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# Annual Progress Report



Fiscal Year 1993

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Subject report identifies the research activities conducted at William Beaumont Army Medical Center by 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 1993. 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).

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

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**Annual Progress Report  
Fiscal Year 1993**

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**Clinical Investigation Program  
RCS MED-300 (R1)**

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

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## FORWARD

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Fiscal year 1993 was another year of advancement and accomplishment for the Department of Clinical Investigation (DCI) at WBAMC. DCI contributed greatly to the continued support of Graduate Medical Education (GME) at our medical center by providing outstanding assistance to clinical investigators throughout the hospital in the basic science components of their studies, protocol coordination, editorial assistance, statistical support and overall facilitation of the research process.

The American Association for Accreditation of Laboratory Animal Care (AAALAC) conducted its triennial inspection of our program, and after an extensive, comprehensive, and thorough on-site review, granted us a clear re-accreditation. We were proud to hear praises from the inspectors during their out-briefing. The Food and Drug Administration (FDA) also conducted an inspection (unannounced) and determined that we were in full compliance with regulations related to the protection of human subjects.

A new and exciting initiative involved collaboration with the El Paso Managed Health Care and Education Consortium, which includes WBAMC, Texas Tech University Health Science Center, Providence Memorial Hospital, The University of Texas at El Paso (UTEP) School of Public Health, and El Paso Community College. Several joint research protocols were formulated and integrated into grant proposals, underscoring the increasing cooperation and establishment of a functional network interlacing these institutions.

We bid a fond farewell to LTC Robert Martig, who departed for Germany after admirable service to DCI as Assistant Chief. MAJ William Nauschuetz was promoted to this position and is already blazing a successful trail. Following the retirement of Ms. Sandra Edgerton, the duties of protocol coordination were assumed by Ms. Vivian Maheu, our Editorial Assistant. She has provided a high polish and efficiency to both jobs with outstanding professionalism.

The responsiveness to the research needs of our medical center, team work, facilitation, support, commitment, efficiency and effectiveness were of the highest order by all members of DCI. Thank you and congratulations to all for a job well done.

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*Manuel Schydlower, MD*

MANUEL SCHYDLOWER, MD  
COL, MC  
Chief, Dept of Clinical Investigation

## **UNIT SUMMARY FY 93**

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### **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 AAALAC.

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 strength of the Department of Clinical Investigation during FY 93.

<u>Description</u>	<u>Grade</u>	<u>MOS</u>	<u>Br</u>	<u>Req</u>	<u>Auth</u>	<u>Name</u>	<u>Rank</u>
C, DCI	O6	60P	MC	1	1	Schydlower	O6
Dir, HP/SCT	O5	60F	MC	1	0	Weisman	O6
Immunologist	O3	68E	MS	1	1	Nauschuetz	O4
Biochemist	O3	68C	MS	1	1	vacant	
C, Bio Res Svc	O3	64C	VC	1	1	Harris	O4
Animal Care NCO	E6	91T	NC	2	1	Williams	E5
Animal Care Sp	E4	91T		1	1	Milbradt	E5
Animal Care Sp	E3	91T		2	1	Iron Mocassin	E4
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 Tech	07	645	GS	2	1	Lund	07
Med Tech	07	645	GS	2	1	Manna	07
Med Tech	07	645	GS	2	1	McIntyre	07
Health Tech	07	640	GS	1	1	Revels	07
CI Prot Coord	07	303	GS	1	1	Edgerton	07
Ed Asst	07	1087	GS	1	1	Maheu	07
Sup Clk	05	2005	GS	1	1	Turner	05
Anim Caretaker	04	5048	WG	1	1	Sigholz	04
Anim Caretaker	01	5048	WG	2	1	Burton	01

### Civilian Personnel with Special Project Funding

Co-Director HP/SCT						Zeballos
Exercise Physiologist	09	413	GS			Taylor
Editorial Assistant	05	1087	GS			Peterson

## **PERSONNEL**

Officers	4	4	4
Enlisted	5	3	3
Civilian	16	12	15*

\*3 civilians are funded through special projects

Changes in personnel during FY 93:

LTC Robert Martig replaced by MAJ Bill Nauschuetz

Ms. Sandra Edgerton retired May 93; duties assumed by Ms. Vivian Maheu

Mr. Matthew Taylor replaced Mr. Ariel Linden

## **GRANTS**

### **USA Medical Research and Development Command**

Intestinal Anastomosis with an Interpositional Absorbable Stent and a Neodymium (Nd):YAG Laser in the Rabbit Model \$15,020

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. \$2,000

Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model. \$4,000

Efficacy of Passive Immunization in the Prevention of Infection due to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* \$54,000

Tracheobronchial Mucins in Health, Disease, and Toxic Exposures \$66,145

Effect of Fibrin Sealant on Skin Graft Inhibition of Wound Contraction in the Porcine Model \$1,000

Effect of Fibrin Sealant on Breaking Strength of Incisional Wounds in the Porcine Model \$2,390

### **USN Medical Research and Development Command**

Joint Navy-Army Human Performance/Sickle Cell Trait Research Project at WBAMC. \$88,000

## PROTOCOLS, PRESENTATIONS, PUBLICATIONS

<u>Protocols</u>	<u>Ongoing</u>	<u>New</u>	<u>Completed</u>	<u>Terminated</u>
FY 91	112	50	17	18
FY 92	114	67	39	26
FY 93	110	54	29	30

	<u>Publications</u>	<u>Presentations</u>
FY 91	48	26
FY 92	40	57
FY 93	32	78

## EXPENDITURES

	<u>FY 91</u>	<u>FY 92</u>	<u>FY 93</u>
Personnel (Civilian)	549,234	533,655	520,798
Consumable Supplies	233,612	229,484	258,409
Capital Equipment	46,884	131,810	15,007
TDY	8,030	10,762	8,127
Printing and Publications	<u>2,886</u>	<u>2,494</u>	<u>1,760</u>
Total	840,646	908,205	804,101
MEDCASE Equipment	58,000	164,964	0
Military Pay	<u>536,758</u>	<u>543,248</u>	<u>559,043</u>
TOTAL	1,435,404	1,616,417	1,363,144

**Biological Research Service**

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The William Beaumont Biological Research Service laboratory animal facility has been fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1968. Currently, this facility, totaling 7,134 square feet, occupies three buildings on the William Beaumont Army Medical Center (WBAMC) complex. The main facility, in Building 7776, contains the surgical suites, radiology, treatment rooms, necropsy, the majority of the animal holding areas, and the administrative offices. Building 7774, is utilized as large equipment storage, plus a newly operational 250 square foot, Class 10,000 bioclean room. The third unit is a recently completed 150 square foot, walk-in refrigerator which upgrades and expands the storage capabilities for the research animals.

The Biological Research Service has been extremely active in increasing its support of training, research, and collaborative protocols of WBAMC during 1993. Of the presently 39 active protocols, 15 protocols were supported in 1993 for the training of medical personnel encompassing emergency trauma life support, general surgery, laser surgery, laparoscopic techniques, and vascular microsurgery. Particularly noteworthy was the support provided to the Pediatric Advanced Life Support (PALS) Course in airway management using the ferret as the animal model. By virtue of this support, WBAMC has become a regional center for conducting this course sponsored by the American Heart Association.

The 21 research protocols supported by the Biological Research Service were not only practical and militarily relevant, but established areas of research capabilities heretofore lacking at WBAMC. Research continued in the disciplines of microsurgery, soft tissue and orthopedic reconstruction materials and techniques, surgical laser applications, therapeutic efficacy, molecular biology, and immunology. However, with the establishment of a colony of immunodeficient rodents, WBAMC has the ability to support protocols dependent upon xenografts and biological propagation of foreign organisms particularly important for oncology and breast cancer research.

WBAMC has continued its collaboration with the Sierra Medical Center in the certification of physicians in the applications of the surgical laser, as well as expanding training protocols for the combat medical units of Fort Bliss.

