will again be given the Boder and SORT.

After a 3 month period, the Boder and SORT will again be administered as a long term follow-up measure to determine the success or failure of NLP as a learning strategy. This follow-up will include an interview of the children to determine to what degree they are using NLP strategies routinely.

Progress: Study could not be initiated in a timely manner since this required coordination with schools around the end of the school year. A modified version of this study may be submitted in FY 90-91.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/20 STATUS: Ongoing

TITLE: DHEA Trends in a Population of Health Males

START DATE: Jan 90 ESTIMATED COMPLETION DATE: Dec 90

PRINCIPAL INVESTIGATOR: MAJ Rita L. Svec

DEPARTMENT: Ped FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: LTC Michael A. Smutok, AMSC; LTC Molly Maguire, AMSC; CPT Suzanne Cuda, MC

KEY WORDS: DHEA trends

Study Objective: To define the following variables in a population of healthy males: DHEAS, Insulin/glucose ration, % body fat, cholesterol, and lipid profile in an effort to define subgroups to use for a secondary study of the predictors for sudden cardiac death.

Technical Approach: Exclusion Criteria: Actively attempting weight loss, taking antihypertensives or psychotropic medications.

Number of subjects: 150 - 40% are smokers.

Type of subjects: Men entering the SMA January 1990 class.

Laboratory procedures used: During the routine venipuncture for health risk appraisal, an extra 10cc tube will be drawn for our studies. Blood will be aliquotted and frozen for later assay for insulin, DHEAS and lipid profiles.

Duration: This is a single blood draw, which will be compared to the SMA health risk appraisal questionnaire, and % body fat measurement already being performed as part of the routine for entrance into the SMA.

Data analysis: Comparisons will be made between groups subdivided by age, comparing DHEA, % body fat, and insulin glucose ratios. We hope to be able to subdivide the groups into low risk, moderate risk and high risk, based on these preliminary data, and use these criteria in later studies. Statistical correlation using Analysis of Covariance, and Linear Regression Analysis will be used.

Risk to subject: 10 cc of blood loss, which is inconsequential. Participants are already having a venipuncture for health risk appraisal.

Potential benefit: Subjects will be informed if their data places them in a potentially higher risk group for sudden cardiac death.

Progress: Due to laboratory constraints, full lipid profiles and glucose have not been performed on all samples. This will be done as soon as the Sergeants Major Academy lab has completed its set-up. Thus far, the principal investigator has DHEA and insulin data and epidemiologic data. These are being evaluated to see whether trends can be found between smokers/non-smokers, high risk FH/low risk FH, and DHEA levels.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/52 STATUS: Ongoing

TITLE: The Impact of Special Pay on Army Physician Retention

START DATE: Jul 90 ESTIMATED COMPLETION DATE: Mar 91

PRINCIPAL INVESTIGATOR: CPT Kim C. Strunz

DEPARTMENT: Personnel FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Susan A. MacManus, Ph.D.

KEY WORDS: Special pay, Physician retention

Study Objective: Test the following hypotheses:

1. The larger the total amount of special pay a physician receives, the more likely he/she is to cite it as a major reason for remaining in the Army rather than going into private practice.

2. The greater the number of different types of special pay a physician receives, the more likely he/she is to cite special pay as a major reason for remaining in the Army rather than going into private practice.

3. Special pay is more likely to be cited as a major reason for remaining in the Army by physicians assigned to a medical facility in the U.S. than by physicians assigned to a medical facility in a foreign country.

Technical Approach: *The study will be based on survey data generated through a mail questionnaire with one follow-up contact of those not responding to the first request by the suspense date. The survey will be distributed to the universe of Army physicians assigned to WBAMC as of 27 June, 1990. A number of different types of statistical analytic techniques, ranging from simple percentage distributions to contingency table analysis, discriminant function analysis, and other relevant techniques, will be utilized. The variables are a mixture of nominal-, ordinal-, and interval-level measures, necessitating a wide range of analytic techniques.*

Progress: Questionnaires were first mailed on 17 and 18 July. A follow-up questionnaire was mailed on 6 August to non-respondents. A 78% response rate was achieved. Of the 154 physicians surveyed, 2 PCS'd prior to completing the questionnaire and 32 others were non-respondents. The cut off date has been reached, and all completed questionnaires are ready for data entry and "cleaning".

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/71 STATUS: Ongoing

TITLE: Emergency Procedures Laboratory (Goat)

START DATE: Jul 87 ESTIMATED COMPLETION DATE: Open-ended

PRINCIPAL INVESTIGATOR: CPT Michael Peterson

DEPARTMENT: DPCCM FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ C. Eaves, MAJ J. Aponte, MAJ M. Stolpe

KEY WORDS: Emergency procedures laboratory

Study Objective: To train accredited physicians who are not dealing with emergencies on a day-to-day basis, but may be called upon to perform this function. The goat model will simulate the human emergency patient.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Technical Approach: Cricothyroidotomy, venous cutdown, chest trauma management, and peritoneal lavage procedures will be accomplished in accordance with training manuals for each procedure.

Progress: No Emergency Procedures Labotory was held in FY 1990 and no animals were used.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/10 STATUS: Completed

TITLE: Early Detection of Alcohol-Related Cognitive Impairments in Young Alcoholics

START DATE: Mar 90 ESTIMATED COMPLETION DATE: Jun 90

PRINCIPAL INVESTIGATOR: MAJ E. Thatcher Beaty

DEPARTMENT: Psych FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: K.M. Lockney, MS

KEY WORDS: Alcohol, Neuropsychology

Study Objective: To determine if a group of young adults can be reliably separated into two groups, alcohol abusers/non abusers, based on their performance on a battery of sensitive neuropsychological tests.

Technical Approach: A short screening battery will be administered to patients admitted to the Residential Treatment Facility (RTF). Subjects selected for the study will be under the age of 35, and will be screened for a history of poly-substance abuse, learning disability, or loss of consciousness which required medical attention or treatment. Control subjects will be obtained from the Junior and Senior classes at the LPN (91C) course at William Beaumont Army Medical Center. They will be screened in a similar manner for alcohol or poly-substance abuse, learning disability, or history of head injury. They will be matched to the alcoholic group on the basis of age, education, and entry to service GT score.

The subjects will consist of two groups of 30 males each. The alcoholics will be assessed within four days of admission in an attempt to evaluate them while still experiencing the post-acute effects of alcohol withdrawal. It is assumed that this would be their "normal" condition prior to admission, as they fluctuate between states of intoxication and withdrawal. The control subjects will be assessed as they become available, during their off-duty time (so as to not interfere with their training).

Progress: There was no significant difference between groups on the following measures: Wonderlic, Attentional Capacity Test, 2 & 7 test, Grooved Pegboard, Visual Search Test. An analysis of variance found significant differences (two-tailed) on the following measures:

Card Sorting Task ($p = .001$)
Figural Fluency Unique Designs ($p = .001$)
Lanthony Color Discrimination Score ($p = .002$)
Verbal Concept Attainment Test ($p = .002$)
Austin Maze ($p = .008$)

By setting cutoff scores for each of these measures, and calculating a resulting Impairment Discrimination Index, 20 alcoholics (66%) and 29 controls (96%) in this sample were correctly classified. This battery of five tests requires less than one hour to administer, and shows promise as a practical measure of cognitive and perceptual impairments associated with alcohol abuse in younger adults. Further research is needed to cross-validate this battery on a different sample of alcoholics and controls. In addition, the performance of females, and subjects of different ages and levels of education needs to be evaluated.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 89/76 **STATUS:** Terminated

TITLE: Red Blood Cell Indices (MCV, MCH, MCHC) as Estimators of Alcohol and Smoking Status and Relationship to Nutritional Status

START DATE: Oct 89 **ESTIMATED COMPLETION DATE:** Aug 90

PRINCIPAL INVESTIGATOR: LTC Gerald M. Cross

DEPARTMENT: RTF **FACILITY:** William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Richard C. Keniston, M.D.; G. William Lucker, Ph.D.

KEY WORDS: RBC Indices, Alcohol and Smoking, Nutritional status

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Study Objective: Determine relative contribution of alcohol consumption, cigarette smoking, and iron, folate, vitamin B-12, and vitamin B6 to red blood cell indices.

Technical Approach: One-hundred-twenty consecutive RTF patients diagnosed as alcohol dependent will each have blood drawn for SMAC-22 (including iron), CBC, plasma PLP (vitamin B6), folate and vitamin B12 on their admission blood samples (36 cc blood, as opposed to 22 cc previously drawn). Stepwise regression analysis will be used to determine the relative contribution of each parameter to the red blood cell indices and also to determine which red blood cell index best estimates alcohol status, both initial and post-treatment. We will include last drink interval as a variable for defining alcohol status. Alcohol status will be defined two ways (drinks/month and yes/no to heavy drinker status) and cigarette smoking status will be defined three ways (cigarettes/day, by never smoked/ex-smoker/light smoker/heavy smoker status, and yes/no to current cigarette smoking).

Progress: The study was terminated due to the departure of principal investigator and no desire for its continuance by other RTF.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/61 STATUS: Terminated

TITLE: An Investigation of Substance Abuse and Aggressive Antisocial Behaviors Among Soldiers Indentified as Child and/or Spouse Abusers

START DATE: ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Elwood R. Hamlin

DEPARTMENT: Soc Wk FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: W. Lucker, Ph.D., D.J. Kruzich, Ph.D.

KEY WORDS: Substance Abuse and Family Violence

Study Objective: To determine the extent to which child and/or spouse abuse reflects a probability of involvement in substance abuse as well as other, unrelated, aggressive antisocial behaviors.

Technical Approach:

a. Subjects: Records of 100 soldiers residing in Army housing who have been identified and referred to Social Work Service, WBAMC for child or spouse abuse.

b. Controls: 100 age, race, rank and sex matched-controls who have NOT been identified as spouse or child abusers.

c. Design of Experiment: *Records of 50 soldiers identified for spouse abuse and 50 soldiers identified for* child abuse will be obtained from WBAMC SWS. The following information will, if available, be extracted from their records: age, race, rank, offense, number of domestic violence offenses, number of children, number of marriages, number of years in current marriage, number of months living in Ft. Bliss housing, any prior treatments for substance abuse, and any referrals to other agencies (e.g. RTF, MHCS, CCC). Names and SSN's of these soldiers will be compared with client lists as the DWI Program and Ft. Bliss C C C to determine whether they have sought or been referred for services at those agencies. Then their Ft. Bliss Military Police records will be examined and all arrests and convictions recorded for data processing. Finally, a matched control group of soldiers NOT apprehended for domestic violence will be obtained through the Ft. Bliss PAO. Their names and SSN's will be compared with DWI and CCC client lists and their MP records will be screened for any arrests. Statistics to be utilized are non-parametric frequency counts, including chi-squared, and log-linear analysis.

d. Forms: No special forms will be used.

e. Patient notification: This is a non-intrusive screening of existing records. No patient contact is required. To guarantee confidentiality once complete subject information has been compiled, each subject will be assigned a study case number (from 1 to 100) and all other identifying information will be destroyed. Original data will only be reviewed by one individual - the research associate who will gather the data. Computer data files will have no information that can be used to personally identify any individual.

Progress: This study was to be conducted in conjunction with the Residential Treatment Facility (RTF) consulting psychologist. Funding ceased for the consultant and consequently the protocol was not initiated.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 78/03 STATUS: Terminated

TITLE: National Intraocular Lens Implantation Study

START DATE: Oct 1977 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: LTC George Amegin

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Surgery/Ophthalmology

Study Objective: To participate in the study of clinical results of implantations of intraocular lens organized by the Intraocular Lens Manufacturer's Association in response to directives of the Ophthalmic Classification Panel, FDA.

Technical Approach: An intraocular lens is a prosthetic replacement for the eye's crystalline lens. It is placed in the eye at the time of cataract surgery, where it is fixated by a variety of means, with the intention that it remain permanently and correct the large refractive error remaining after conventional cataract surgery.

Progress: All investigational and core study lenses have been eliminated. The principal investigator does not plan to purchase lenses under this study in the future. Most lenses are now approved or pre-approved.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/02 STATUS: Ongoing

TITLE: Surgical Stapling Procedures Laboratory (In Dogs)

START DATE: Jun 1988 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Warren F. Bowland

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Stapling

Study Objective: To train accredited attending physicians and residents in the use of automatic suturing devices including their applications and limitations in a laboratory environment before they are called upon to use these instruments in human surgery.

Technical Approach:

I. Gastrointestinal Applications Procedures
   a. Splenectomy
   b. Hemigastrectomy w/Billroth II Reconstruction or Hemigastrectomy w/Billroth I Reconstruction
   c. Small Bowel Resection w/Functional End-to-End Anastomosis

II. Other Abdominal Applications
   a. Nephrectomy
   b. Large/Small bowel Resection w/End- to-End Anastomosis by Triangulation

III. Closure
   a. Fascial Closure Techniques
   b. Skin Closure Techniques

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: The animal lab has proven to be very important in improving technical skills for the general surgery residents. It has been utilized in two ways: (1) learn new procedures for junior residents; (2) practice specific operations by residents who have an identified weakness.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/59 STATUS: Ongoing

TITLE: Animal Model (Ovine) Laboratory, Advanced Trauma Life Support Course (ATLS)

START DATE: Jun 1988 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Warren F. Bowland

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Steve Carey, MC

KEY WORDS: Trauma

Study Objective: To train accredited physicians who are not dealing with major trauma on a day-to-day basis, but may be called upon to perform this function. The goat model will simulate human trauma.