The Biological Research Service was visited by AAALAC in June 1993 as part of critical re-accreditation inspection. The results were extremely favorable, no deficiencies noted, and full accreditation granted until 1996. A similar inspection was conducted in the fall by a team from the DoD Inspector General with the mission of collecting data for a Congressional report. Once again, there were no deficiencies noted, and only commendable comments given.

## Chemistry Section

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The chemistry section of DCI is engaged in research projects concerning retinoic acid regulated differentiation and mucin gene expression of rat and rabbit tracheal epithelial cells in culture exposed to different toxic substances and respiratory drugs, analysis of hemoglobin peptides from humans and animals by high pressure liquid chromatography and capillary electrophoresis, and analysis of drug metabolites in children of addicted parents.

We have demonstrated that retinoic acid (a component of vitamin A) is one of the most important constituents of the culture medium in which tracheal epithelial cells differentiate and propagate normally. Without retinoic acid, the cells tend not to grow properly, nor do they produce mucin, the secretion of which is the normal function of these cell lines. Ultrastructural examination of the tracheal cells grown in medium containing retinoic acid shows well-established mucociliary epithelium with abundant microvilli and secretory granules. On the other hand, when the cells are grown in medium without retinoic acid, the cells tend to become squamous and lose most microvilli and secretory granules. Hybridization analysis of total RNA isolated from cells grown in medium with retinoic acid indicates the strong expression of mucin gene. The expression becomes weaker in cells grown without the compound. Addition of retinoic acid to the cells grown in medium without retinoic acid results in full expression of mucin gene. Additionally, we have found that retinoic has a protective action against many toxic substances which were injurious to these cell lines. We have also found that mucin antisense oligomer has an inhibitory effect on retinoic acid-induced mucin gene expression and secretion in tracheal epithelial cell lines. These findings have important implications regarding respiratory diseases such as asthma, chronic bronchitis and cystic fibrosis, where excessive secretion of mucous is a common phenomenon.

We are also involved with two other protocols, entitled, "The effect of bovine TSH on hemoglobin proportions in adult rats," and "Determination of the prevalence of drug affected babies in a military population." The first was prompted by observations that in patients with beta globin chain hemoglobin abnormalities, a high level of fetal hemoglobin is associated with a milder clinical course and that during the postnatal period in humans, there is a switch from fetal hemoglobin (HgbF) to adult hemoglobin (HgbA). A model system has been developed to study the level of hemoglobin components in adult and neonate rats. However, estimation of HgbF level by classical procedures was slow and tedious. We have developed a rapid and sensitive procedure which utilizes high pressure liquid chromatography with a weak cation exchange column and capillary electrophoresis to characterize and compare adult and neonate rat hemoglobin components more effectively. The last ongoing protocol is concerned with determination of drug metabolites in meconium of babies that may have been acquired from mothers before delivery. We are now analyzing drug metabolites in meconium by employing gas chromatography/mass spectrometry methods.

## Molecular Biology Service

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The Infectious Disease Research Laboratory (IDRL), Department of Clinical Investigation performs clinical gene amplifications. The laboratory is staffed by one 0-6 and one GS-07 Medical Laboratory Technician. Current protocols include the polymerase chain reaction (PCR) to determine the effect of 5FU treatment on female patients with PAP smears indicating HPV infection. The section has also collected specimens, and is ready use in situ PCR amplification for, E6 and E7 mRNA in genital specimens from adolescent males and females.

The laboratory is working with Texas Tech University Health Sciences Center, El Paso RACH, the University of Texas Health Science Center at San Antonio, and the Instituto Nacional de Pediatría, Mexico City to determine the efficacy of PCR for the diagnosis of tuberculous meningitis. We are also using PCR in a protocol with the El Paso City/County Health District and the University of Texas Health Science Center at San Antonio for the rapid detection of TB, and drug-resistant TB, from clinical specimens originating from El Paso and Juarez, Mexico.

Projects which have been approved by the IRB, or are undergoing IRB review, include use of PCR to detect Hepatitis C virus and methicillin-resistant *Staphylococcus aureus*.

The equipment used by the IDRL in these protocols includes the Bactec 460 with TB Hood, Perkin Elmer Model 392 DNA Synthesizer, the Perkin Elmer 9600 thermal cycler, and the Perkin Elmer QPCR 5000.

## Immunology and Microbiology Section

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Research interests of the Immunology and Microbiology Section have been focused primarily on two major projects: (1) the study of immunoregulatory subsets of T cells in Bermuda grass allergy and, (2) an MRDC-funded study of growth regulatory factors such as estrogen, epidermal growth factor, transforming growth factors, and insulin-like growth factors which influence the growth of human breast cancer cells.

Extensive evidence suggests that suppressor T cells develop as a consequence of allergy immunotherapy and that these suppressor cells are responsible, at least in part, for inhibiting the IgE-mediated release of chemical mediators that are associated with the allergic reaction. In an attempt to determine whether immunotherapy of Bermuda grass allergy patients results in the development of the putative suppressor cells, lymphoproliferative responses were measured in peripheral blood lymphocytes from Bermuda grass allergy patients and in short-term (< 2yrs) and long-term (> 2yrs) immunotherapy patients. Peripheral blood lymphocytes were co-cultured in the presence or absence of the putative suppressor cells which were obtained by incubation of autologous peripheral blood lymphocytes with an optimal stimulatory concentration of Bermuda allergen followed by mitomycin C-treatment. Suppressor cell activity to Bermuda allergen was not detectable in any of the patient groups tested. However, parallel studies of response to Ragweed allergen in the same patient groups revealed significant suppressor cell activity. Comparative studies of the components of the suppressor cell assay revealed that, at optimal mitogenic concentrations, Bermuda allergen had a much greater stimulation index than did Ragweed allergen. Reducing Bermuda allergen concentration 5-fold below that required for optimal stimulation resulted in the detection of suppressor cell activity to Bermuda grass allergen. Flow cytometric analyses of Bermuda grass allergen suppressor cell populations (at optimal mitogenic concentration of Bermuda allergen) revealed increased percentages of CD4<sup>+</sup>/IL-2R<sup>+</sup> T cells and decreased percentages of suppressor-inducer cells and CD8<sup>+</sup> T cells (presumably suppressor T cells). The proliferative response of autologous responders cells in the presence of suppressor cells exhibited a statistically significant correlation with duration of immunotherapy: low response in normals and long-term immunotherapy patients and high response in allergy patients and short-term immunotherapy patients. Plasma allergen-specific IgE levels and CD4<sup>+</sup>/IL-2R<sup>+</sup> T cell levels correlated well with immunotherapy course: the levels of each decreased as length of immunotherapy increased.

Our results suggest that Bermuda grass allergen-specific IgE synthesis may be down-regulated by a suppressor cell mechanism. However, optimally stimulatory concentrations of Bermuda allergen induce a vigorous proliferative response thereby "masking" suppressor cell activity. The results of comparative studies of the components of the suppressor cell assay indicate that proliferative responsiveness of suppressor cells rather than suppressive activity, appears to correlate more closely with immunotherapy outcome.

Our study of human breast cancer focuses on the regulatory influences of autocrine and paracrine growth factors on breast cancer cells. Breast tumors with high S-phase fractions have a higher rate of metastasis and a poorer prognosis despite the fact that the largest tumor cell kill with chemotherapeutic agents is attained in tumors that have high S-phase fractions. Both normal and malignant breast epithelial cells are dependent on paracrine or autocrine growth stimulation to induce their movement into cell cycle. Without the appropriate mitogenic signals, however, quiescent tumor cells will remain in  $G_0$  until they either become activated to enter  $G_1$  or are terminated through one of two processes: (1) necrosis or, (2) apoptosis (programmed cell death). Apoptosis is not a random event, but instead, appears to be initiated by a signal which triggers an increase in intra-cellular free  $Ca^{++}$  which, in turn, activates a  $Ca^{++}/Mg^{++}$ -dependent endonuclease which carries out the orderly degradation of the cell's DNA. It is our belief that the failure of a tumor cell to enter cell cycle constitutes a decision point for that cell. Rather than passively awaiting mitogenic signals in  $G_0$  on an indefinite basis, quiescent tumor cells (those resting in  $G_0$ ) reach a point at which they recognize the absence of a growth factor stimulus and proceed to initiate auto-degradation or apoptosis. Growth factor deprivation may provide an alternative approach to therapeutic elimination of tumor cells. In this regard, treatment modalities which bring about a suppression or modification of growth factor production and/or secretion and/or receptor binding by either stromal cells (paracrine stimulation) or by tumor cells themselves (autocrine stimulation) may be proven to be highly effective as an alternative approach to breast cancer therapy. Flow cytometric analysis and digital image analysis are being used to study DNA ploidy, cell cycle characteristics and growth factor requirements of breast cancer cells from primary surgical biopsies.