Technical Approach: Animal Procedures -

1. Cricothyroidotomy
2. Venous Cutdown
3. Chest Trauma Management
   a. Needle decompression
   b. Tube thoracostomy
   c. Pericardiocentesis
4. Peritoneal Lavage

Training manuals will be used for each training procedure.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: The ATLS course is part of the training for physicians at WBAMC. This lab has been utilized in 6 ATLS classes and 3 medic (91B-C) courses in support of Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/42 STATUS: Ongoing

TITLE: Fiberoptic Endoscope Cholecystectomy in the Porcine Model

START DATE: Oct 90 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Warren Bowland

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL John F. McPhail III, MC; MAJ Stephen Carey, MC; CPT Anthony J. Canfield, MC; CPT Dennis Eastman, MC; CPT Steve Bodney, MC.

KEY WORDS: Fiberoptic Endoscope Cholecystectomy

Study Objective: To determine feasibility of conducting cholecystectomies at WBAMC with endoscopic equipment rather than a laparoscope. The experience gained by the professional staff will enable them to develop proficiently to perform such operations in human patients and to determine if additional equipment will be required for the conduct of this procedure.

Technical Approach: No surgical procedures will be conducted without the administration of general anesthesia. Anesthesia will be administered and monitored by Dr. O'Hair and animal care specialists in the Biological Research Service. The animals' food will be withheld for a period of 18 hours prior to surgery. The pigs' hair will be clipped from the abdomen. The animals will be placed in dorsal recumbency. After the skin is prepped, an insufflation needle will be inserted and the abdomen will be filled with CO_2. A trocar will be placed near the umbilicus for introduction of the fiberoptic video endoscope to enable monitoring of the procedure on a video screen. Two to three additional trocars will be placed for introduction of alligator forceps. The cystic duct and artery will be bluntly dissected free, double ligated or clipped, and transected. The gall bladder will be dissected free from the liver bed by sharp, blunt, and electrosurgical techniques. The laser may be used to control hemorrhage and to cut adventitial tissue. Once free from hepatic parenchyma, the gall bladder will be approximated to the body wall and drained with suction. After the bladder is decompressed, it will be pulled through one of the central trocar puncture sites.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This protocol teaches residents the techniques for laparoscopic cholecystectomy. Two cases have been done with no adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 89/12** **STATUS: Ongoing**

TITLE: Combat Trauma Surgery Using a Portable contact Nd-(YAG) Laser

START DATE: Feb 89 **ESTIMATED COMPLETION DATE: Indefinite**

PRINCIPAL INVESTIGATOR: CPT Anthony J. Canfield

DEPARTMENT: Surg **FACILITY: William Beaumont Army Medical Center**

ASSOCIATED INVESTIGATORS: COL John McPhail, MC; CPT Michael J. Snyder, MC; MAJ Steven Carey, MC

KEY WORDS: Surgery, Laser training

Study Objective: The main purpose of this laboratory will be to train physicians who are involved in the care of trauma victims, in the use of the Neodymium (Nd):YAG laser in surgery, and to familiarize them with the laser's applications in trauma management.

Technical Approach: Prior to the actual experiments, each participant in the protocol will be instructed in the safety precautions and the proper use of the (Nd)-YAG laser. Two animals will be used to demonstrate proper technique to the surgeons participating. After proper instruction, two surgeons and one to two assistants will perform the procedures on each animal, allowing each surgeon to be the primary surgeon on two operations. The actual operations will proceed as follows: Each animal will undergo one survival and one non-survival abdominal surgical procedure. After the animal is adequately anesthetized (see alleviation of pain and distress below), IV lines and EKG monitors will be placed.

A midline abdominal incision will be made and a brief exploration of the abdomen will be performed. A segment of the liver will then be injured with a combination of blunt and sharp trauma so as to cause injury deep into the parenchyma of the tissue. At this point, the (Nd)-YAG laser will be used to obtain hemostasis via a combination of resection and coagulation techniques. After appropriate repair of the liver, similar injuries to the pancreas, spleen, kidney, and intestines will be produced. Each injury will be repaired using the (Nd)-YAG Laser. No more than 50% of the liver parenchyma, or the parenchyma of the other abdominal organs will be injured during the operation. After appropriate hemostasis is obtained, the abdomen will be closed with a standard 3 layer closure, and the animal will be allowed to recover from general anesthesia. The animals will be managed as described below in the post operative care plan.

Each animal will be allowed to recover 1-2 weeks from the initial surgery prior to the second operation. At this surgery the abdomen will be entered in similar fashion and explored. The healing of the liver, pancreas, spleen, kidney, and intestinal repair sites will be assessed by the operating team for the following items: 1 Hemostasis, 2 tissue necrosis, 3 and evidence of any injury to surrounding organs and tissue. After evaluation of the intra-abdominal healing, a similar procedure will be performed on other segments of the above named organs, as described above, and the repair will be made using the (Nd)-YAG laser. At the conclusion of the surgery the animal will then be euthanatized according to the protocol listed below. At no time during the operation or the recovery time will the animal be allowed to suffer, and if appropriate alleviation of pain can not be achieved, the animal will be euthanatized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This is a training protocol that has been used to train laser techniques and safety to surgeons. This has been useful to refine laser techniques prior to their use in the OR. Three animals were utilized in 1990.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/31 STATUS: Ongoing

TITLE: Combat Trauma surgery Using a Portable contact Nd-(YAG) Laser in the Porcine and Ovine Models

START DATE: Apr 89 ESTIMATED COMPLETION DATE: Feb 91

PRINCIPAL INVESTIGATOR: CPT Anthony J. Canfield

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL John F. McPhail, III, MC

KEY WORDS: Surgery, Laser visceral

Study Objective: Compare the use of the Nd-(YAG) to conventional surgical techniques, with respect to blood loss and operative time. Actually test this laser in a field environment using an animal model in a F.A.S.T. unit with a wartime casualty scenario. Determine if advanced surgical techniques using a new portable contact Nd-(YAG) laser can be realistically and effectively used in a field surgical unit.

Technical Approach:

1. Phase I: Comparison of ND:YAG Laser Trauma Surgery Repair to Conventional Repair Techniques.

(a) This study will be comprised of two animal groups of ten swine each: GROUP A- Solid visceral trauma repaired with the ND:YAG laser; GROUP B- Solid visceral trauma repaired by conventional means. The following parameters will be measured immediately before and after the initial surgery, prior to the evaluation by exploratory laparotomy, and at other times as clinically indicated: Complete blood counts, chemistries (SMA 22), body weight. During the surgical procedures, physiological parameters (heart rate, arterial pressure, and body temperature) will be measured at 15 minute intervals. All data will be utilized for chronological comparisons to determine immediate post operative blood loss and to follow changes from baseline during the recovery period.

(b) Surgeries will be conducted in the operating room of building 7776 and observed in the recovery room for 24 hours prior to returning to the routine housing. After an appropriate level of anesthesia is reached, all animals will be instrumented with a femoral arterial pressure line, an electrocardiogram, and a body temperature probe. A left paramedian incision will be made and a standardized traumatic lesion will be made in the liver, spleen and left kidney. This will be accomplished under laparoscopic visualization with a fabricated instrument which will produce both sharp and blunt visceral trauma (see figure 1). This will ensure uniformity of the injuries to each organ, so that the surgical repair of the injuries can be objectively compared. After the injuries are created, the left paramedian incision will be closed. The repair of the injuries will begin after 15 minutes have elapsed from the wounding of the first organ, and a stopwatch will be started to measure the time from the midline abdominal incision to the completion of the 3 layer closure.

(c) Animals will be selected for either laser or conventional repair at random. The procedures will also be completed in blocks such that the procedures are completed in one animal from each group before continuing to the next block of experimental animals. The injuries in each animal will be identical, regardless of the group to which it will be assigned. A staff surgeon and a resident surgeon will comprise the surgical team, and this team will perform all the procedures in both Group A and Group B. This will eliminate the variability from surgeon to surgeon, and allow assessment of improved skill with experience. The surgeons that will be assigned to this surgical team are Dr. John F. McPhail, Chief, Department of Surgery, Dr. Stephen Carey, Chief of Trauma Surgery, and Dr. Anthony J. Canfield, Surgical Resident.

(d) Two weeks following the initial surgery the animals will be re-explored to assess healing. Gross examination of the organs and surrounding tissues will be made and tissue from each repair site will be excised and submitted for histopathological examination. Statistical analysis of the data obtained will be performed to determine the quality and speed of both Laser and Conventional repair techniques.

2. Phase II- Field Testing Exercise- The field exercises (FTX) will be conducted in early September. It is anticipated that the FTX will be conducted over a two day period and will require approximately 8 sheep per day. A new group of participants will attend the exercise each day in order to maintain adequately staffed duty positions. Animals will be anesthetized as stated below and surgically traumatized prior to the exercise. The physicians will be required to triage patients and conduct emergency care procedures taught in Advance Trauma Life Support Courses. In addition they will also utilize the laser unit to verify effectiveness compared to conventional means. All animals will be euthanatized as stated below following the surgical procedures.

ADDENDUM: Prior to induction of surgical injury to the liver, spleen, and kidney, heparin 50 U/kg will be infused intravenously. This degree of heparinization will produce more severe hemorrhage for both the laser and the conventional repair groups.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Several animals were removed due to inadequate data collection; one animal was removed due to technical difficulty with the equipment (the laser was not functioning properly).

The field portion of this study has been completed. The laboratory portion is still underway. Delays have been due to scheduling problems due to the increased ATLS training for medics being deployed. The results, so far, are promising and in the next several months, completion of the project should be accomplished.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/32 STATUS: Terminated

TITLE: Intestinal Surgery Evaluation with the Neodymium (Nd): YAG Laser in the Rabbit

START DATE: ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: CPT Anthony J. Canfield

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL John F. McPhail, III, MC

KEY WORDS: Surgery, Bowel, Laser, Anastomosis

Study Objective: Demonstrate the ability to weld an end to end intestinal anastomosis utilizing a ND:YAG laser and an absorbable stint.

Technical Approach: Four rabbits will be used initially to evaluate the procedure and determine if it is a feasible project. The small bowel will be transected in four rabbits. The bowel of two rabbits will be anastomosed with the laser technology described above and the other two by conventional suturing techniques. Two rabbits will be assigned to each group to allow evaluation of the surgical sites on days 4 and 10 post surgical. If there is a trend demonstrated that the laser anastomosis site is equal to or stronger than the sutured site, then a full study will be considered.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This was a pilot protocol and is now not necessary. No animals were used in this study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/41 STATUS: Ongoing

TITLE: Intestinal Anastomosis with an Interpositional Absorbable Stent and a Neodymium (Nd): YAG Laser in the Rabbit Model

START DATE: Indefinite ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: CPT Anthony J. Canfield

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: John F. McPhail, COL, MC; Stephen Carey, MAJ, MC; Ann Price, CPT, MC

KEY WORDS: Laser, Intestinal anastomosis

Study Objective:

1. Demonstrate the ability to weld an end-to-end intestinal anastomosis utilizing a ND:YAG laser and an absorbable stent.

2. Test the strength of the intestinal anastomosis after different periods of healing.

3. Evaluate the long term healing of the intestinal anastomosis.

Technical Approach:

Initial Phase: Four rabbits will be used initially to evaluate the procedure and refine the technique. The small bowel will be transected in two locations in each of the four rabbits. One of the anastomosis will be performed with the laser technology described above and the other by conventional suturing techniques. This will This will provide a laser and conventional anastomosis in each animal for easy comparison. Two rabbits will be assigned to each group to allow evaluation of the surgical sites on days 4 and 10 post surgical. Gross appearance will be recorded and bursting strength will be measured with a standard manometer. Techniques will be assessed and, if necessary, minor modifications to the procedures will be made prior to the start of the main phase.

Main Phase: Sixty rabbits will be randomly assigned to one of four groups of 15 rabbits each:

Group 1 will receive a laser anastomosis and a conventional anastomosis at 15 and 30 cm from the ligament of treitz. They will be recovered for 15 days post-anastomosis. At this time, ten of the rabbits will be re-explored surgically and the anastomoses will be photographed, evaluated for evidence of leakage, and then tested for bursting strength. These animals will then be euthanatized as outlined below. The other five animals from this group will be euthanitized and necropsied.

Group 2 will receive anastomoses in the identical manner to group 1, but will be re-explored or necropsied at 30 days post-anastomosis. The same manner of evaluation will be used as for group 1.

Group 3 will receive anastomoses in the identical manner to group 1, but will be re-explored or necropsied at 60 days post-anastomosis. Evaluation will be the same as for groups 1 and 2.

Group 4 will receive anastomoses in the identical manner to group 1, but will be re-explored or necropsied at 60 days post-anastomosis. Evaluation will be the same as for groups 1 and 2 and 3.

At no time during the operation or the recovery time will the animal be allowed to suffer, and if appropriate alleviation of pain can not be achieved, the animal will be euthanatized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This protocol has been approved by WBAMC, HSC and MRDC. Funding is pending budget appropriations for fiscal year 1991. After the funds are available and the equipment is purchased, we will begin the actual work on the project.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/26 STATUS: Ongoing

TITLE: Artificial Substitutes for the Urinary Bladder in the Porcine Model

START DATE: May 90 ESTIMATED COMPLETION DATE: Oct 92

PRINCIPAL INVESTIGATOR: COL Fernando Diaz-Ball

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL Leonard Maldonado, MC; Chief Resident, General Surgery

KEY WORDS: Bladder Substitute, Continent Urinary Diversion

Study Objective: Our objective is to provide training in a variety of techniques previously described in the literature for fashioning a bladder substitute from autologous bowel. Our experience with this will enable us to perform these operations in our patient population. The ongoing nature of the protocol is necessary to maintain technical proficiency and add refinements.

Technical Approach: NOTE: In studies requiring surgery, no surgical procedures will be conducted without the administration of general anesthesia. Anesthesia will be administered and monitored by veterinary staff assigned at Biological Research Service.

The Urology clinic Attending Staff shall devote one or two days each month to performing previously agreed upon continent urinary reservoir procedures. These shall include eg. the Mainz Pouch, the Koch Pouch, and the Indiana Reservoir. (1,2,3)

The common denominator of the various procedures is that autologous bowel is fashioned into a urinary reservoir out of continuity from the fecal stream. This reservoir is then anastomosed to the urethra or to a continent catheterizable stoma.

The proposed model is the porcine. At this time within the training protocol we have elected to euthanatize the animals at the end of the surgical procedure prior to recovery from anesthesia. In the future we may choose to request an amendment allowing us to do survival studies as long as animal suffering can be prevented.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Status in progress; starting date was May 1990 and have performed only one operation at this time (due to key personnel participating in Operation Desert Shield), but the outlook is 1-2 operations a month during the rest of the fiscal year. General Surgery Residents will have the opportunity to perform this type of surgery with the principal investigator and associate investigators. This is in preparation for the performance of this procedure in humans.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/07 STATUS: Terminated

TITLE: The Use of Intraoperative Ultrasound During Cholecystectomy

START DATE: Jan 89 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: CPT Dennis P. Eastman

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: John McPhail, Colonel, MC

KEY WORDS: Intraoperative ultrasound

Study Objective: Comparison of intra-operative ultrasound vs. cholangiogram in the evaluation of common bile duct abnormalities during cholecystectomy. The study will be an attempt to show that ultrasound is as effective as and can replace intraoperative cholangiogram (IOC) during cholecystectomy. It will also afford the General Surgery residents and staff the opportunity to gain facility in the use of intraoperative ultrasound.

Technical Approach:

a. Experimental design - 2 phase study

(1) Group 1 - Ultrasound vs. IOC

(a) During cholecystectomy prior to IOC, an intraoperative ultrasound of the CBC will be performed and interpreted by the investigator. Results of the ultrasound will then be compared to the IOC. Variables measured will be: size of the CBC, and presence of CBD stones. Estimated time for completion of the ultrasound is 10 minutes. By videotaping the ultrasound in each case a permanent record of the exam will be made and can be compared to the IOC by an independent observer, this data can be compared to the data obtained by the investigator and determine if investigator bias exists.

(b) The number of cholecystectomies in each group (normal/abnormal) will be at least 10.

(c) If no significant difference is noted between modalities in phase I, then phase II will be undertaken.

(2) Group 2 - Ultrasound vs IOC taking into account operator variability.

This phase will be conducted the same as phase I, except the ultrasound will be performed by the surgeon. The objective of this phase is to determine the effect of interoperator variability on ultrasound results and to determine if ultrasound has a wide applicability during cholecystectomy.

Progress: This study was terminated due to the inability to use present equipment to obtain adequate intraoperative study. No funds were available to obtain necessary new equipment via Med Case.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/70 STATUS: Ongoing

TITLE: Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model

START DATE: Nov 90 ESTIMATED COMPLETION DATE: Nov 91

PRINCIPAL INVESTIGATOR: MAJ Frederick T. Garner

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Anthony J. Canfield, MC; COL Miller F. Rhodes, MC; LTC Troy Reyna, MC

KEY WORDS: Tracheal reconstruction, Tracheal prosthesis

Study Objective: To identify a tracheal prosthesis material and surgical technique which may be suitable for reconstruction of the human trachea.

Technical Approach: This study will be conducted in two phases. Phase I will be to determine the maximum graft length allowing successful tracheal reconstruction; Phase II will be designed to determine the minimum interval for subcutaneous implantation required to have successful tracheal reconstruction.

In both Phase I and II the grafts will be implanted in two stages. The first stage will consist of implantation of the Gore-Tex prosthesis in the subcutaneous tissue with a silastic stent to keep the lumen patient and induce fibrous capsule formation. The animals will then be recovered from anesthesia and monitored for a prescribed period of time. The second stage will consist of harvesting the graft, after an appropriate amount of time is allowed for ingrowth of fibrous tissue, and replacing a segment of trachea with the graft. The animals will then be recovered and observed for a period of three weeks time while receiving prophylactic antibiotics.

Initially, two animals will be used to develop the technique and verify suitability of the rabbit as a model. The graft length for these animals will be 1 cm for each rabbit. The graft will remain in the subcutaneous pouch for three weeks prior to the tracheal reconstruction. Three weeks following the tracheal reconstruction, the rabbits will be evaluated to verify patency, infection rates, and degree of re-epithelization in the following manner: The animals will be anesthetized with spontaneous ventilation occurring. Utilizing telescopic bronchoscopy the lumen will be inspected for stenosis. The animal will be euthanatized and the graft cultured and histologically examined for infection and tissue morphology, respectively.

If the outcome of the pilot is successful and the model appears to be appropriate, then the study will proceed as follows:

Phase I

Rabbits will be divided into four groups of six rabbits each:
Group I - 3 cm. prothesis length
Group II - 4 cm. prothesis length
Group III- 5 cm. prothesis length
Group IV - 6 cm. prothesis length

The grafts in these animals will be evaluated at intervals of 3 days, 1 week,

3 weeks, 6 weeks, 9 weeks, and 12 weeks. The evaluation will consist of direct laryngoscopy and bronchoscopy with video recording of the procedure and computer analysis of the dynamic change in lumen size with inspiration and expiration.

Criteria for a failed graft will be 30% obstruction of the resting lumen size or a dynamic decrease to 30% of the lumen diameter with respiratory movement. Brush biopsies of the lumenal surface will be taken for bacterial culture and for microscopic evaluation of lumen epithelium.

All surgical and bronchoscopy procedures will be conducted only after animals are appropriately anesthetized as stated below. If unable to prevent animal pain or suffering following procedures, the respective rabbits will be euthanatized according to methods stated below. Any animals that die or are euthanatized prior to the termination of the experiment will be necropsied to determine the cause of death, if applicable, and to evaluate the graft sites grossly and microscopically.

With the exception of 8 long term animals, all remaining animals will be euthanatized 12 weeks following the tracheal reconstruction. The grafts will then be excised and examined grossly and microscopically. Two of the remaining animals from each group will be observed for a total of 6 months to determine if any long term complications occur.

Phase II

After determination of the maximum graft length allowing successful reconstruction, the interval between subcutaneous implantation and transfer of the graft for tracheal reconstruction will be evaluated. On this basis the minimal allowable time between subcutaneous transplantation of the Gore-Tex graft and the tracheal reconstruction can be determined. This will be the final phase of the study as planned. Four groups of six animals each will be required. The graft will be implanted as described in Phase I.

Grafts will be harvested as follows:
Group I - one week
Group II - two weeks
Group III- three weeks
Group IV - four weeks

Following harvesting of the PTFE graft and tracheal reconstruction, each group of animals will undergo evaluation as described in Phase I.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Principal investigators are still in the process of collecting all equipment necessary for this study. As soon as all equipment arrives, project will be initiated. Equipment is estimated to arrive by Nov 90.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/24 STATUS: Ongoing

TITLE: True Negative Rate of Mammography as Confirmed by Biopsy

START DATE: Jun 90 ESTIMATED COMPLETION DATE: Jun 91

PRINCIPAL INVESTIGATOR: CPT John Haeberlin

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL John F. McPhail, III, MC; MAJ Stephen Carey, MC; CPT Anthony J. Canfield, LTC Henry Butler, MC

KEY WORDS: True negative mammography

Study Objective: Check how many nonpalpable breast lesions, thought to be benign by mammography, are actually benign pathologically.

Technical Approach: Inclusion criteria for subjects are: (1) nonpalpable breast lesion seen by mammography, (2) no calcifications, (3) lobulated lesion, or (4) lesions with a less-than-25% indistinct border.

Preliminary data will be reviewed after 100 patients admitted to the study group. There will be only one study group. Any patient that has a mammogram which fulfills the admission criteria and is 18 years of age or older will be offered a biopsy as part of the study. Dr. Woisard will be the screening physician deciding admission into the study based on his mammographic reading.

Patients with coagulopathies will have necessary clotting, to include all or part of the following: P.T., PTT, CBC, thrombin time and/or bleeding time, studies besides being counseled on additional risks of the biopsy.

A subjects participation will be terminated either when a negative biopsy report and proper wound healing is achieved or after patient has proper surgical therapy for a cancerous lesion.

One year is the expected duration, and the success criteria are truly negative lesions supported by a negative biopsy. Failure criteria are cancerous biopsies.

The data will be collected and maintained by Dr. Haeberlin in both hard copy and computer disc. Mammographic data will be relayed by Dr. Woisard. Pathology reports will be relayed by Dr. Nguyen.

The risk to the subject will be minimized by proper pre-operative evaluation for risks to excisional biopsy, preparation for biopsy and close follow-up after biopsy checking wound healing progress. The risk to benefit ratio is believed to be low. The major risks of biopsy to include infection and bleeding are easily averted with good surgical technique. The benefits include finding new criteria for evaluating mammography as a screening tool. Instead of repeating mammography with suspected benign lesions at six month intervals, this study may provide further assurance that lesions are truly benign thus making repeat mammography unnecessary. This can only help lower the cost of medicine.

Progress: The principal investigator has not been able to begin this project due to insufficient time. He endeavors to initiate this study in the near future.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/40 STATUS: Ongoing

TITLE: Determination of Intrinsic Compartment Pressures in the Hand in Patients with Metacarpal Fractures (Medical Monitor: COL Scully)

START DATE: Apr 90 ESTIMATED COMPLETION DATE: Jun 91

PRINCIPAL INVESTIGATOR: CPT Eric Hirsch

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Larry Donovan, MC; MAJ Monte Watson, MS

KEY WORDS: Intrinsic compartment pressures, metacarpal

Study Objective:

1. Establish normal intrinsic hand compartment pressures.

2. Determine the intrinsic compartment pressures in skeletally mature patients sustaining metacarpal fractures.

3. Obtain data regarding elevated compartment pressures by measuring those pressures with a compartment pressure monitor.

4. Identify those groups of patients at risk for intrinsic compartment syndrome of the hand (e.g., associated crush injury, multiple fractures, etc.).

Technical Approach: The first 50 patients age 18 years and older, presenting to the Orthopaedic Surgery Service with metacarpal fractures (closed or open), or to the Trauma Unit, and who are skeletally mature, will be evaluated. Upon obtaining an informed consent, the intrinsic compartment pressure monitor. Also, the compartment affected hand will be determined with a portable compartment pressure monitor. Also, the compartment pressures of the uninvolved hand will be evaluated with this monitor. If there are metacarpal fractures in both hands, then pressures will be measured in both hands as well. All patients included in the study will have their blood pressure measured. All compartment pressures will be performed by the evaluating orthopaedic resident or attending. A portable compression monitor allows for accurate, easily reproducible measurements. Historical information to be recorded includes the patients name, identification number, address, and phone number. Also, the date, time, mechanism of injury, and other injuries found will be recorded. A presumptive diagnosis of compartment syndrome is made based upon pain with passive stretching; this is done by passively abducting and adducting the fingers with the MP joints in full extension and the PIP joints in flexion. Also, the thumb is stretched in palmar abduction and radial abduction. The little finger is examined by passive extension and adduction. All patients are to have a distal neurovascular exam, with particular attention to any loss of two point and pin prick sensation. Fasciotomy will be done for patients with a compartment syndrome. Patient follow up in the Orthopaedic Clinic and the Occupational Therapy Clinic will record the neurovascular status. Additionally, the range of motion of each digit at the MP, PIP, and DIP joints will be recorded for both hands. Muscle strength will be graded for finger abduction and adduction, thumb adduction and extension, and little finger MP flexion and abduction. Data will be analyzed to determine the risk of compartment syndrome with isolated fractures, multiple fractures, and crush injuries.

Progress: Twelve patients have been entered to date. No elevated pressures are yet documented. Efforts continue to enroll more subjects. Follow-up has not been as good as hoped, but the investigators feel good information can be gathered from measuring the subjects'pressures.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/28 STATUS: Terminated

TITLE: Anastomosis of Flap Veins to Bone: An Alternative for Microvascular Free Flaps in Tibial Wound Coverage (Pig Model)

START DATE: Mar 89 ESTIMATED COMPLETION DATE: Jun 90

PRINCIPAL INVESTIGATOR: CPT S.D. Jones

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Dr. Icochea, MC

KEY WORDS: Surgery Anastomosis, Tibial Wound Coverage

Study Objective: To determine the efficacy of anastomoses of free flap veins to bone via pre-drilled channels into the Haversian canals.

Technical Approach: The pig will be prepped and placed in dorsal recumbent position. An incision will be made over the medial aspects of the lower extremity bilaterally. The tibias will be exposed and holes drilled into the bone in two sites per tibia. The resting pressure of the Haversian canals will be measured. The holes will be approximately 2mm in diameter to correspond with the veins found in the flaps. Free myocutaneous flaps will then be taken from the calf of each lower extremity. These flaps will be designed with one artery and two veins per flap. The anastomoses of the veins will be to periosteum immediately adjacent to the predrilled holes.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Project is being terminated due to principal investigator's PCS. No other investigators available to continue this study.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/93 STATUS: Terminated

TITLE: TPA as Treatment for Experimental ARDS in the Porcine Model

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: CPT Joseph J. Kaplan

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Henry E. Butler, LTC, MC; Robert M. Hardaway, BG, MC (Ret); Charles H. Williams, Ph.D.; Michael J. Sborov, LTC, MC

KEY WORDS: TPA, ARDS

Study Objective: (1) To confirm the beneficial effect of tissue plasminogen activator (TPA) on experimental ARDS in a porcine model, as recently demonstrated by Hardaway and Williams. (2) To determine whether the beneficial effect of TPA is present when the drug is given after the onset of hypoxia, as would be the case with patients. (3) To determine the most beneficial time and method of TPA treatment. (4) To determine if correlation between phospholipid levels and the degree of severity of ARDS exists.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Project is terminated; principal investigator PCS'd.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 85/56 STATUS: Completed

TITLE: Porocoat Synatomic Knee Device (Depuy IND #G830152) (Monitor: COL Scully)

START DATE: Dec 85 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: CPT Steven Kulik

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Synatomic Knee Device

Study Objective: To demonstrate the safety and efficacy of the Porocoat Synatomic Knee System.