Our studies should provide a better understanding of the relationship between growth factor deprivation and the initiation of apoptosis. Therapeutic approaches which facilitate growth factor deprivation and, hence, apoptosis, may provide an alternative method of tumor destruction.

## Human Performance Laboratory

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The Human Performance Laboratory at William Beaumont Army Medical Center is a full service cardiopulmonary exercise testing laboratory with multiple research and clinical exercise testing capabilities. As a major regional tertiary referral hospital (300 bed) WBAMC serves a large retired, active duty military and dependent population. The Human Performance Lab is responsible for all asthma exercise protocols as well as cardiopulmonary exercise testing for the medical center and its regional responsibilities.

The Human Performance Laboratory's personnel include an active duty military M.D., an M.D., Ph.D. (civilian), and a GS-9, DAC exercise physiologist. The laboratory is contiguous to a state of the art pulmonary function laboratory which includes: two body plethysmographs, two pulmonary function systems with nitrogen washout for lung volume and  $D_LCO$  determinations, bronchial provocation capability, and arterial blood gas machines.

A large clinical and extremely large volunteer population at Fort Bliss make research projects with large n values feasible.

A comprehensive listing of the laboratory's capabilities include: state of the art cardiopulmonary exercise testing which consists of ability to measure metabolic ( $VO_2$ ,  $VCO_2$ , Anaerobic threshold, R), Ventilatory ( $VE$ ,  $VT$ , F), Cardiovascular (ECG, HR,  $HR/VO_2$ ,  $VO_2$ /work rate) and gas exchange ( $PaO_2$ ,  $P(A-a)O_2$ ,  $SaO_2$ ,  $VD/VT$ , pH,  $P(a-ET)CO_2$ ) parameters; simulation of different environmental conditions utilizing  $FIO_2$  manipulation (inspiratory hypoxia simulating, 2300 m, 4000 m, etc.); study of  $O_2$  transport including  $O_2$  dissociation curve ( $P_{50}$  capability and separate tonometry set-up); treadmill, cycle ergometry and arm crank modalities; reactive airways dysfunction - diagnostic - exercise induced bronchoconstriction, broncho-provocation, isocapnic hyperventilation, cold air ( $-10^\circ C$ ) hyperventilation decrease; vocal cord dysfunction - exercise induced, inhalational challenge, bronchoscopy with flow volume loop set-up for documentation; mechanics of breathing including  $P_{DI}$  determined (esophageal balloons) and pressure-volume (compliance) curve relationships; sub-maximal exercise  $D_LCO$  and measurement of pulmonary capillary blood volume (developing); non-invasive determination of cardiac output using  $CO_2$  rebreathing technique and acetylene during intrabreath technique; invasive determination of pulmonary gas exchange:  $SaO_2$ ,  $PaO_2$ ,  $P(A-a)O_2$ ,  $VD/VT$ ,  $P(a-ET)CO_2$ ; monitoring: weight - sauter scale (accuracy 10 gm), temperature - esophageal, rectal, skin probes (sensor tech system),  $SpO_2$  - HP and pulse oximeters, BP - direct BP monitoring; lactate determination capability; capability of  $VO_2$ ,  $VCO_2$ , and  $VE$  determination under field conditions using dry gas meter and Douglas bag collection; state of the art in house nuclear cardiology and cardiovascular laboratories provide in house research/clinical interaction on issues related to human performance.

The Human Performance Lab has in the past gained national recognition for its work in Sickie Cell Trait. Presently, it is a force in standardization of clinical exercise testing. As such, it serves as a major reference laboratory.

The Human Performance Lab has received extramural funding through the Jackson Foundation for research in COPD; additional extramural funding opportunities are presently being considered.

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Flynn TW: Pelvis and thigh injuries. In: Lillegard WA, Rucker KS, eds. *Handbook of Sports Medicine. A Symptom-Oriented Approach*. Boston: Andover, 1993;123-134.

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Morey A, Deshon GE, Rozanski T, Dresner M: Technique of biopsy gun testis biopsy. *Urology* 42:325-326, 1993.

Morey A, Leckie R, Adams S, Kennon W, Murphy T: Clinical urologic conference: Extensive retroperitoneal mass. *Urology* 41: 185-188, 1993.

## **PRESENTATIONS**

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### **Department of Clinical Investigation**

**Bhattacharyya S, Lund M, Manna B:** Effect of Drugs on Mucin Gene Expression in Rat Airways in Vitro. 21st Annual Meeting of Society for Complex Carbohydrates. Nashville, TN, 11-14 Nov 92.

**Bhattacharyya S:** Mucin in Health and Diseases. Presentation to UTEP Biology Department. El Paso, TX, 16 Nov 92.

**Enriquez J, Pearson JT (Pathol), Critz W (Pathol), Casey T (Pathol), McKell D, Brady KM (Pathol):** An Analysis of Postnatal Changes in Rat Hemoglobin Utilizing a Cation Exchange HPLC Method (poster). 45th National Meeting of the American Association for Clinical Chemistry. New York, NY, 11-15 Jul 93.

**Mahon C, Nauschuetz W:** Clinical Microbiology Review. American Society of Clinical Pathologists. Irvine, CA, Jun 93.

**Nauschuetz W:** The Exudative STDs. Lecture at School of Public Health at University of Texas at El Paso. El Paso, TX, 7 Sep 93.

**Nauschuetz W:** The Ulcerative STDs. Lecture at School of Public Health at University of Texas at El Paso, TX, 14 Sep 93.

**Nauschuetz W, Harrison L:** STDs: Still a Catchy Subject. American Society of Clinical Pathologists meeting. San Antonio, TX, Feb 93.

**Nauschuetz W, Martig R:** STDs: Still a Catchy Subject. American Society of Clinical Pathologists meeting. Boston, MA, Mar 93.

### **DENTAC**

**Dickerson N:** Maxillofacial Trauma and Reconstruction. 7th Annual Trauma Conference. Memorial Medical Center. Las Cruces, NM, Sep 93.

**Donovan M:** Airway Management. ACLS Course. Thomason Hospital. El Paso, TX, Nov 92 and Jun 93.

**Donovan M:** Calvarial Bone: Applicators for Implant and Reconstructive Surgery. Presentation to Department of Neurosurgery, Case Western Reserve University. Cleveland, OH, Apr 93.

**Donovan M:** Cranial Base Tumors: A New Approach and Reconstruction. Presentation to Departments of Neurosurgery and Oral and Maxillofacial Surgery. Tripler Army Medical Center, Hawaii, Apr 93.

**Donovan M:** Cranial Base Tumors: A New Approach and Reconstruction. Presentation to Department of Neurosurgery, Case Western Reserve University. Cleveland, OH, Apr 93.

**Donovan M:** Innovations in Oral and Maxillofacial Surgery. Presentation at Medical College of Georgia. Augusta, GA, Jun 93.

Donovan M: Oral and Maxillofacial Surgery Service Short Course. Walter Reed Army Medical Center. Washington, DC, Oct 92.

Donovan M: Pre-Hospital Management of Maxillofacial Trauma. 11th Annual Trauma Symposium, William Beaumont Army Medical Center. El Paso, TX, Nov 92.

Donovan M: Presentation at 44th Annual Postgraduate Short Course in Oral and Maxillofacial Surgery. Walter Reed Army Medical Center. Washington, DC, Oct 93.

Filler TC: Midline Approach to the Posterior Ilium for Cortico-cancellous Bone Graft Harvest. Southwest Society of Oral and Maxillofacial Surgeons Annual Meeting. South Padre Island, TX, Apr 93.

Gustafson R: Maxillofacial Reconstruction Utilizing Calvarial bone Grafts and Titanium Implants. A Preliminary Report. 75th Annual AAOMS Annual Meeting, Scientific Sessions and Exhibition. Orlando, FL, Sep 93.

Gustafson R: Reconstruction of the Glenoid Fossa with Autologous Calvarial Bone and Rigid Fixation. Southwest Society of Oral and Maxillofacial Surgeons Annual Meeting. South Padre Island, TX, Apr 93.

Hanson L: Maxillofacial Reconstruction Utilizing Calvarial bone Grafts and Titanium Implants. A Preliminary Report. Southwest Society of Oral and Maxillofacial Surgeons Annual Meeting. South Padre Island, TX, Apr 93.

#### Department of Medicine

Do, Thien: Predicting Mortality of GI Bleed Patients by APACHE II and Hepatic Function Tests in Triage Settings. 74th Annual ACP Meeting. Washington, D.C., 1-4 Apr 93.

Jimenez C: A Review of Prevalence of Do Not Resuscitate Orders and Living Wills Documented Among Patients Dying in an Army Teaching Hospital Prior to the Enactment of the Self-Determination Policy. 9th Annual ACP/Army Regional Meeting. San Francisco, CA, 5-8 Nov 92.

Lane WN: Critical Care Medicine: Where Are We Now and Where Should We Go. 9th Annual ACP/Army Regional Meeting. San Francisco, CA, 5-8 Nov 92.

Lane WN: Evaluation of House Officers' Knowledge of Critical Care Procedures. 15th Annual Spring Meeting of Association of Program Directors in Internal Medicine. Washington, DC, 29-31 Mar 93.

#### Department of Nursing

Graham JI: Current Challenges in Nursing Administration. Management Course held at University of Texas at El Paso. El Paso, TX, Spring 1993.

Graham JI: Integration of Leadership Into Administrative Practice. Principles of Advanced Nursing Administration Course. Fort Sam Houston, TX, Sep 93.

McAnnany D: The Hospital Information System: Nursing Pathways (WBAMC). 1993 Army Nurse Corps Postgraduate Short Course: Computer Applications for Nursing. Rockville, MD, 26-30 Sep 93.

Moreno C: Neonatal Surgical Emergencies. University of Texas at El Paso Advanced Neonatal Intensive Care Course. El Paso, TX, Sep 93.

Moreno C: Perinatal Loss. Presented at Ft. Bliss Chaplain's Office (Jan 93) and AWHONN Chapter Meeting (Sep 93). El Paso, TX.

Moreno C: Presentation to Loss-Support Group at Thomason Hospital. El Paso, TX, Jul 93.

Piper C: The Clinical Nurse Specialist in Trauma. Advanced Nursing Practice Conference; Formula for the Future. New Orleans, LA, 11-12 Mar 93.

Piper C: Free Trade and Its Impact on border Health: Cultural Nursing Perspectives. TONE Workshop. El Paso, TX, 15 Apr 93.

Piper C: Stress Management and Post Traumatic Stress Disorder. Military Professional Skills for the Practical Nurse Course. El Paso, TX, 16-20 Aug 93.

Piper C, Clark S: Post Traumatic Stress Disorder. Texas Nurses Association Meeting. El Paso, TX, 11 Jan 93.

Piper C, Beeman W: Conflict Resolution. University of Texas at El Paso CEU Management Course. El Paso, TX, Spring 93.

Rettig F: Reduction of Discomfort from Dorsogluteal Injection by Using Different Body Positions. Sigma Theta Tau Nursing Research Conference. El Paso, TX, 2 Oct 92.

Rettig F: Domestic Violence. National Black Nurses Association 21st National Institute and Conference. Orlando, FL, 4-8 Aug 93.

Shinners K: AIDS in Women and Children. Presented at AWHONN Chapter Meeting (Mar 93) and at University of Texas at El Paso Advanced Neonatal Intensive Care Course (Sep 93). El Paso, TX.

Shinners K: Fetal Monitoring. Armed Forces District Meeting. Norfolk, VA, Nov 92.

Shinners K: Preterm Labor, OB/GYN Emergencies. AWHONN Fetal Monitory Course. Gorgas Army Community Hospital, May 93.

Steinmetz MA: The Hospital Information System: CHCS - The DOD System. 1993 Army Nurse Corps Postgraduate Short Course: Computer Applications for Nursing. Rockville, MD, 26-30 Sep 93.

Varner A: Presentation at Churchill Middle School Health Fair. El Paso, TX, Oct 92.

Varner A: Respiratory Emergencies. Pediatric Advanced Life Support Course at Texas Tech. El Paso, TX, Apr and Sep 93.

Weaver L: Pulmonary Module for Basic Critical Care. Course held at University of Texas at El Paso. El Paso, TX, 8 Feb and 21 Jun 93.

**Department of Ob/Gyn**

Benson C, Hawley-Bowland C: Pelvic Prolapse (poster presentation). Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Brittain PC: Effect of Epidural Anesthesia in Trial of Labor for Vaginal Birth After Cesarean Section. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92. 1-5 Nov 92.

Brittain PC, Page T, Soisson AP: Fatty Infiltration of the Liver in Pregnancy: A Case Report. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Chamales I, Ladwig M, Berg E (Pathol), Soisson AP: Acardiac Amorphous Triplet. A Case Report. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Feeley J: Spontaneous Abortion and the Gulf War. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Fontenot JP, Chamales I, Soisson AP: Purple Toe Syndrome. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Kingsley GM: Necessity of Post Immunoglobulin Administration. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Kingsley GM, Soisson AP: Uterine Sacculation: A Rare Complication of Pregnancy. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Maxwell GL: A New Ureteral Anastomotic Device: The UNILINK System. A Pilot Study. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Maxwell L, Soisson AP, Miles P: Failure of GnRH Therapy in Patients with Metastatic Ovarian Sex Cord Stromal Tumors. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Murphy J: Asymptomatic Adnexal Absorption: A Series of Four Cases. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Murphy J: Potter's Sequence: An Unusual, Early Presentation. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Napolitano P: Pregnancy After Failed Tubal Ligation: A Review of WBAMC's Experience. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Napolitano P, Hawley-Bowland C: Incontinent Woman (poster presentation). Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Soisson AP, Clarke-Pearson D: Subcutaneous Retention Sutures in the Prevention of Superficial Wound Dehiscence. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Webb JC, Baylis P: Pregnancy Complicated By Primary Hyperaldosteronism. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Webb JC, Demarest G, Davis VH, Jones DA: Hemoperitoneum As a Result of Traumatic Rupture of a Hemorrhagic Ovarian Cyst. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

Wharton G: Male Dysplasia. Armed Forces District Meeting of the American College of Obstetricians and Gynecologists. Norfolk, VA, 1-5 Nov 92.

#### Department of Pediatrics

Atkinson AW: Attention Deficit Disorders in Adolescence. Bliss Army Hospital, Ft. Huachuca, AZ, 7 Oct 92.

Atkinson AW: Types of Attention Deficits and Their Medical Management. 28th Annual Meeting of Texas Association for Children with Learning Disabilities. Houston, TX, 12 Nov 92.

Rupp RE, Schydlower M: Demographics of Military Dependent Children and Adolescents: Projected Shift Toward an Adolescent Patient Population in the Military Pediatric Health Care System (abstract). Tri-Service Seminar 1993.

Weisse ME, Eberly B, Person DA: In Vitro Superiority of Wine vs Pepto Bismol Against Enteropathogens (abstract). 41st Annual Meeting of the Society of Am Trop Med Hygiene. Seattle, WA, Nov 92.