Technical Approach: Investigators will follow the manufacturer's protocol, which has been approved by the FDA. This protocol is extensive and is available in the Department of Clinical Investigation.

Progress: This project was completed. Results in abstract form were submitted to the International Society for the Knee and International Arthroscopy Association; accepted for presentation as a poster exhibit at their meeting in Toronto (15-17 May 91).

Conclusion: Twenty-nine patients were entered into this protocol. Results showed overall good scores in these patients. However, in comparison with cemented total knee arthroplasty, the results are not favorable. The investigators concluded that cemented total knee arthroplasty remains the procedure of choice in comparison to uncemented synatomic total knee arthroplasty.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/28 STATUS: Completed

TITLE: The Flexor Carpi Ulnaris: Anatomy

START DATE: Mar 89 ESTIMATED COMPLETION DATE: 1990

PRINCIPAL INVESTIGATOR: M.D. Umesh Raturi

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL Thomas J. Scully, MC, CPT Cameron S. Perkins, MC, MAJ Kevin C. O'Hair, COL William Burkhalter, MC (Retired)

KEY WORDS: Flexor carpi ulnaris

Study Objective: The feasibility of using this forearm muscle as a transposition flap to replace tissue loss due to blast injuries, high velocity wounds and side swipe injuries of the elbow is to be confirmed. The shattered elbow is now routinely aggressively fixed with orthopedic hardware to maximize early motion and rehabilitation. Coverage of this area remains a problem and usually needs microvascular free flap transfers.

Technical Approach: The study would be done on fresh cadaver (eg: autopsies with consent). The subject shou'd not have had anatomical injuries to the forearm to be included. A total of ten muscles would be needed. Commercially available radiopaque latex (microfil), would be injected into the brachial artery above the elbow. The muscle would then be removed from the forearm, weighted and measured (length,with markers placed). The specimen will be fixed in a receptacle and cooled overnight for latex consolidation. Twenty four hours later, the soft tissues would be progressively digested with an mild acid (Clorox or household bleach) and the arterial supply documented. Photographs and X-Rays will be taken. The nerve supply, though not essential would also be documented when the muscle is elevated.

Progress: Ten adult fresh cadaver forearms were dissected to study the flexor carpi ulnaris. Latex injections were done for delineation of the primary (dominant) vascular pedicle which enters the muscle an average of 4/06 cm distal to the anterior elbow joint line. The use of this muscle as a safe, reliable and expeditious pedicle flap for selected injuries with soft tissue loss in the elbow region is presented.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/64 STATUS: Ongoing

TITLE: Microvascular Anastomosis of the Rat Femoral Vessels

START DATE: Nov 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Franklin D. Richards

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS:

KEY WORDS: Microvascular Anastomosis

Study Objective: To gain proficiency in microvascular technique so that the technical proficiency gained can be applied to clinical conditions.

Technical Approach: Two survival femoral vessel anastomosis procedures and a third non-survival abdominal vessel surgical procedure will be conducted on each of 40 rats during the training year. At least one staff surgeon will supervise the resident training until they have become proficient. The first procedure (right femoral vessel anastomosis) will be conducted on day 0; the second (left femoral vessel anastomosis) on day 14; and the third (aortic artery anastomosis) will be conducted on day 28 for each respective rat. By the third training day, one of each of these procedures will be done every training period using 3 different rats. The rats will always be euthanatized immediately following completion of the abdominal procedure.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This study has been a huge success to date. Several microvascular procedures have been performed for the benefit of teaching residents. Microvascular surgery is learned in the laboratory and not on the patient. This protocol has been invaluable in teaching the Plastic Surgery residents microsurgery. Our Chief Resident is competent in microsurgery and our Junior Resident is learning rapidly. We need to continue the protocol for their benefit.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 86/42 STATUS: Completed

TITLE: Torsion as a Factor in Patency of Microvascular Anastomosis in a Rat Model

START DATE: Oct 88 ESTIMATED COMPLETION DATE: Dec 89

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Dr. Jose Monsivais

KEY WORDS: Microvascular anastomosis

Study Objective: To determine the effect of torsion on the patency rates of microsurgical venous grafts.

Technical Approach: The rat will be prepped with surgical scrub, sterile drapes applied and placed in a dorsal recumbent position. An incision will be made over the medial aspects of the lower extremities bilaterally. The femoral artery will be exposed from the femoral canal to the bifurcation of the profundus, as well as exposing numerous branches.

The femoral artery of the rat will be transected and a vein graft of equal diameter will be sutured into place. A series of five grafts using 20o, 40o, 60o, and 90o of torsion will be performed. The contralateral leg will be used as a control, grafting a vein with 0o torsion into the transected femoral artery.

The animals are to be kept alive and allowed to heal for approximately two weeks, at which time they will be explored, and the patency of the vascular grafts determined by direct visualization.

AMENDMENT #1: One hundred rats will be randomly selected and divided equally into 5 groups of 20 animals. The groups will be delineated as follows: 0° torsion (control); 90° torsion; 180° torsion; 270° torsion; and 360° torsion. The procedures will be completed in blocks completing one procedure from each group before repeating the same surgical prep. This will reduce differences between groups which could result due to improvements in surgical techniques during the progress of the research or differences in animal health or physiological status during the study. This method will also allow the investigator to statistically evaluate the data throughout the study to determine when adequate numbers of animals have been utilized, thus, possibly reducing the total number of animals required for the study.

AMENDMENT #2: Having determined that free flap survival is at its greatest risk at 90° and above, but does not progressively decrease after 90°, the question arises addressing the affects of free flap rotation within the implied safety margin below 90°. To confirm that there is also no significant affect on the patency of the vascular pedicle within the safety margin, 20 animals from the original experiment will be divided into 2 groups of 10 animals per group. The free flaps and pedicles will be based on the left femoral artery and vein. In one group, the free flaps will be rotated at 30°. The remaining group of 10 animals will have the free flaps rotated at 60°. Additional animals will not be required for this investigation. All other procedures will be in compliance with the original protocol.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: **Project was completed and published in Microsurgery 11:285-287, 1990. Conclusion: While it is not clear that this information is applicable to other sepcies, particular man, prudence would dictate that large vessel discrepancy (greater than 0.5:1 be avoided for end-to-end anastomosis with small vessels. Alternatives would include end-to-side anastomosis, alternative graft selection, or tailoring one or both vessels to result in a tapered, presumably less turbulent, interface. The potential for improvement in anastomotic patency with pharmacologic agents remains to be explored.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/80 STATUS: Terminated

TITLE: **The Role of the Flexor Carpi Radialis and its Retinaculum in the Stability of the Wrist**

START DATE: Undetermined ESTIMATED COMPLETION DATE: Undetermined

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ Joan Sullivan, MC

KEY WORDS: Wrist, stability

Study Objective: We hypothesize that the flexor carpi radialis and its retinaculum is the strongest stabilizer of the wrist on the radial side and as such should be included in the surgical repair of wrist injuries.

Technical Approach: Thirty fresh frozen adult cadaver wrists will be rapid loaded to ailure utilizing Instron biomechanical testing equipment. Each wrist will be prepared by stripping the soft tissue from the radius and ulna to within 4cm of the wrist. The intraosseous membrane and the flexor carpi radialis will be preserved. The radius and ulna will then be cemented into a steel pipe to preclude forearm rotation. The forearm assembly will be mounted vertically in the Instron with a force place across the pal%+'(+ t of the metacarpal head at an angle of leading to create wrist extension with ulnar deviation (equivalent to forces observed in actual clinical injuries). Proximal portion of the FCR will be fixed in one group by attaching it to the acrylic base and the tension should be 1.2 kilogram. Radiographs will be obtained of the wrists prior to and following loading. *Photographs and dissection of the wrists will document the type and extent of injury.* Three groups of 10 wrists each will be loaded to test the author's hypothesis:

Group I - Whole undissected cadaver wrists.

Group II - Wrists with the FCR and its retinaculum divided.

Group III - Wrists with radial side wrist ligaments divided (radial collateral ligament, radio-capitate ligament, radio-triquetral ligament), but with the FCP intact.

The force required to disrupt each wrist will be measured by the Instron. Then each disrupted wrist will be radiographed, photographed and a limited dissection performed to document extent and type of injury.

The second portion of the cadaver wrist study will retest surgically repaired wrists. Wrists from Groups I, II, and III will be equally divided (five from each group) and balanced for extent of injury, then repaired surgically. Repair Group A *will be corrected in the "Standard" manner, i.e., without requiring the FCR and* its retinaculum. Repair Group B will be surgically corrected to include the FCR and its retinaculum. Force loading will then be repeated in each repair group in the same manner as above.

Progress: Terminated because of delay in acquiring equipment and departure of personnel interested in the study

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 87/93 STATUS: Ongoing

TITLE: **Prevention of Stress Fractures Through Modification of Basic Combat Training Physical Training Activities Based on Biodynamics**

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Jul 91

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL Roy W. Tate, MAJ Bruce H. Jones, MC, Janice E. Morales, RN/BioMedical Engineer

KEY WORDS: Stress fracture, Bone

Study Objective: To compare the incidence and distribution, over the course of basic training, of the occurrence of stress fractures, stress reactions, and other musculoskeletal injuries, among Army Basic Combat Trainees participating in one of four variations in physical training. The variations to be studied are (1) progressive training, (2) cycle training with avoidance of running and jumping during the second week, (3) cyclic training with avoidance of running and jumping during the third week and (4) reduced total running mileage.

Specifically, the purpose of this study is to determine whether avoidance of running and marching in the second or third week of training will reduce the incidence of stress fractures, stress reactions of bone and musculoskeletal injuries in general, when compared to progressive training. If there is a decrease in injury is specific to the response to cyclic training or rather due to the decreased running miles.

Technical Approach: The study will be conducted at USATC, Fort Bliss, Texas and WBAMC. 1200 basic combat trainees, 12 companies (80-100 per company) with 3 companies per study group. (Progressive, rest week 2, rest week 3, decreased training mileage.) Treatment groups will be assigned by random lot drawing at the beginning of each basic training cycle. Trainees' medical history will be followed through the completion of their individual AIT assignments.

Each company will be studies in four phases.

(1) Phase 1: Preliminary measurements will be documented on each trainee from review of their physical entrance examination and their personal response to the questionnaires. Age, race, height, weight, flexibility of their feet, history of athletic activity, during the one month before start of basic training, history of past injury to lower limbs, and age of athletic shoes used prior to basic training will be obtained.

(2) Phase 2:

(a) Initial, intermediate, and final physical fitness test scores will be recorded on each trainee.

(b) The DI or Company commander will keep a daily training check list log to be picked up twice weekly at random times to insure logs are truly kept on a daily basis.

(c) All injuries and illnesses will be documented by screening of all medical records. All cases of lower limb pain will be treated according to the Stress Fracture Algorhythm.

(d) All discharges (medical, EPTS, ELS) and recycles will be documented.

(3) Phase 3: Advanced Individual Training - 2nd follow-up period.

(a) Record initial and final PT test performance.

(b) Have commanders document unit level physical training in AIT with check list log.

(c) Follow medical records of subjects after BT through end of AIT for injuries and illness.

(d) Document administrative outcomes.

(4) Phase 4: Analysis.

(a) Univariate - Company vs. company chi square test of: fitness within each company, contrast injury experience of different quartiles of performance using partitioned chi squares.

(b) Multivariate analysis

(1-1) MH-CHI SQ stratified on age, race, and flexibility of foot, or same variables in a logistic regression model.

(2-2) Survival analysis conditional on age, race flexibility.

(c) Debriefing Post HQ, TRADOC HQ, MRDC HQ.

Progress: All data collection on 1515 trainees is complete. Results of the study are being prepared for publication.

Summary of Findings: Preliminary statistical analysis of this data is complete and reveals:

(1) The incidence of stress fractures in trainees who run five days each week is 20/1000. The incidence of stress fractures in trainees who run three days each week and avoid running during the third week of training is 4/1000.

(2) Bone scans have a very high rate of false positive findings in the evaluation of stress fractures. Twenty-two percent (22%) of successful asymptomatic graduates of basic training have Grade III or Grade IV (severe) stress fractures by bone scans.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/17 STATUS: Completed

TITLE: **Free Vascularized Parathyroid Gland Transfer in Dogs**

START DATE: 1988 ESTIMATED COMPLETION DATE: Jul 90

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT Paul R. Cordts, MC; MAJ Albert J. Moreno, MC

KEY WORDS: Parathyroid, transplant

Study Objective: To determine if a total parathyroidectomy with vascularized autotransfer can be performed with consistently greater success than avascular autotransfer techniques.

Technical Approach: A total of 12 dogs are required. Each will be identified by ear tattoo and randomly selected for one of two equal sized groups (6 experimental, 6 controls). The experimental dogs will undergo a total thyroparathyroid excision with a unilateral microvascular thyroparathyroid autograft and the control animals will undergo a total thyroparathyroid excision with an avascular unilateral parathyroid autograft.

All dogs will have baseline serum, parathyroid hormone, calcium, phosphate levels drawn prior to surgery.

All experimental and control dogs will undergo the following evaluations postsurgically in order to assess parathyroid gland viability:

1. Proof of the function of the gland will be accomplished by technetium-Thallium parathyroid scan at 3 weeks.
2. Proof of the production of parathyroid hormone will be accomplished by measuring parathyroid hormone levels in the femoral vein proximal to the parathyroid graft.
3. Proof of the preservation of normal histology of the parathyroid gland will be accomplished by pathologic microscopic examination. The parathyroid tissue will be surgically removed following euthanasia.
4. Frequent postsurgical clinical examinations will be conducted in order to identify animals with symptoms of acute parathyroid insufficiency.