#### Department of Surgery

Beck, WG: Advances in Electrocochleography. Military Audiology Short Course. Norfolk, VA, 2-4 Mar 93.

Flynn TW (presenter), Connery SM (DCI), Smutok MA, Zeballos RJ (DCI), Weisman IM (DCI): Comparison of Cardiopulmonary Responses to Forward and Backward Walking and Running in Normals. 1993 Annual Meeting of the American College of Sports Medicine. Seattle, WA, 2-5 Jun 93.

Gormley TS: Testes Cancer. Tumor Board Conference, William Beaumont Army Medical Center. El Paso, TX, 19 Aug 93.

Harvey PT: A Comparison of Static Grip Strength Measurements Taken on the Jamar Dynamoter and the BTE. American Society of Hand Therapists 15th Annual Meeting. Phoenix, AZ, 5-9 Nov 92.

Kestner MS: Guided Percutaneous Drainage For Post-Traumatic Empyema Throacis-Safe and Effective Therapy. Society of Critical Care Medicine's 1993 Educational and Scientific Symposium. New York, NY, 9-13 Jun 93.

Knott MC, Thompson R, Pannbacker M, Middleton G, Sanders K: Guidelines, Regulations, Romance: Let's Discuss It (Speech Pathology Training, Certification, License), A Panel Discussion. Texas Speech-Language-Hearing Annual Meeting. Corpus Christi, TX, 14-18 Apr 93.

Knott MC: Opportunities in Speech-Language Pathology. Ysleta Independent School District - Del Valle Hight School Career Day. El Paso, TX, 5 Mar 93.

Knott MC: Alaryngeal Speech Devices for the Laryngectomee. Inservice, El Paso Cancer Society Lost Chord Club. El Paso, TX, 12 Jul 93.

Morey A: Clinical Experience with Biopsy Gun for Testis Needle Biopsy. 1993 AUA Chief Resident's Meeting.

Scully TJ: Accuracy of Diagnosis of Stress Fractures by Radiotracer Bone Scans is Limited by a High Incidence of Clinically Insignificant Positive Findings. AAOS Annual Meeting. San Francisco, CA, 17-19 Feb 93.

Zumwalt M: Eosinophilic Granuloma. Carrie Tingley Seminar. Albuquerque, NM, 15-16 Jan 93. Carrie Tingley Hospital. Albuquerque, NM, 15-16 Jan 93.

# DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 86/17

STATUS: Ongoing

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

START DATE: Mar 86

ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: B Manna, JI Enriquez

KEY WORDS: Tracheal mucin, Human

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**Study Objective:** This protocol 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:**

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 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:** A polyclonal antibody has been raised in the rabbit against human mucin apoprotein. Recently, our laboratory, in collaboration with Drs. B. Kaufman and S. Batra of Duke University Medical Center, Durham, N.C., has been able to clone the mucin gene in a cell line by utilizing this antibody. Sequencing of the mucin cDNA is now underway.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/16A

STATUS: Ongoing

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

START DATE: Jan 89

ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: B Manna, JI Enriquez

KEY WORDS: Mucin, animal

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**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 establishing 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 studied 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 studied 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 excised aseptically, 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  $1-2 \times 10^6$  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% CO<sub>2</sub>, 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 <sup>3</sup>H glucosamine and <sup>35</sup>SO<sub>4</sub> 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 <sup>3</sup>H glucosamine and <sup>35</sup>S O<sub>4</sub> 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).

**Amendment (Jan 94):** Time extended to Oct 94. Additional number of rabbits is required to complete project.

**Progress:** Rabbit tracheal epithelial cells, cultured in collagen-coated dishes in serum-free and hormone-supplemented medium containing retinoic acid, have been found to express mucin gene and to secrete mucins into the medium. When cultured in the same medium without retinoic acid, the cells did not differentiate, nor did they express the mucin gene. Different pharmacologic agents had little effect on the mucin gene expression. Only the steroid prednisolone had definite inhibitory effect. A chemical carcinogen, N-methyl-N-nitrosoures, had a profound effect on the cell morphology and inhibited the mucin gene expression. Withdrawal of the chemical and incubation of the cells in the medium containing retinoic acid reversed the nature of the cells to a more normal condition with the reappearance of the mucin gene. We are now studying the control mechanism involved in the production of mucins.

**Reference:**

Bhattacharyya SN, Ashbaugh P, Lund M, Manna B: In vitro effects of drugs on production of mucin in rabbit tracheal epithelial cells expressing mucin gene. *Inflammation* 16:371-382, 1992.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/37A

STATUS: Ongoing

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

START DATE: Oct 90

ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: BC Veit

KEY WORDS: Bronchial mucin

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**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<sub>2</sub>, and NO<sub>2</sub>, 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:** We have made tremendous progress on this protocol. We have just completed two major studies concerning the effect of retinoic acid (Vitamin A) on the differentiation as well as the expression of mucin gene in rat tracheal epithelial cells in culture. We observed that rat tracheal epithelial cells did not express the mucin gene in the absence of retinoic acid in the culture medium. When the medium was supplemented with retinoic acid, the mucin gene reappeared. The mucin gene was found to be stabilized by inhibitor of both transcription and translation. Steroid has inhibitory effect on mucin gene expression.

**Reference:**

Manna B, Lund M, Ashbaugh P, Kaufman B, Bhattacharyya B: Effect of retinoic acid on mucin gene expression in rat airways *in vitro*. *Biochem J* (London). In press 1993.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/06

STATUS: Terminated FY93

**TITLE:** Development of an Isothermic Gene Amplification-Enzyme Immunoassay (GA-EIA) System for *Mycobacterium tuberculosis* Suitable for Use in DEPMEDS Laboratories

**START DATE:** Jan 93

**ESTIMATED COMPLETION DATE:** Terminated

**PRINCIPAL INVESTIGATOR:** MAJ William Nauschuetz

**DEPARTMENT:** DCI

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** HM Gelston, W Sun, M Lund

**KEY WORDS:**

*Mycobacterium tuberculosis*, Gene Amplification-Enzyme Immunoassay

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**Study Objective:** To adapt routine clinical microbiology techniques, suitable for use in DEPMEDS, to a system for the amplification and detection of sequences specific for *M. tuberculosis*.

**Technical Approach:** This study is triphasic. In Phase I, primers specific for the amplification of IS6110 will be modified for use in self-sustained strand replication (3SR), an isothermic amplification technique which does not require a thermal cycler. The primers will be evaluated on ATCC strains of mycobacterial species. If the primers amplify a specific sequence, Phase II will then compare the detection of 3SR-amplified *M. tuberculosis* DNA with standard mycobacteriologic isolation and identification procedures. In Phase III, a 3SR-EIA protocol, using the technology of the VIDAS, will be evaluated.

**Progress:** This protocol has been withdrawn and has been resubmitted in a new format. It has been replaced with WBAMC #93/46.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/46

STATUS: Ongoing

TITLE: Use of High Technology to Determine Risk of Drug-Resistant Tuberculosis in the El Paso Region

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Oct 95

PRINCIPAL INVESTIGATOR: MAJ William Nauschuetz

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: MA Escobedo, L Nickey, VV Tryon, M Lund, GA Handal

### KEY WORDS:

Drug-Resistant Tuberculosis El Paso

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### Study Objective: Short Range Goals

Mobilize key medical treatment facilities within the El Paso region to recognize the threat of TB and MDRTB: We have already accomplished this goal. The Dept. of Clinical Investigation, WBAMC has agreements with the El Paso City/County Health District and with the El Paso Managed Health Care Consortium (representing four academic institutions and three medical centers) to address the threat of TB and MDRTB in the El Paso region.

Introduce Polymerase Chain Reaction (PCR) technology for the identification of *M. tuberculosis* and MDRTB: The Dept. of Clinical Investigation, WBAMC is cooperatively working with the El Paso City/County Health District to investigate the sensitivity of PCR compared to routine TB culture and susceptibilities for the detection of *M. tuberculosis* and MDRTB. We also have an agreement with members of the El Paso Managed Health Care Consortium to share clinical specimens to compare PCR with routine TB culture and susceptibilities.

### Intermediate Range Goals

Establish the rate of TB and MDRTB for a stable population in Juarez and for Mexican nationals being treated in El Paso medical centers: Clinical specimens submitted to medical facilities in Juarez for the diagnosis of TB are stained for the presence of acid-fast bacilli. Those specimens that are AFB smear positive are transported to the El Paso City/County Health District for culture confirmation and antimicrobial susceptibilities. However, the sensitivity of AFB smears is about 50%, so many citizens in Juarez are not laboratory-diagnosed properly. By choosing a stable population within Juarez and doing a sweep collection, we can determine the incidence of TB and MDRTB by performing routine culture on all specimens, despite smear results, and by running PCR on each specimen submitted. The PCR should provide a more sensitive method of detecting latent and subclinical TB. We would also use PCR for TB and MDRTB on all Mexican nationals admitted to El Paso medical centers showing respiratory symptoms.

### Long Range Goals

The data derived from this study can be used to establish the El Paso region as a high-risk area for TB and MDRTB and as an area that has fulfilled the CDC Task Force Guidelines of implementing high technology for the rapid detection of TB and MDRTB. The data can then be used as a baseline for efficacy studies of newer generation antimycobacterial agents, including those requiring shorter periods of treatment.

**Technical Approach:** This study is triphasic. In Phase I, primers specific for the amplification of IS6110 will be used for PCR amplification of *M. tuberculosis*. The primers will be evaluated on ATCC strains of mycobacterial species. If the primers amplify a specific sequence, Phase II will then compare the detection of PCR-amplified *M. tuberculosis* DNA with standard mycobacteriologic isolation and identification procedures. In Phase III, we will use a primer set that specifically amplifies a 411 base pair sequence from the RNA polymerase gene (*rpoB*) of *M. tuberculosis*. Amplification will be done only on pure growth from routine mycobacteriologic media. The 411 base pair fragment that occurs as a result of the amplification will be sent to Dr. Tryon's laboratory at UT-Health Science Center at San Antonio. He will sequence the fragment and determine if mutations are indicative of rifampin-resistance are present in the sequence.

**Progress:** Specimens have been collected from the El Paso City/County Health Department and are being stored frozen. Due to personnel shortages, DCI has had to seek technical help for this project outside the medical center. A technologist from Texas Tech University Health Sciences Center will work 20 hours a week on the project. A memorandum of agreement between the two institutions has been written and is currently being staffed. An approximate start date is Nov 93.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 88/04

STATUS: Ongoing

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

START DATE: Nov 87

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: Bruce C. Veit, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Smiley, S McIntyre

KEY WORDS: Allergy, T-cells subsets, Immunoregulation

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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:** Our studies of T cell activation in Bermuda grass allergy patients have focused on putative immunoregulatory effects of subsets of T cells in peripheral blood of such patients. Our working hypothesis has been that suppressor T cells develop as a consequence of immunotherapy and that these suppressor cells are responsible, at least in part, for inhibiting the IgE-mediated release of chemical mediators that characterize the allergic reaction. We have utilized various approaches in an attempt to detect this subset of suppressor T cells in the blood of patients with Bermuda grass allergy who were undergoing immunotherapy. Use of a protocol that had been reported to demonstrate the existence of such a population in patients with ragweed allergy, confirm those findings in our study population but did not yield any evidence of suppressor cell activity that was directed toward Bermuda grass allergens. We concluded 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. It is possible that the allergen preparation that we are using contains a variety of substances which may have counteractive effects that interfere with the development of or mask the expression of the suppressor cells. Our data suggest that the inability to demonstrate suppressor cell activity to Bermuda grass allergen in patients whom exhibit suppressive activity to Ragweed allergen may be due to a hyper-responsiveness which masks the suppressive activity. A manuscript which describes the results of this study is now in preparation.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/04

STATUS: Ongoing

TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: Bruce Veit, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Breast cancer

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**Study Objective:** The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanism(s) of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer. Our studies will attempt to answer the following questions:

**Technical Approach:** The proposed research program consists of three approaches:

(1) Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemotherapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; and (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations

(2) Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc); use of flow cytometry on single-cell suspensions and immunohistochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3) Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; and (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemocytotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility during cell cycle.

**Progress:** Due to a prolonged contracting process in the purchase of our image analysis system and to an even longer and more involved contracting process that required extensive and technically demanding justification in the purchase of our flow cytometer/cell sorter, we have been delayed almost 1 year in initiating our studies of breast cancer cells.

At the present time, we have our flow cytometer/cell sorter in place and operational and we have our image analysis system in place and operational. Ms. Rebecca Smiley, GS-9 Microbiologist, received formal training in the operation of our flow cytometer/cell sorter at the Becton-Dickinson facility in Boston, Massachusetts in mid-September 1993. Dr. Veit, PI, and Ms. McIntyre, GS-7 Medical Technologist, received formal training in the operation of our image analysis system at the Roche Image Analysis Systems facility in Research Triangle, North Carolina during the first week in October 1993.

Several human breast cancer cell lines have been obtained from the American Type Culture Collection Company and are currently being maintained by serial passage in *in vitro* culture in our laboratory. Samples of all lines have been frozen in 10% DMSO and are being stored in our liquid nitrogen repository. These cell lines have been utilized for establishing the various staining procedures for the immunohistochemical (image analysis) and flow cytometric analyses of DNA (S-phase fraction, cell cycle, and ploidy), epidermal growth factor receptor expression and production, estrogen/progesterone receptor expression, HER-2/neu expression, Ki-67 expression, PCNA expression, transforming growth factor expression, and insulin-like growth factor expression.

Additional training may be required for the implementation of our DNA modeling software (Modfit) in our flow cytometric studies of DNA. Due to the delay in onset of our studies because of a prolonged contracting process in obtaining our flow cytometer/ cell sorter and image analysis system, the PI will request that a no-cost extension of 18 months be granted by the contracting officer for this project (that the termination of this contract be extended from September 30, 1994 to March 31, 1996). The personnel involved in this project are fully trained (with the exception of DNA modeling training) in the operation of our flow cytometer/cell sorter and image analysis system and are currently involved in the analysis of established breast cancer cell lines and primary breast cancer biopsies with respect to growth factor requirements and/or growth factor receptor expression. *In vivo* studies, utilizing growth of breast tumors in nude mice, as well as studies of apoptosis, will be initiated within the next six months.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/05A

STATUS: Ongoing

TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors using the Murine Model

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Oct 95

PRINCIPAL INVESTIGATOR: Bruce Veit, PhD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: K Nauschuetz

KEY WORDS: Breast cancer

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**Study Objective:** The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanisms of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer. Our studies will attempt to answer the following questions: (1) What are the phenotypic and biological characteristics of variant sublines within breast cancers? (2) Do human breast tumors that grow in athymic nude (nu/nu) mice retain their histological grade and variant subline profiles? (3) What are the selective pressures which create heterogeneity in breast cancers? (4) Do breast cancer relapses occur because of physiological (non-genetic) or mutational (genetic) alterations in growth factor signaling pathways? (5) Do normal stromal cells exert growth regulatory influences on tumor cells via growth factor secretion and/or cytokine production? (6) Does growth factor deprivation of growth factor-dependent tumor cells result in the initiation of apoptosis?

**Technical Approach:** The proposed research program consists of three approaches:

(1) Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor-associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemo-therapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations.

(2) Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc.); use of flow cytometry on single-cell suspensions and immunohistochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3) Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility

during cell cycle.

**Progress:** Due to a prolonged contracting process in the purchase of our image analysis system and to an even longer and more involved contracting process that required extensive and technically demanding justification in the purchase of our flow cytometer/cell sorter, we have been delayed almost 1 year in initiating our studies of breast cancer cells.