Experimental dogs only will undergo the following: Proof of the patency of the anastomosis will be accomplished by arteriogram at 3 weeks.

ADDENDUM - After the completion of several parathyroid transfer surgical procedures it has become a concern that a few animals may have undetected parathyroid tissue locate in abnormal locations.

In order to confirm that no aberrant parathyroid tissue exists, it is necessary to remove the transferred thyroid/parathyroid complex (microvascular group) and the transferred parathyroid tissue (avascular group) from each animal. Following removal the animals will subsequently be recovered until symptoms of hypoparathyroidism occur. The transferred parathyroid tissue is located just below the skin of the right medial thigh and will require only a minor surgical procedure for its removal. However, butorphanol tartrate (0.2mg/kg s.c.) will be administered postsurgically to alleviate any undue pain and/or distress. The tissue will then be submitted for histopathologic examination as stated in the original protocol. Removal of the grafted tissue will not be conducted until all other previously describe tests are completed. In addition, blood samples will be drawn just prior to the excision and at daily intervals afterward to determine PTH, Thyroid, Calcium, and Phosphorous levels.

In animals with no significant residual tissue early symptoms of muscle fasciculation or tremor is expected within 2-3 days. Frequent postsurgical clinical examinations will be conducted in order to identify animals with

parathyroid insufficiency. At the first symptoms of distress associated with the lack of parathyroid secretions, a blood sample will be drawn and the animal will be euthanatized by intravenous pentobarbital overdose (60 mg/kg).

After one week if the PTH and Calcium levels are not so low as to be life threatening then their levels will be re-evaluated at weekly intervals until they stabilized. If all endocrine and electrolyte levels return to within a normal range after 2-4 weeks the dogs will be survived and released back to the Biological Research Colony. The data from any animal which survive after the excision will have to be eliminated from the data set.

All other procedures will be conducted as stated in the original protocol.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Project was completed and presented at the American Society of Reconstructive Microsurgery (Sep 89, Seattle, WA) and American College of Surgeons, South Texas Chapter (Jan 90). Conclusion: Free parathyroid autografting produced unpredictable results with a high incidence of ' parathyroidism. Vascularized autografting is technically feasible and produced predictable outcomes. Fu e management of parathyroid pathology using this technique seems highly probable.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/44 STATUS: Ongoing

TITLE: Determination of Bone Manganese Levels in Patients with Chondromalacia Patella. (Monitor: COL Maldonado)

START DATE: May 88 ESTIMATED COMPLETION DATE: May 90

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ John Cook, MC; MAJ John Uhorchak

KEY WORDS: Chondromalacia, Manganese

Study Objective:

1. Identify and characterize by symptoms and physical findings the patient group with patellofemoral pain syndrome.
2. When performing diagnostic arthroscopy of patients with knee impairments, observe and record the character of the patellofemoral articular cartilage including objective measurement of cartilage softness.
3. Obtain 1 gram bone biopsy specimens from the distal femoral metaphysis at the time of arthroscopy and determine manganese content of bone mineral.
4. Perform multivariate analysis of data to observe possible correlations of bone manganese levels with severity of signs and symptoms of chondromalacia, cartilage appearance and measure cartilage softness.

Technical Approach: The study will be conducted at WBAMC and UTEP. Clinical evaluation will take place at WBAMC. The patients presenting to the Orthopaedic Clinic with knee disorders requiring arthroscopy or arthrotomy will be counseled and asked to volunteer for this study. If their informed consent is obtained they will be asked to provide information to complete the clinical questionnaire. The results of a comprehensive physical examination of the knees will also be recorded. At arthroscopy or arthrotomy the character of the articular cartilage will be noted and graded for severity of chondromalacia by the criteria of Hugston, et al. The indentation hardness of the cartilage will then be measured by a modification of the Brinell hardness measurement technique. This will be done with a locally fabricated instrument which can be autoclave sterilized. A biopsy specimen consisting of 1 gram of bone will be obtained from the distal femoral metaphysis using standard bone biopsy techniques. A portion of the specimen will be submitted for routine histology and the remainder will be analyzed for manganese content. The portion for manganese assay will be asked at 900 degrees centigrade, the ash weighed, dissolved in EDTA decalcifying solution, and analyzed with a Beckman plasma spectrophotometer at UTEP. All biopsy specimens sent to UTEP will be identified by code number only.

Progress: Records of the two subjects who had been entered in this study were being maintained by Dr. John Cook who was deployed to Saudi Arabia. The location of these records is presently unknown. Efforts are being made to contact Dr. Cook to obtain the records.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/25 STATUS: Ongoing

TITLE: Vascular Changes Associated with Stress Reaction of Bone in the Rat

START DATE: May 89 ESTIMATED COMPLETION DATE: May 90

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: MAJ John M. Uhorchak, MC

KEY WORDS: Stress reaction, bone

Study Objective: To determine the sequence and character of vascular changes which occur in living bone after it has been subjected to repeated physical stress.

Technical Approach: We will study the character and chronological sequence of vascular changes which occur in rat legs subjected to mechanical stress in the absence of confounding electrical shocks.

a. Thirty anesthetized rats will have their left leg cyclicly mechanically stressed using the techniques of Scully et.al. The tibias will be cyclicly strained to 0.5 mm by repeated application of a 3 point bending load. 10,000 cycles of strain will be applied to the left tibia of each rat at a rate of 10 Hz. The animals will then be recovered from anesthesia and maintained in standard laboratory cages with unrestricted activity, on a standard laboratory diet. Groups of 2 animals will be selected at random on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 12, 15, 18, 24 and 30 days after the initial strain loading.

b. On the date selected the animals will be anesthetized with Nembutal at a dose of 25mg/kg intravenously. The rats will then be heparinized and injected with Xylocaine to prevent vascular thrombosis and to ensure maximum vasodilation. The animals will then be given a lethal dose of Nembutal. After euthanasia the abdomens will be opened through a midline abdominal incision. The aorta and inferior vena cava will be transected and cannulated. Using techniques prescribed in the Microfil product literature the aorta and both lower extremities will be perfused with Microfil at a pressure of 150 mm of mercury. Perfusion will continue until the flow of the Microfil is returned via the inferior vena cava. At that point the animals will be refrigerated to allow overnight curing of the Microfil. As each animal has had only one leg stressed, the contralateral leg will serve as a control. Radiographs will be taken of both lower extremities to delineate the microvascular structure. Microfil is a radio-opaque material. After the radiographs are obtained, tissue clearing will be performed by the following technique: on the first day both tibias will be immersed in a 25% ethanol solution. On the second day 50% ethanol, on the third 75% ethanol, on the fourth day 95% ethanol and on the fifth day a new solution of absolute alcohol. On the sixth day the specimen will be immersed for 24 hours in methylsalicylate. If the tissue is not clear it will be returned to a 95 % ethanol solution and the fine cleaning procedure steps will be repeated. Photographs will then be taken of the vascular tree which will have been filled with colored Microfil. The tibias will then be imbedded and sectioned for standard histologic sectioning.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Fourteen rats have had their left tibias cyclicly stressed. The animals were recovered from anesthesia and observed until sacrifice according to protocol. All rats were then sacrificed and their vascular systems injected with Microfil. The lower extremities were then isolated. X-rays were obtained and all specimens were fixed in alcohol and cleared with methylsalicylate. The specimens are being maintained without further processing until techniques to imbed them in plastic are perfected. Efforts to date have shown excessive artifact due to shrinkage of the embedding medium.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/82 STATUS: Ongoing

TITLE: Ultrasound Screening for AAA in Asymptomatic Males Over Age 55

START DATE: Sep 89 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: CPT James B. Smith

DEPARTMENT: Surg FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: COL John F. McPhail III, MC; CPT Donna Corvette, MC; MAJ Cass Conaway, MC; LTC James C. Griffith, MC

KEY WORDS: AAA, Ultrasound Screening

Study Objective: To ascertain the incidence of AAA (Abdominal Aortic Aneurysm) in asymptomatic males over age 55 admitted to WBAMC for other reasons.

Technical Approach: All males age 55 and older admitted to Internal Medicine or Department of Surgery wards at WBAMC will be included in the study (approximately 180 per month) and will receive an abdominal aortic ultrasound examination. Patients with prior abdominal aortic surgery for aneurysm or occlusive disease will be excluded. All participants will be provided with a written explanation of the protocol. Patients with known AAA previously proven by ultrasound or CT Scan need not be submitted to repeat examination, if last previous study was within the past 6 months. Patients will be notified of the results of the ultrasound examination. Patients with positive findings for AAA will be referred to Vascular Surgery Service for Appropriate follow-up. A negative finding will result in completion of participation in the study. The study will run for six months.

Success/failure criteria: Aneurysm will be defined as enlargement of the anteroposterior or transverse aortic diameter more than 1.5 times the diameter of the proximal aorta, or greater than 4 centimeters in diameter.

Data Collection: Patients will be interviewed by a physician for pertinent history of smoking, HTN, CAD, ASPVD, hyperlipidemia, or family history of AAA (maternal versus paternal).

Ultrasound examination will be performed by the Department of Radiology using their standard real-time ultrasound equipment: Diasonics model DRF 400, and read by a staff radiologist.

Progress: Principal investigator has had difficulty with having subjects identified for enrollment. He is considering modifying the procedures for enrollment.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/52 STATUS: Ongoing

TITLE: Combat Trauma Life Support Procedure in the Sheep Model

START DATE: Oct 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: CW2 Rex Incledon

DEPARTMENT: FBT FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: CPT David Bradshaw, MC; CW3 Robert Martinez, PA; CW2 David Fisher, PA

KEY WORDS: Life support, combat trauma

Study Objective: To train Physicians Assistants and Line Medics who are not dealing with major trauma on a day-to-day basis, but may be called upon to perform this function in a combat environment. The sheep model will simulate human trauma.

Technical Approach:

ANIMAL PROCEDURES:

1. Cricothyroidotomy
2. *Venous* Cutdown
3. Intubation
4. Chest Trauma Management
   a. Needle decompression
   b. Tube thoracostomy

ATLS training manuals will be used for each training procedure.

Progress: A total of 80 field medics received training in emergency trauma life support techniques utilizing the sheep model. The training proved invaluable in that the medics gained a great deal of confidence and skill by directly participating in these laboratories.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/38 STATUS: Completed

TITLE: Oxygen Desaturation in Patients Using Nalbuphine or Midazolam for Sedation Under Spinal Anesthesia

START DATE: Mar 89 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: CPT Kimberly A. Beres

DEPARTMENT: Nursing FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: Steven P. Kelsch, MAJ, AN; Joel J. Schretenthaler, CPT, AN

KEY WORDS: Oxygen desaturation, Nalbuphine, Midazolam

Study Objective: To determine if sedation, using nalbuphine or midazolam, is associated with oxygen desaturation under spinal anesthesia.

Technical Approach: Fifty ASA I patients undergoing lower limb surgery under spinal anesthesia (to a dermatomal level of T-4 or below) who have given informed consent will be studies. This is a small sample and it will provide an answer to the question posed in this study, although it is too small to allow for generalized assumptions.

Each study patient will randomly be assigned to one of two study groups using the last digit of their sponsor's social security number. The odd numbers will be assigned to the nalbuphine group and the even numbers to the midazolam group.

All patients will be premedicated with diazepam, 0.15 mg/kg up to 10 mg. by mouth, one hour before induction of anesthesia. Upon arrival in the operating room, an intravenous cannula will be placed in the nondominant hand. Baseline values for heart rate, blood pressure, respiration, temperature, oxygen saturation, and time of premedication will be recorded. After the lumbar puncture, vital signs, oxygen saturation, and upper level of the spinal block (analgesia to pinprick) will be recorded at 5 minutes after the block and every 5 minutes up to 45 minutes or until the end of the case, which ever comes first. Sedation will begin 10 minutes after the xylocaine has been injected into the subarachnoid space. The dose will be recorded on the data collection sheet. Maximum dosages are as follows: nalbuphine, up to 0.4 mg/kg; midazolam, up to 0.1 mg/kg, with the optimal level of sedation determined by the investigators as a score of 2. This level of sedation will also be recorded. If the oxygen saturation falls below 5% of baseline for any given patient, the study will be terminated and oxygen, 3 liters via nasal cannula, will be administered and normal intraoperative monitoring will continue.

Progress: Patients were randomly selected (after informed consent was obtained) to either receive one or the other of the above IV sedatives and the numerical value of oxygen saturation as well as level of consciousness was recorded. Due to the small sample size, the results were analyzed as statistically insignificant (17 subjects).

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/18 STATUS: Completed

TITLE: **A Prospective Evaluation of Subcutaneous Epinephrine Combined with Nebulized Albuterol in the Initial Treatment of Acute Asthma in the Emergency Department**

START DATE: Mar 89 ESTIMATED COMPLETION DATE: Mar 90

PRINCIPAL INVESTIGATOR: MAJ Richard E. Collister

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: CPT Daniel J. Dire, MC

KEY WORDS: Asthma, Epinephrine, Albuterol

Study Objective: Firstly, to determine whether subcutaneous epinephrine adds significantly to bronchodilation obtained with a nebulized beta-agonist alone in the setting of an acute asthmatic exacerbation. Secondly, to determine any additional side affects of simultaneously administered subcutaneous epinephrine and nebulized albuterol.

Technical Approach: Patients aged 18 to 65 who present to the Emergency Department "with a history of asthma and clinical evidence of an acute exacerbation (dyspnea, diffuse wheezing, and a significantly reduced FEV_1) or those presenting with new-onset asthma will be considered for enrollment in this double-blinded study. Those with a history of albuterol allergy, cardiovascular disease, chronic steroid dependence, emphysema, chronic bronchitis, or cigarette smoking will be excluded. Pregnant women will also be ineligible. After a brief history is obtained and supportive (such as nasal oxygen) instituted, initial spirometry will be performed. The best FEV_1 of three attempts will be recorded as the pre-treatment baseline. Those with an initial FEV_1 in the 25% to 75% range of predicted values will be randomized (with their informed consent) into one of two treatment groups by alternating every other patient.

The first group (GROUP 1) will receive an initial treatment consisting of 0.01 mg/kg of subcutaneous 1:1000 epinephrine (maximum of 0.3 mg or 0.3 cc). The second group (GROUP 2) will receive 0.3 cc of sterile normal saline subcutaneously. Simultaneous with the injection, both groups will receive an aerosolized updraft of albuterol 2.5 mg in 2.5 cc of normal saline. Both treatment groups will receive additional doses of aerosolized albuterol at 20 minutes and 40 minutes after the initial doses, if clinically indicated. All patients will be placed on a cardiac monitor and have their vital signs taken every 15 minutes. Post-treatment spirometry will be performed 30 minutes and 60 minutes after the initial treatment.

Once post-treatment spirometry has been completed, the physician in attendance may use any and all therapeutic modalities he/she deems necessary, to include theophylline loading and intravenous corticosteroids. Since all study participants receive prompt bronchodilator therapy and since the study's design excludes those with severely impaired pulmonary function, the risk of participation should be minimal. The treating physician will be blinded to the treatment group. Only the ER nurse who gives the subcutaneous injection will know whether the patient received epinephrine or placebo. If a patient's clinical condition deteriorates, the physician will remove him/her from the study, the ER nurse will inform the physician what treatment group the patient was entered into (i.e., did the patient receive epinephrine or placebo), and maximum therapy will be initiated.

Data will be entered into a computer data base and statistical analysis will be based upon the following null hypothesis: the mean FEV_1 percent-improved observed in Group 1 is not significantly better than that observed in Group 2. The two-tailed t-test will be utilized to accept or reject the null hypothesis.

Progress: **The data collection has been completed and is currently being analyzed. A manuscript will be submitted for publication upon completion.**

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/74 STATUS: Ongoing

TITLE: **Effectiveness of Splinting for Carpal Tunnel Syndrome During Pregnancy**

START DATE: Nov 89 ESTIMATED COMPLETION DATE: Dec 91

PRINCIPAL INVESTIGATOR: CPT Robbie Courts

DEPARTMENT: OT FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS:

KEY WORDS: Carpal tunnel syndrome, pregnancy, splinting

Study Objective: To determine if volar wrist splints are effective in decreasing subjective and objective symptoms of carpal tunnel syndrome during pregnancy.

Technical Application: Use of survey form to assess subjective and objective symptoms of CTS during pregnancy, to be measured over a period of time: (1) initial referral, (2) one week after splinting, (3) additional follow-up if no improvement of symptoms after one week of splinting, (4) four weeks postpartum to see if symptoms are absent without splinting (indicating full recovery), (5) additional follow-up or referral to orthopedics PRN if symptoms persist postpartum.

Treatment includes patient education on carpal tunnel syndrome and importance of wrist positioning during sleep and activities, fabrication of thermoplastic volar wrist splint(s), measurements of grip and pinch strength, sensation (sharp/dull and two-point), range of motion (if not within normal limits), and documentation of subjective symptoms. Nerve conduction studies will not be ordered due to expense, uncomfortableness of the test, and expected short duration of the CTS symptoms during pregnancy.

The subjects included in the study will consist of all pregnant women referred to OT with symptoms consistent with CTS.

OT staff will collect data on a survey form using patient interview and standard methods of testing for grip, pinch, sensation, Tinnel's and Phalen's.

Progress: The expected number of subjects for the study is 100. At present, data collection has been completed on 19 subjects; 26 other subjects are in various stages of data collection. Twenty-five subjects have withdrawn from the study, primarily due to not completing follow-up appointments. It is questionable if symptoms have improved at such an extent that subjects are not interested in making the effort to return for the follow-ups, or what other factors may be involved. Phone call reminders have been started to increase compliance in this area.

Principal investigator has been working with personnel from TEXCOM on setting up a computer program for data collection and statistical comparison. Early data indicates a decrease in all subjective symptoms except swelling after one week of the splinting protocol, and an increase in bilateral grip and pinch strength. At one month post-partum, 90% of patients are symptom free (the remaining 10% are symptoms free by 10 weeks post-partum). Grip and pinch were still less than average (for age/sex) at one month post-partum.

Treatment will be the same for all subjects. The method of treatment used in the study (splinting and education) is the present standard of treatment. Since there is no alternate treatment method which is universally accepted as risk free during pregnancy other than "no treatment", a control group will not be used.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/02 STATUS: Ongoing

TITLE: A Comparison of the Stimson and Hennepin Techniques in the Reduction of Anterior Shoulder Dislocation (Monitor: MAJ R. Wilkerson)

START DATE: Nov 88 ESTIMATED COMPLETION DATE: Dec 90

PRINCIPAL INVESTIGATOR: CPT Robert G. Creath

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: Daniel J. Dire, CPT, MC

KEY WORDS: Shoulder dislocation

Study Objective: To determine if three are significant differences between the Hennepin and Stimson techniques of shoulder reduction in regards to the time required for reduction, subjective patient appraisal of discomfort during reduction, and post-reduction complications.

Technical Approach: All patients who present to the Emergency Department with suspected anterior shoulder dislocations will be evaluated for participation in this study. Patients who meet the following conditions or circumstances will be excluded from participation.

Pregnant patients
Patients allergic to neperidine or hydroxyzine
History of liver dysfunction
History of renal dysfunction
Head injury
Altered mental status
presence of pre-reduction fracture
Intoxication from drugs or alcohol
Prior administration of pain medication

All patients will be examined radiographically, with standard scapular AP and lateral views to examine for pre-reduction fractures and the type of dislocation. A strict neurovascular examination will then be performed. After the completion of the above, an initial injection of Meperidine, 1.5mg/kg and Hydroxyzine HCl, 8.5mg/kg will be given intramuscularly. The patient will then be allowed to relax for 30 minutes. At that time, the patient will be randomized, by the draw of random numbers, to one of two treatment groups.

Treatment Group 1: Patients within this treatment category will undergo attempted reduction of their dislocation by the technique previously described by Leidelmeyer and Mirick, commonly referred to as the *Hennepin maneuver. If the reduction* is not successful, two additional attempts may be made with or without added analgesia or muscle relaxers. If reduction is unsuccessful after repeated attempts, the Stimson technique will be attempted once. Immediate referral to the Orthopaedic Surgery Service will be made for those patients in whom reduction has not been achieved.

Treatment Group 2: Patients within this treatment category will undergo attempted reduction by the Stimson technique, as previously described. If unsuccessful after one attempt for 20 minutes, the Hennepin technique will be attempted once. Immediate referral to the Orthopaedic Surgery Service will be made for those patients in whom reduction has not been achieved.

All attempted reductions of dislocated shoulders will be performed by one of four physicians, who shall standardize their technique prior to the study. All are experienced in the above methods of reduction.

After the completion of attempted reduction, radiographic survey will be made using the scapular AP, lateral and axillary views.

After post-reduction radiographs are taken, the patients in both groups will undergo immobilization. All patients will be re-examined for neurovascular integrity. All patients will then be referred to the Orthopaedic Surgery Service, as usual, for follow-up care.

Patients who at any time during the study exhibit respiratory depression, hypotension, dystonic reactions, and/or significant discomfort will be withdrawn from the study and will be treated for these complications in the appropriate fashion.

Patients who exhibit a return to normal function, relief of pain, and a radiographically reduced glenohumeral joint will be deemed a success. Failure to meet the above criteria will be deemed a failure.

Data regarding the amount of analgesia, time required for reduction, subjective appraisal of the pain felt, and complications resulting from reduction will be collected for entry into a computer data base (see enclosed data form). This information will be analyzed by discriminant analysis or other method of multivariant analysis for statistical difference between the two groups and their inherent measurements. A t-test analysis will be used to ascertain matching between the groups in relation to age, sex, body build, time from injury to first attempt at reduction, and to completion of reduction.

Progress: Twenty-four patients have been entered into this study. No complications occurred, and there is no data analyzed to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/77 STATUS: Ongoing

TITLE: Use of Venous pH in the Initial Evaluation of Pediatric Patients with Diabetic Ketoacidosis

START DATE: Oct 88 ESTIMATED COMPLETION DATE: Oct 91

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS:

KEY WORDS: Venous pH, diabetic ketoacidosis

Study Objective: To determine the utility of venous pH to define the degree of acidosis in the initial evaluation of the pediatric patient with diabetic ketoacidosis.

Technical Approach: We will compare an arterial and venous pH sample in all patients who present in diabetic ketoacidosis to the emergency room at Darn Army Community Hospital over an 18 month period, or until a sufficient population size is reached (N = 100). Patients will be eligible for this study if they are between the ages of 1 and 18 years old, and have clinical and laboratory evidence consistent with ketoacidosis or who are known diabetics who have presented with similar symptoms of ketoacidosis in the past. A single (1.5cc) sample of arterial blood will be obtained from the radial artery of the patient by an emergency room staff member or by the investigators, as is the standard for defining acidosis in this setting. A single (1.5cc) sample of venous blood will also be obtained simultaneously with the other venous samples taken from the IV once intravenous access has been established. These two values will be compared and the results analyzed statistically. consent for the additional laboratory study will be obtained, although no additional sampling procedures will be necessary.

Demographic and laboratory data will be recorded on a database form initiated in the emergency room and subsequently entered into a computer for statistical analysis in collaboration with the department of Clinical Investigation at William Beaumont Army Medical Center.

Progress: Principal investigator PCS'd and MAJ Dire, Associate Investigator is taking over this study. Data is continuing to be collected. There is no progress to report.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/16 STATUS: Completed

TITLE: A Prospective Analysis of Demerol, Phenergan, and Thorazine Administration to Pediatric Emergency Department Patients (Monitor: CPT Bernard Smyle)

START DATE: May 89 ESTIMATED COMPLETION DATE: Dec 89

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: CPT Howell E. Davis, MC

KEY WORDS: Demerol, Phenergan, Thorazine

Study Objective: This study is being undertaken to prospectively identify specific measures of efficacy and determine the incidence of minor side effects for the use of Demerol, Phenergan, and Thorazine (DPT) in combination for a preselected group of pediatric emergency room (ER) patients. The study will demonstrate the benefits of using DPT in preselected patients in terms of patients time in the ER as well as how DPT can prevent some of the emotional trauma that frequently besets children and parents during ER care (i.e. suturing lacerations). We hope to demonstrate the enhanced means by which the health care provider can perform their work on the child while obtaining excellent results.

Technical Approach: Pediatric ER patients will be preselected upon their arrival to the ER based on a set criteria for entry into the study. By preselecting the patients according to a set criteria we can standardize our results and comment accurately on appropriate dosage, efficacy, side effects, and monitoring procedures pertaining to the study population. In order to complete the study a minimum of 200 participants will be selected pertaining to age, presenting complaint, history of chronic illness, initial vital signs, indications, and initial mental status with further assessment pertaining to dosage of DPT required, interval exams pertaining to vital signs and mental status, and complications both serious and minor. The dosage utilized for the DPT injections will be 2 mg/kg for Demerol with a maximum dose of 50 mg; 1 mg/kg of Phenergan with a maximum dose of 25 mg; and 1 mg/kg of Thorazine with a maximum dose of 25 mg, all to be given intramuscular.

Progress: Analysis of the efficacy of intramuscular (IM) meperidine, promethazine, and chlorpromazine (MPC) for various Emergency Department (ED) procedures in children has not been performed despite widespread use. By prospectively examining 63 ED patients, less than 16 years of age, receiving IM MPC, we determined the onset and duration of action, effectiveness of sedation and cooperation, and complications. Children were treated in a university hospital (N=47) or a community hospital (N=16) ED. Measurements of respiratory rate (RR), heart rate (HR), arterial systolic blood pressure (BP), oxygen saturation (OS), and Glasgow Coma Scale (GCS) were performed at baseline and at 30 minute intervals. Effectiveness was assessed by two, independent observers using separate visual analogue scales (VAS) for cooperation and sedation. Parents returned post-ED observations in 71% of cases. There were significant changes in RR (-2.5 ± .6 breaths/min;mean ± SD), HR (+4.5 ± .8 beats/min), OS (-0.7 ± .3%) and GCS (-2.5 ± .6) for 120 minutes after MPC (repeat measures ANOVA). Onset of sleep (27 ± 24 min), duration to sit upright ± (103 ± 87 min), total ED time (4.7 ± 2.4 hr), recovery time (5.5 ± 4.3 hr), eat time (11 ± 7.9 hr), and normal time 19 ± 15 hr) were acceptable. Agreement between observers VAS scores was very good (cooperation, r = 0.79 and effectiveness, r = 0.80, Pearson correlation coefficient). Mean VAS scores were > 5.0/10.4 in 72% of cases. We conclude that IM MPC is a safe and frequent and effective agent for ED use in children. Paper was submitted to Annals of Emer Med.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/87 STATUS: Ongoing

TITLE: A Prospective Evaluation of Topical Antibiotics in Preventing Infections in Uncomplicated Soft Tissue Laceration

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Dec 90

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: David A. Dwer, CPT, MC; Marco Copola, CPT, MC; Jerry Karr, CPT, MC; John J. Lorette, Jr., CPT, MC

KEY WORDS: Infections, Topical Antibiotics

Study Objective: To show whether there is a statistically significant difference in the infection rates among uncomplicated repaired lacerations that are dressed with topical Bacitracin, NeosporinR, SilvadeneR, or placebo.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: 408 patients have completed their participation in this study. Approximately 15 patients were entered and then excluded for failing to follow the protocol. No data has been analyzed yet. There have been no major complications.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/02** **STATUS: Ongoing**

TITLE: A Prospective, Multicenter, Clinical Trial Comparing Single Dose Intravenous Ceftriaxone and Oral Amoxicillin for the Prevention of Wound Infection in Cat Bites

START DATE: Sep 90 **ESTIMATED COMPLETION DATE: Sep 92**

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER **FACILITY: Darnall Army Community Hospital**

ASSOCIATED INVESTIGATORS:

KEY WORDS: Cat bite

Study Objective: To study the effectiveness of three antibiotic regimens (ceftriaxone alone, amoxicillin alone, and ceftriaxone plus amoxicillin) in preventing infection after a cat bite.