At the present time, we have our flow cytometer/cell sorter in place and operational and we have our image analysis system in place and operational. Ms. Rebecca Smiley, GS-9 Microbiologist, received formal training in the operation of our flow cytometer/cell sorter at the Becton-Dickinson facility in Boston, Massachusetts in mid-September 1993. Dr. Veit, PI, and Ms. McIntyre, GS-7 Medical Technologist, received formal training in the operation of our image analysis system at the Roche Image Analysis Systems facility in Research Triangle, North Carolina during the first week in October 1993.

Several human breast cancer cell lines have been obtained from the American Type Culture Collection Company and are currently being maintained by serial passage in *in vitro* culture in our laboratory. Samples of all lines have been frozen in 10% DMSO and are being stored in our liquid nitrogen repository. These cell lines have been utilized for establishing the various staining procedures for the immunohistochemical (image analysis) and flow cytometric analyses of DNA (S-phase fraction, cell cycle, and ploidy), epidermal growth factor receptor expression and production, estrogen/progesterone receptor expression, HER-2/neu expression, Ki-67 expression, PCNA expression, transforming growth factor expression, and insulin-like growth factor expression.

Additional training may be required for the implementation of our DNA modeling software (Modfit) in our flow cytometric studies of DNA. Due to the delay in onset of our studies because of a prolonged contracting process in obtaining our flow cytometer/ cell sorter and image analysis system, the PI will request that a no-cost extension of 18 months be granted by the contracting officer for this project (that the termination of this contract be extended from September 30, 1994 to March 31, 1996). The personnel involved in this project are fully trained (with the exception of DNA modeling training) in the operation of our flow cytometer/cell sorter and image analysis system and are currently involved in the analysis of established breast cancer cell lines and primary breast cancer biopsies with respect to growth factor requirements and/or growth factor receptor expression. *In vivo* studies, utilizing growth of breast tumors in nude mice, as well as studies of apoptosis, will be initiated within the next six months.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 83/37

STATUS: Ongoing

TITLE: *Cardiopulmonary Effects of Stressful Exercise at 4,000 Feet on SCT Individuals (Monitor: MAJ Keenan)*

START DATE: Jul 84

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Sickle cell trait, Stress, Hypoxia, Exercise

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**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 DLCO<sub>SB</sub> (ml/min/mmHg) and steady state diffusing capacity DLCO<sub>SS</sub> (ml/min/mmHg) (Filly 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 (HgbAS) 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.

**Addendum (Mar 85):** Added testing at 7,500 ft

**Progress:** 120 subjects were tested. Data collected at simulated 4,000 m (Phase III) is being evaluated. MAJ Keenan has replaced MAJ Becker as medical monitor. MAJ Becker has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

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 Keenan)

START DATE: Jul 89

ESTIMATED COMPLETION DATE: 1995

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RJ Zeballos, J Little, TW Martin

KEY WORDS: Sickle cell trait, Endurance exercise

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### Study Objective:

1. To determine if submaximal (50-70% VO<sub>2</sub> 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.

Semiannual Review: Apr 93 - no new enrollments. Narrative unchanged from annual report.

Progress: No new enrollments; data analysis is still underway. MAJ Keenan has replaced MAJ Becker as medical monitor. MAJ Becker has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/68

STATUS: Ongoing

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

START DATE: Jul 89

ESTIMATED COMPLETION DATE: Feb 94

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RJ Zeballos

KEY WORDS: Sickling, Sickle cell trait, Kinetics

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**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 Venous 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  $FIO_2=21\%$ ,  $PIO_2=127\text{mmHg}$  and then breathing a hypoxic gas mixture ( $FIO_2=14\%$ ,  $PIO_2=85\text{mmHg}$ ) 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 ( $V_{O_2}$ ), carbon dioxide production ( $V_{CO_2}$ ), 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 ( $VD/V_T$ ) and the alveolar-arterial oxygen pressure difference [ $P(A-a)O_2$ ] 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 (b) a one-way back pressure valve placed between the venous catheter and the port where (c) the 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 (e) a 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%  $FIO_2$ ), 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.

**Semiannual Review:** Apr 93 - no new enrollments. Narrative unchanged from annual report.

**Progress:** No change since FY91 report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/34

STATUS: Ongoing

TITLE: The Effect of Advanced Individual Training on Anaerobic Power (Monitor: LTC Tremper)

START DATE: Jun 93

ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RJ Zeballos, A Linden, R Belbel

KEY WORDS: AIT anaerobic

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### Study Objective:

(1) To characterize the anaerobic power of soldiers, and to determine whether current AIT physical training regimens improve anaerobic power.

(2) To determine the impact of intense anaerobic work on cardiopulmonary functions.

### Specific Objectives:

◦ To develop a database that may be used as a reference to gauge performance levels of peak anaerobic power in military personnel.

◦ To study the changes in maximal aerobic power and anaerobic power of soldiers, pre- and post-AIT course.

◦ To determine whether the cardiopulmonary and metabolic responses to the post-AIT exercise test differ from pre-AIT values.

◦ To study the changes in cardiopulmonary physiology during and after intense, all-out anaerobic work.

◦ To apply these results to different military operational field tasks so that specific training standards can be appropriately modified if necessary.

**Technical Approach:** Prospective study. The same volunteers will be used as their own control. All subjects will undergo the same treatment (AIT) and testing (pre-and post-AIT) protocols.

**Progress:** Study has just begun—no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/44

STATUS: Ongoing

TITLE: Early Cardiopulmonary Exercise Abnormalities in Asymptomatic Smokers (Monitor: LTC Tremper)

START DATE: Jan 94

ESTIMATED COMPLETION DATE: Jan 96

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RJ Zeballos

KEY WORDS: exercise abnormalities asymptomatic

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### Study Objective:

1. To recruit a group of asymptomatic smokers with at least a 15 pack years smoking history and normal spirometry and carefully match them by age, race, and activity level to a comparable group of non-smokers. Both groups will be well characterized based on extensive health questionnaire responses, complete baseline PFTs (spirometry, lung volumes, diffusing capacity of carbon monoxide [DLCO], selected "small airway" tests), bronchial hyperreactivity testing and coronary risk stratification analysis. The results of previous studies (Cooper et al 1968, Daniels et al 1984, Sue et al 1985) that have attempted to evaluate cardiopulmonary differences between smokers and non-smokers were clouded by poor characterization of the populations studied with respect to: level of physical activity, carboxyhemoglobin (COHb) level, concurrent conditions, abnormalities of resting PFTs, and description of symptoms, etc.

2. To determine whether maximal exercise testing is an effective diagnostic tool for the early detection of cardiopulmonary abnormalities in asymptomatic smokers.

a. To determine if exercise capacity as determined by a  $VO_2$  max and by 2 mile run time is different between asymptomatic smokers and non-smokers (Daniels et al 1986, Bahrke et al 1986) when physical activity level and COHb are controlled.

b. To determine whether other more subtle differences in the cardiopulmonary response to exercise can be detected between asymptomatic smokers and non-smokers. These may include pulmonary gas exchange abnormalities (Frans et al 1975) and abnormal tidal flow-volume loop differences as indicators of early expiratory flow limitation which in asymptomatic smokers may only be seen at maximal exercise. Both of these types of abnormalities would possibly be reflective of "peripheral airways" dysfunction. Also, subtle cardiovascular patterns suggestive of occult heart disease may also be discerned.

3. To relate the cardiopulmonary abnormalities observed in asymptomatic smokers to various components of the health questionnaire including smoking history, activity level, coronary risk analysis, etc. and to resting PFTs and results of a bronchial hyperreactivity testing.

4. To generate a data base of asymptomatic smokers with and without abnormal cardiopulmonary response to exercise.

**Technical Approach:** Prospective controlled study.

**Progress:** Investigators are awaiting receipt of equipment to begin study.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/57

STATUS: Ongoing

TITLE: Effect of ATROVENT® in Exercise Performance in Patients with Chronic Pulmonary Disease  
(Monitor: LTC Tremper)

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Apr 94

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RJ Zeballos

KEY WORDS: ATROVENT®, COPD

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### Study Objective:

Ipratropium bromide (ATROVENT®) is an anticholinergic agent with well established bronchodilative properties in patients with chronic obstructive pulmonary disease (COPD) (NEJM 1993;328:1017-22). Ipratropium treatment also reduces the volume of sputum without altering its viscosity (Chest 1991;86:871-6). Recent *in vitro* evidence also suggests that ipratropium may have anti-inflammatory effect (Rennard, Personal Communication).