Technical Approach: All patients who present to the ER with a cat bite, and satisfy the criteria for entry into the study, will be invited to participate in the study as per the guidelines set out.

Those consenting to the study will be assigned to one of the three treatment groups based on a pre-determined schedule based on the date presentation to the ER. The study is not blinded and no placebo will be used. All of the patients entered will receive antibiotic prophylactic.

All wounds, regardless of the group, entered will be cultured before wound care is begun using standard culture medium. Local wound care will include high pressure irrigation using a 20 cc syringe and a 18 gauge catheter with 500 to 1000 cc of normal saline, debridement of devitalized tissue if needed. Wounds will be left open unless closure is deemed necessary for cosmesis. Topical antibiotics will not be used. The wounds will be covered with dry dressings. All patients will receive tetanus prophylaxis and rabies prophylaxis if necessary in accordance with existing ER protocols.

Group I patients will receive 1 gram ceftriaxone (50mg/kg in children <40 kg) intravenously in 50cc of normal saline over 30 minutes).

Group II patients will receive amoxicillin 250mg orally (pills or suspension) 3 times a day for 5 days.

Group III will receive both ceftriaxone and amoxicillin in the same dosages as for Groups I and II.

All of the patients will receive the first dose of antibiotics in the ER as soon as possible after their entry into the study and the wound culture has been obtained, but prior to any wound care.

All wounds will be re-examined at 24, 48, and 72 hours after being seen in the ER. Wound will be evaluated using a standardized graduated scale for evidence of erythema, swelling, tenderness, warmth, drainage, lymphangitic spread, lymphadenopathy, systemic symptoms, overall clinical impression, and disposition. Follow-up cultures will be obtained from any wound discharge, if present. A phone call to the patient 7 days after presentation to the ER will conclude our follow-up period.

Progress: One patient has completed the protocol. No data has been analyzed to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/44 STATUS: Ongoing

TITLE: Comparison of Intramuscular Meperidine and Promethazine, with and without Chlorpromazine for Pediatric Sedation

START DATE: Sep 90 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: John J. Lorrette, MAJ, D.O.; Thomas E. Terndrup, M.D.

KEY WORDS: Pediatric sedation

Study Objective: To determine if there is a significant difference in the efficacy of sedation and frequency of moderate complications after intramuscular meperidine and promethazine, with and without chlorpromazine.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This is a newly approved study with no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/57 STATUS: Ongoing

TITLE: A Double-Blinded Comparison of Diphenhydramine Versus Lidocaine as a Local Anesthetic

START DATE: Oct 90 ESTIMATED COMPLETION DATE: Dec 90

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Dire

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: MAJ David E. Hogan, MC

KEY WORDS: Anesthetic, Lidocaine, Diphenhydramine

Study Objective: To determine if there is a significant difference in the efficacy and side effects of 1% diphenhydramine versus 1% lidocaine as a local anesthetic.

Technical Approach: Twenty volunteers (residents or nursing personnel) will be recruited for this double-blinded study if they are over the age of 21, healthy by history, and not on any prescription or over-the-counter medications, have not taken any antihistamines within the last week, are not pregnant by history, and are not allergic to lidocaine or diphenhydramine.

The pharmacy will randomly prepare coded syringes which will contain either 2 cc of 1% (20 mg) lidocaine or 2 cc of 1% (20 mg) diphenhydramine.

The volunteers mid-volar forearm will be cleaned with an alcohol pad and a 2.4 cm diameter circle will be drawn on it with a sterile skin marker. Baseline sedation levels and sensation to pinprick will be recorded by each patient using a visual analog scale. The 2 cc volume of study solution will then be injected into the skin (subcutaneously) inside of the circle utilizing a 27 ga needle. The determination of sensation to pinprick will be done using a separate sterile 18 ga needle for each volunteer with care taken not to penetrate the dermis. After a one week washout period, the volunteers will be asked to return, at which time the other study solution will be tested in the same manner on the volunteer's opposite forearm.

The emergency department is equipped with all the equipment and medications and the investigators are residency trained board certified or board prepared emergentologist trained to treat any allergic reactions that might be encounters in the subjects.

Progress: This is a newly approved study with no results to date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/17 STATUS: Ongoing

TITLE: The Incidence of Abnormal Electrocardiograms in Emergency Department Patients with Head Trauma

START DATE: Mar 89 ESTIMATED COMPLETION DATE: Jul 91

PRINCIPAL INVESTIGATOR: CPT David E. Hogan

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: CPT Daniel J. Dire, MC

KEY WORDS: Electrocardiograms, Head trauma

Study Objective: To show whether there is a significant incidence of electrocardiographic (EKG) abnormalities especially dysrhythmias in Emergency Department (ED) patients with head trauma.

Technical Approach: All patients who present to the ED for initial treatment of any head injury (e.g. blunt trauma such as from falls, assaults, or vehicular accidents, and penetrating trauma such as gunshot wounds or open skull fractures) will be evaluated for participation in this study. Informed consent will be obtained from all patients except those with an altered mental status.

Patients will be excluded from this study if they have any of the following:

1. History of chest pain, cardiac disease, prior abnormal electrocardiograms, or a history of prior dysrhythmias.
2. History of seizure disorders or patients who are actively seizing.
3. Patients on any of the following type of drugs: anticholinergics, antihistamine, antidysrhythmics, antileptics, beta blockers, calcium channel blockers, decongestants, theophylline, sympathomimetics (including cocaine and amphetamines.
4. Age less than 16 years old.
5. Major blunt or penetrating chest trauma with signs or symptoms of myocardial injury, pulmonary contusions, or hypoxia.
6. Patients in circulatory shock.

All patients will have cardiac monitoring initiated upon their presentation for treatment to the ED and continued for a minimum of one hour. A 12 lead EKG will be performed during the course of their treatment.

A healthy, nontraumatized, age/sex matched control will be solicited from the ED waiting room who must not have any of the exclusion criteria listed above. Also, they must not be a patient waiting to be seen. Informed consent will be obtained from these subjects, a 12 lead EKG will be taken, and cardiac monitoring will be initiated for 1 hour.

Epidemiological and clinical data will be collected at the time of initial presentation.

All EKG's will be read by a staff internist who will be blinded to its source. The EKG interpretations will be recorded. Data will be entered into a computer database and analyzed in collaboration with the Department of Clinical Investigation, WBAMC.

Progress: The investigation is currently being conducted in full accordance with the protocol guidelines. It is, however, taking longer than anticipated to collect patients meeting the inclusion criteria. I request an extension of the original time frame to July 1991.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 88/57** **STATUS: Terminated**

TITLE: Animal Model (Caprine) Laboratory, Advanced Trauma Life Support Course (ATLS)

START DATE: Jul 88 **ESTIMATED COMPLETION DATE: Sep 90**

PRINCIPAL INVESTIGATOR: COL John W. Kolmer

DEPARTMENT: HQ **FACILITY: Darnall Army Community Hospital**

ASSOCIATED INVESTIGATORS: MAJ Michael W. Yehle

KEY WORDS: Trauma

Study Objective: This protocol will mandate the following - proper procurement of animals, humane care of animals prior to and during surgical procedures, appropriate anesthetics and monitoring of anesthesia level during the procedures, detailed description of surgical procedures involved, and humane euthanasia with proper disposal of euthanitized animals.

Technical Approach: The Advanced Trauma Life Support (ATLS) training program is designed for physicians who are primarily responsible for managing the critically injured patient; The American College of Surgeons (ACS) Committee on Trauma defines the standards that the ATLS course must adhere to. Initial assessment and management of specific types of injuries are presented to the students through lecture and slide presentations. Students then rotate through practical skill stations associated with the lecture content previously presented. The skill stations and animal lab allow the student to observe and practice to proficiency those life-saving skills necessary in the initial management and stabilization of the trauma patient. The animal lab is a one hour affair with one instructor and four students assigned to each animal.

Procedures:

a. **Preparation of animals**
b. **Intravenous administration of fluids**
c. **Tracheal intubation**
d. **Venous cutdown**
e. **Peritoneal lavage**
f. **Needle Thoracocentesis**
g. **Chest tube insertion**
h. **Pericardiocentesis**
i. **Cricothyroidotomy**

Progress: Principal investigator PCS'd and the only data available was reported in 1988. This protocol appears to have been a one-time lab to support ER resident training in ATLS.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/16 STATUS: Ongoing

TITLE: An Evaluation of Clinical Criteria for Predicting Serious Bacterial Infections in Febrile Infants Two Months of Age or less

START DATE: Mar 90 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: CPT Kenneth D. Locke

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: Charles W. Callahan, Jr., CPT, MC; Daniel J. Dire, CPT, MC

KEY WORDS: Febrile infants, Two months

Study Objective:

1. To test the predictive value of a predetermined set of clinical and laboratory findings along with subjective "impression of sepsis" for predicting serious bacterial illness in febrile infants two months of age or less in a community hospital emergency department.

2. To compare the use of these criteria and the subjective impression of three groups of physicians: emergency medicine residents, emergency medicine staff physicians, and staff pediatricians.

Technical Approach: This will be an observation study only. All of the diagnostic tests performed are those tests that we routinely perform in the evaluation of a febrile infant less than or equal to 8 weeks old (except the C-Reactive Protein which will not require any additional blood to be drawn).

All febrile (T > 100.3 R) infants 8 weeks of age or less who present to the emergency department of Darnall Army Community Hospital will be eligible for the study. Patients will be excluded if they have had a previous hospitalization or were delivered prematurely. Patients will be evaluated and treated according to the usual practices employed in the setting where the infant is seen. This will include a physical examination; laboratory tests to include a complete blood count, SMA 7, urinalysis, urine culture and Welcogens, blood culture (1 set), erythrocyte sedimentation rate, C-reactive protein titer, and a stool culture (if indicated based upon the history); chest X-ray; and CSF will be obtained for cell counts, protein, glucose, gram stain, culture and Welcogens. An intravenous line with D5W in 0.25 NS is usually established during venipuncture for laboratory specimens. No changes in the management of these patients will be necessary. No new interventions will be made in the care of these patients as a result of their inclusion into this protocol.

Serious bacterial illness will be defined as bacteremia, meningitis, cellulitis, osteomyelitis, bacterial pneumonia, bacterial gastroenteritis or colitis, or urinary tract infections. Patients will be considered to be high risk for serious bacterial illness if they have any one of the following predictor variables:

1. Strong clinical impression of sepsis based on the general appearance of the patient, irritability, consolability, the presence or absence of a social smile, and subjective assessment of "toxicity" by the examining physician.
2. Total white blood cell count less than 5,000/mm3 or greater than 15,000/mm3.
3. Absolute band neutrophil greater than 1,500/mm3.
4. Urinalysis with 10 or more white cells per high power field in a spun specimen or the presence of any WBC's or bacteria on an unspun specimen.
5. Stool with 25 or more white cells per high power field in a child with diarrhea.
6. Erythrocyte sedimentation rate greater than or equal to 55% by the Zetafuge Sedimentation Rate (Coulter Electronics).

7. Positive C-Reactive Protein.
8. The presence of neutrophilic vacuolization or toxic granulations on the peripheral smear.

Patients who do not have one or more of these predictor variables will be considered to be low risk for serious bacterial illness. The clinical impression of sepsis by the emergency resident, emergency staff, and pediatric staff will be recorded along with the laboratory values.

The investigators will examine all of the patients' peripheral smears to evaluate for the presence or absence of neutrophilic vacuolization or toxic granulations.

The Staff Pediatrician on call will be consulted to evaluate every patient for hospitalization and antibiotic therapy. Outcome variables will include the standard definitions for each of the serious bacterial illnesses noted above; for example, bacteremia defined as a positive blood culture for a pathogenic organism within 72 hours of admission.

Progress: Progress is satisfactory; there has been an unusually low number of patients qualifying for this study, but it is hoped that numbers will increase. It is anticipated that there will be sufficient numbers to allow for completion by estimated date.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/22** **STATUS: Ongoing**

TITLE: A Simple Approach to Scalp Laceration Repair

START DATE: Sep 90 **ESTIMATED COMPLETION DATE: Jun 91**

PRINCIPAL INVESTIGATOR: MAJ John T. McDonnold

DEPARTMENT: ER **FACILITY: Darnall Army Community Hospital**

ASSOCIATED INVESTIGATORS: James Alan Morgan, MAJ, MC; Donald M. Yealy, CPT, MC

KEY WORDS: Scalp laceration repair

Study Objective: To compare the wound infection complication rates of simple scalp lacerations that have been sutured with and without prior hair shaving.

Technical Approach: The details are [illegible]y and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: There have been no patients entered into this study. No progress to report.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/19 STATUS: Ongoing

TITLE: **Effect of Multidose Activated Charcoal on Ethanol Elimination**

START DATE: Mar 90 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: CPT Ronald Moscati

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: Paul Vinsel, CPT, MC; Donald Yealy, CPT, MC

KEY WORDS: Activated charcoal, Ethanol

Study Objective: Demonstrate whether multidose charcoal can enhance the elimination of ethanol in humans.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No progress has been made on this project due to the principal investigator participating in Operation Desert Shield.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/21 STATUS: Completed

TITLE: Do Patients Awaking with Abdominal Pain Have Significant Abdominal Pathology?

START DATE: Sep 90 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: CPT Robert T. Pinson

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: MAJ Douglas B. Ferguson, MC

KEY WORDS: Abdominal pain

Study Objective: This study will evaluate patients awaking with abdominal pain to determine if this correlates with significant abdominal pathology.

Technical Approach: All patients who present to our Emergency Department with abdominal pain will be evaluated for the presence of significant abdominal pain. We define significant abdominal pain as any abdominal pain that requires surgical or medical intervention other than only non-steroidal anti-inflammatory or anti-emetic medications and/or hospitalization for the treatment of their abdominal condition. Included in this category of significant abdominal pain is renal stones, pyelonephritis, appendicitis, cholecystitis, pancreatitis, diverticulitis, liver disease, peptic ulcer disease, abdominal aneurysm, inflammatory bowel disease, bowel infarction, perforated viscus, incarcerated hernia, volvulus, and carcinoma. Those patients who meet the following conditions or circumstances will be excluded from participation:

1. Patients age 17 years or younger.

2. Abdominal pain due to pelvic disease, intrathoracic disease, and metabolic disease, and neurogenic causes.

3. Referred pain due to intrathoracic disease.

Each of these patient's charts will be stamped at the front desk in the ER with a stamp that reads as follows: "Did abdominal pain awake patient from sleep? Yes___ No___, Physician's Initials ." The patient will be examined in the usual manner. The physician examining the patient will complete the information on the stamp, as above. All patients admitted will be followed until discharged from the hospital. Those other patients discharged from the Emergency Department will be contacted by telephone in one week to follow-up the course of their illness.

Non-parametric nominal data such as significant abdominal pain will be analyzed by the chi-square method. Variables such as age and gender will be analyzed by the paired T-test.

Progress: One hundred subjects have been entered into this study; none withdrew, and there were no adverse reactions. Data is currently being analyzed for significance.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #: 90/28** **STATUS: Terminated**

TITLE: Job Satisfaction and Its Correlation on the Retention of U.S. Army Nurse Anesthetists

START DATE: Mar 90 **ESTIMATED COMPLETION DATE: Aug 90**

PRINCIPAL INVESTIGATOR: 1LT Charles M. Price

DEPARTMENT: Nsg **FACILITY: Darnall Army Community Hospital**

ASSOCIATED INVESTIGATORS: Richard H. Tateishi, MAJ, AN; Deborah D. Warner, MAJ, AN

KEY WORDS: Job satisfaction, U.S. Army Nurse Anesthetists

Study Objective: To determine if job satisfaction has a significant correlation on the retention of U.S. Army Nurse Anesthetists. As the Army Nurse Corps and the AMEDD deal with this shortage, our timely study will collect and correlate data related to six specific factors of job satisfaction of U.S. Army Nurse Anesthetists, to include pay and benefits, autonomy, task requirements, organizational requirements, job status and interactions. Demographic data of U.S. Army Nurse Anesthetists will also be collected and correlated; determine attrition propensity of U.S. Army Nurse Anesthetists, analyze the information and correlate the relationships between job satisfaction and retention.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Authorization to proceed with this study was disapproved by U.S. Army Personnel Integration Command in Alexandria, VA, per AR 600-46.

DETAIL SUMMARY SHEET

DATE: 1 October 90 **PROTOCOL #:** 90/25 **STATUS:** Ongoing

TITLE: The Effect of Visual Imagery as an Adjunct Therapy to Narcotic Analgesia in the Perioperative Period

START DATE: Apr 90 **ESTIMATED COMPLETION DATE:** Nov 90

PRINCIPAL INVESTIGATOR: 1LT Maureen Reilly

DEPARTMENT: Nsg **FACILITY:** Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS:

KEY WORDS: Visual imagery, Pain

Study Objective: To examine visual imagery as an effective adjunct therapy to narcotic analgesia in the male perioperative client undergoing lower limb surgery.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: The overall hypothesis of the study appears to be supported by the current collection of data. Subjects report less anxiety and more comfortable immediate post operative period.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 90/07.5 STATUS: Completed

TITLE: The Actual Role of the Army Emergency Nurse

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Sep 90

PRINCIPAL INVESTIGATOR: MAJ Michelle Renaud

DEPARTMENT: Nsg FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS:

KEY WORDS: Army Emergency Nurse, Emergency Nurse; role

Study Objective: To examine the actual role functions as performed by Army Emergency Nurses using a work sampling technique and to compare observed actual role functions to perceived actual role functions from a previous study. This study is based on two previous studies. The first is a nonexperimental descriptive study of Emergency Nurse role functions, using a work sampling methodology (Marsh, 1987). The second study is also a nonexperimental descriptive study that examines the perceived actual and ideal practice role functions of emergency nurses.

Technical Approach: The sample the investigator will utilize will be role function observations made on Army Emergency Department nurses working in one of two level II Emergency Departments. The sampling procedure has three stages: Level II Emergency Departments will be selected since approximately 80% of the Emergency Centers in the Army are designated Level II. These Level II Emergency Centers are found in both Medical Department Activities (MEDDACs) and Medical Centers (MEDCENs) within the Army; thus, one MEDDAC Level II Emergency Center and one MEDCEN Level II Emergency Center will be chosen. The nurses to be observed will be selected by shift availability and amount of experience as a nurse in the emergency care setting. Nurses must have a minimum of 5 months emergency care experience to be included. Role functions performed by the nurse will then be sampled at 5 minute intervals. The observation is an instantaneous one, i.e., whatever the nurse is doing at that instant is the behavior observed and recorded. Observations will be made for 4 days at each facility. both day shift and evening shift will be included. Observations will be collected for 8 hours each day, for a total sample of 384 observations at each institution.

Progress: The sample for this study consisted of 715 role function observations made on 5 Army Emergency Department Nurses working in two level II Army Emergency Departments. The findings of this study reveal that of 114 possible role function activities, only 54 were observed to be performed by Army Emergency Nurses. The category of planning received the greatest percentage of observations (21.5%) with the categories of planning and psychomotor skills combined accounting for 41.5% of the Army Emergency Nurses' observed during the workday. These findings were similar to those from a previous study, although there were more perceived actual role functions than observed actual role functions.

It was concluded that the practice component of Army Emergency Nurse role is consistent with the Emergency Nurses Association Standards of Practice (1983). The remaining role components are present, but not as well developed. It may be that Army Emergency Nurses have a greater delegatory role than their counterparts in the civilian sector because of type and mix of staff assigned to the military emergency department.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/47 STATUS: Ongoing

TITLE: CSCC Program Evaluation

START DATE: Jun 89 ESTIMATED COMPLETION DATE: Sep 91

PRINCIPAL INVESTIGATOR: Ph.D. M. David Rudd

DEPARTMENT: Psych FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS:

KEY WORDS: CSCC

Study Objective: This project is designed to determine the relative therapeutic effectiveness of the CSCC program.

Technical Approach: All subjects will be active duty soldiers treated at Ft. Hood's CMHS. Participation is strictly voluntary. There will be 50 subjects from the CSCC program and 50 matched control subjects from other modalities of outpatient treatment. All subjects will be selected from cases dispositioned at the CMHS. The controls will be matched within five days of their initial CMHS sign in, and will be matched to the CSCC subjects for demographic as well as selected clinical criteria, e.g., type of problem, severity.

This project uses a quasi-experimental approach with a pre-test/post-test design. The project design also includes follow up evaluations at one and three month intervals. Data collection involves the use of three standardized psychometric instruments, (labeled the basic battery) and four instruments of local design addressing the subject's military performance. Of the locally designed instruments, two are intended for use as phone questionnaires, and are to be answered by the subject's first line supervisor regarding performance of the subject within his unit.

Once a subject agrees to participate in the study, he will be given a pre-test consisting of the basic battery and the subject's self evaluation questionnaire. A research assistant will ensure completion of the first line supervisor's pre-evaluation. The post-test will be given after three weeks. It will consist of the basic battery and subject post-evaluation. At both the one month and three month follow-up evaluations, the subject will retake the basic battery and the post self-evaluation. A research assistant will complete post evaluations from first line supervisors at both of the follow-ups. The data collected will be analyzed using a completely randomized block design.

Any of the following will result in premature termination of a subject as a part of the study: failure to complete CSCC, subject refusal to continue participation in the project, ETS or PCS. Otherwise, subject's participation will be terminated after the completion of the three month follow-up evaluation.

Progress: No progress has been reported.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 88/66 STATUS: Ongoing

TITLE: **Treatment of Hypercholesterolemia with Psyllium Hydrophilic Mucilloid (Metamucil)**

START DATE: May 88 ESTIMATED COMPLETION DATE: Oct 90

PRINCIPAL INVESTIGATOR: CPT Richard E. Whitlow

DEPARTMENT: ER FACILITY: Darnall Army Community Hospital

ASSOCIATED INVESTIGATORS: Julia A. Morgan, D.O.; Richard D. Harwood, R.N.P.; Rebecca J. Oskey, R.N.P.; Elizabeth Kist, R.D.; Ann Andersen, R.D.

KEY WORDS: Hypercholesterolemia, Psyllium Hydrophilic Mucilloid (Metamucil)

Study Objective: To define the optimal safe dosing of psyllium hydrophilic mucilloid to lower total and LDL cholesterol and define the long-term efficacy and safety of psyllium hydrophilic mucilloid. this study will be conducted in a randomized prospective, controlled manner.

Technical Approach: Patients will be enrolled from a variety of sources: random cholesterol screening tests, over-40 physical examinations, commanders' physical examination, commanders' total fitness course, and patients referred to Nutrition Clinic for dietary therapy. The patients will initially undergo a battery of screening tests as well as a history and physical exam to determine secondary causes of hypercholesterolemia (untreated hypothyroidism, obstructive liver disease, nephrotic syndrome). The study medication is psyllium hydrophilic mucilloid (blond Plantago psyllium, Metamucil) in varying doses and intervals. Only patients with serum cholesterols between 200 and 260 mg/dl with two coronary heart disease risk factors will be studied since therapy is recommended for this group by the NCEP and the magnitude of expected response is reasonable to assume a lowering of serum cholesterol by Metamucil to a normal range. Throughout the study laboratory evaluations will be obtained to assess known aberrations induced by increased dietary fiber.

Progress: No progress report received.

DETAIL SUMMARY SHEET

DATE: 1 October 90 PROTOCOL #: 89/42 STATUS: Ongoing

TITLE: The Utility of Thermographic Evaluation in the Diagnosis of Lower Extremity Injuries During Army Initial Entry Training

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Jul 91

PRINCIPAL INVESTIGATOR: LTC Bruce H. Jones

DEPARTMENT: USAREM FACILITY: William Beaumont Army Medical Center

ASSOCIATED INVESTIGATORS: Dr. Murray Hamlet, DVM; COL (Ret) Margarete Di Benedetto

KEY WORDS: Thermogram (graphic), Scintigraphic

Study Objective:

1. To document the sensitivity and specificity of thermography to detect the presence or absence of injuries in general compared to clinical standards and more specifically to:

(a) To document the specificity and sensitivity of thermography in the diagnosis of stress fractures verses bone scans and x-rays as the diagnostic standard. Also, to calculate the positive and negative predictive value of thermography in the diagnosis of stress fractures based on the prevalence of stress observed in this and other epidemiologic studies.

(b) To document the sensitivity and specificity of thermography to detect injuries other than stress fractures verses the level of certainty of clinical diagnosis, i.e., the presence or absence of observable signs and the number of positive signs such as swelling, erythema, ecchymosis, point tenderness, decreased range of motion, etc. for a particular diagnosis. Also, to document the sensitivity and specificity of thermography verses the degree of severity of injury measured in days of limited duty or hospitalization. Also, positive and negative predictive value will be assessed once the prevalence of specific injuries in the cohort are established. (As an aside, the potential for paradoxically decreased sensitivity of thermography when such soft clinical standards are used is recognized, however, the use of two or more operationally defined clinical standards, i.e., level of clinical certainty and degree of severity of the diagnosis should help to recognize a paradox when it arises.

2. To qualitatively and quantitatively describe the thermographic patterns for specific injuries if they are perceived to exist.

3. To determine whether the thermographic patterns "normalize" as injuries heal in a way that would assist in making decisions regarding return of soldiers to duty.

4. To determine whether individuals with flat feet or high arches are likely to suffer more injuries to the lower extremities than those with "normal" feet. Also, to determine whether the thermograms of individuals with flat feet or those with high arches are more likely to be positive (indicating "chronic stress") than individuals with "normal" feet at baseline (prior to onset of basic training) and episodically during basic training.

5. To determine the effect of training volume (running and marching mileage) on the incidence of injuries and on the qualitative and quantitative patterns of lower extremity thermograms.

6. To determine whether the thermographic patterns observed are more likely to be positive for sub-populations grouped on the basis of age, race, body composition, past activity, and physical fitness.

7. To determine the incidence of commonly occurring training-related injuries and the amount of morbidity (days of limited duty, etc.) associated with each. With these data estimates of the impact of early diagnosis and appropriate return to duty through use of thermography will be made.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: All of the data needed has been collected and the field study is considered complete. Infrared images were collected from approximately 1200 volunteers in six companies of basic trainees.

The thermographic images for three groups: controls, subjects with positive bone scans but no symptoms of stress injuries and symptomatic subjects with positive grade 3 and 4 bone scans, have been objectively analyzed using Uematsu's criteria. The digitalized information from the images is being statistically reviewed for significant differences between the three groups. The statistical results should be available within 60 days, a manuscript will follow shortly thereafter.

Blind readings by a physician have also been completed for every subject with symptoms of stress injury and a positive bone scan. The physician is now reading the thermograms again with the benefit of physical diagnosis and the bone scan reports. The information derived form this subjective portion of the study will help determine the specificity and sensitivity of clinical thermographic diagnosis for stress injuries in the lower limbs.

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KEYWORD INDEX

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