Improved airway patency observed after inhalation of ipratropium may also lead to a decrease in static lung volumes, in particular, trapped air volume (TAV) (Brit Med J 1988;297:1506-09). This, in turn, may lead to decrease in work of breathing and a decrease in dyspnea, including exertional dyspnea.

Thus, chronic administration of ipratropium, in patients with COPD may lead to the increase in alveolar ventilation and consequent improvement in oxygen saturation and possible attenuation of the inflammatory process, well documented in lungs of patients with COPD. These physiological improvements may be particularly important during exercise. However, the effect of chronic dosing with ipratropium on exercise tolerance was only rarely studied (Am Rev Respir Dis 1992;145:A758).

Thus, in this study we will examine effect of chronic treatment with ipratropium MDI on exercise tolerance in COPD patients.

**Technical Approach:** A double-blind, randomized, placebo-controlled, two-arm parallel multi-center study.

**Progress:** No data to report as study is just beginning.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/48

STATUS: Ongoing

TITLE: Practical Value of Hyper-Reactive Airway Testing in the Assessment of Asthma in Army Recruits  
(Monitor: LTC James Wallingford)

START DATE: Aug 89

ESTIMATED COMPLETION DATE: Jul 95

PRINCIPAL INVESTIGATOR: R. Jorge Zeballos MD

DEPARTMENT: DCI

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: IM Weisman

KEY WORDS: Asthma, AIT, Army recruits, Reactive airway disease, Brochial challenges

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### 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 broncho- constriction 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.

Semiannual Review: Apr 93 - no new enrollments. Narrative unchanged from annual report.

**Progress:** We have been working on the methodology. At the present time, we have conducted only pilot studies. LTC Wallingford has replaced MAJ Becker as medical monitor. MAJ Becker has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/20A

STATUS: Ongoing

**TITLE: Comparison of Osseointegration of Titanium Implants in Cranial and Iliac Autologous Bone Grafts Stabilized with Immediate Titanium Implant Fixtures in Miniature Swine**

START DATE: May 91

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: LTC Nathan C. Dickerson

DEPARTMENT: Dentac

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: MG Donovan

KEY WORDS: Titanium implants, cranial bone grafts, onlay bone grafts

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### Study Objectives:

1. Examine time interval of osseointegration of titanium implants when placed in immediate bone grafts.
2. Compare the rate of osseointegration, i.e., success rate, of titanium implants in immediate autologous calvarial and iliac bone grafts.
3. Compare the rate of osseointegration, i.e., success rate, between immediate placement of titanium implants in grafted bone to titanium implants in mature bone grafts.
4. Determine the recommended time interval of osseointegration required prior to placement of functional load on implants.

**Technical Approach:** Six miniature swine will be used for this study. Each animal will serve as its own control by having an implant placed in a non-grafted facial bone site.

Under general anesthesia, each swine will have autologous bone from the outer table of the frontal and parietal bones harvested and a corticancellous bone graft from the iliac crest harvested. Placement of the bone grafts will be to the nasal bones of the swine. The bone grafts will be rigidly fixed utilizing one or more Branemark titanium implant fixtures of 7mm or 10mm lengths.

Four calvarial bone grafts and four iliac bone grafts will be utilized on each animal. The calvarial bone grafts will be on the right side and the iliac bone grafts will be on the left side of the nasal bones.

One swine will be euthanatized at one month, two months, four months, six months, eight months, and twelve months to obtain specimens for histological studies. Twenty-one days prior to scheduled euthanasia and biopsy, the animals will be marked with an I.M. injection of a tetracycline derivative to assess new bone growth in the bone grafts adjacent to the implant fixtures.

Barium sulfate mixed with heparinized formalin will be infused after euthanasia to mark neovascularization in the bone grafts.

Each bone graft site will be physically measured for evidence of bone resorption or growth, and these measurements will be compared with the dimensions of the bone grafts measured at time of initial placement. The titanium implants are of fixed length and will serve as markers for loss or maintenance of the bone graft heights along with the above physical measurements.

**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:** Histological studies and micro-radiographic studies of the specimens are progressing. Some time

was needed to develop techniques for sectioning the specimens to avoid disruption of the interface between the titanium implants and the bone grafts. Now that a satisfactory technique has been established, completion of the microscopic examinations is expected by the first of the year.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/37

STATUS: Completed FY93

TITLE: Bone-Anchored Craniofacial Prostheses Investigation

START DATE: Oct 89

ESTIMATED COMPLETION DATE: Sep 93

PRINCIPAL INVESTIGATOR: COL Michael G. Donovan

DEPARTMENT: Dentac

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: J Gary

KEY WORDS: Implants, Bone-anchored prostheses

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### 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:** The Oral and Maxillofacial Surgery Service at William Beaumont Army Medical Center has been involved in a multi-center FDA research for approval of extra oral bone anchored prostheses for the reconstruction of facial structures. The implants were produced by Nobelpharma of Sweden and the results from multiple investigation sites are being submitted at this time for final approval with the FDA.

At this investigation center, four patients were treated with cranial implants utilizing 12 cranial implants. One implant did not osseointegrate. This failure was due to the implant being placed in residual alveolar bone of the maxilla. The loss of this implant did not compromise the prosthetic reconstruction of this patient.

Two patients had cranial implants placed in their mastoid bones for ear prostheses which proved to be stable enough to support eyeglasses and had good esthetics. One patient had cranial implants placed to reconstruct his right orbit with a prosthesis with good stability and esthetics. The other patient had cranial placed in the

**piriform rim for a nose prosthesis which was stable enough for the patient to wear his glasses.**

**There were no adverse reactions nor complications associated with the cranial implants, and these implants provided stable supports for facial prostheses with improved esthetics over traditional plastic surgery reconstruction of these structures.**

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/38A

STATUS: Ongoing

TITLE: Evaluation of Osseointegration of Immediately Placed Titanium Implant Fixtures in Allogeneic Onlay Bone Graft in Miniature Swine

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Trent C. Filler

DEPARTMENT: Dentac

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: M Donovan, N Dickerson

KEY WORDS: Titanium implants

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**Study Objective:** To examine if osseointegration of titanium implants occurs in allogeneic onlay bone graft when placed immediately using the concepts of tissue guided regeneration; to examine time interval of osseointegration of titanium implants when placed immediately into allogeneic onlay bone graft using the concepts of tissue guided regeneration; to compare rate of osseointegration, i.e., success rate between placement of titanium implants in allogeneic grafted bone to titanium implants placed in autogenous bone grafts (study #92/20, Comparison of Osseointegration of Titanium Implants in Cranial and Iliac Autologous Bone Grafts Stabilized with Immediate Titanium Implant Fixtures in Miniature Swine); and to determine the recommended time interval of osseointegration required prior to placement of functional load in implants placed in grafted allogeneic bone.

**Technical Approach:** Fifteen miniature swine will be used for this study. Up to three animals will serve as a source for the allogeneic calvarial and iliac bone grafts to be grafted to the other twelve animals. The long bones from these three animals will serve as a source for Demineralized Bone Powder. The bone will be harvested and then processed by the Department of Anatomy, Medical College of Georgia and the protocol on Appendix A.

Under general anesthesia each of the twelve swine will have allogeneic bone from the frontal and parietal region and allogeneic bone from the iliac crest grafted to the nasal bones, maxilla and mandibular. The allogeneic bone grafts will be augmented with bone morphogenic protein. The bone grafts will be rigidly fixed utilizing one or more Branemark titanium implant fixtures of 10 mm length and Luhr rigid fixation screws.

Five calvarial bone grafts and five iliac bone grafts will be utilized on each animal. The calvarial bone grafts will be on the right side, and the iliac bone grafts will be on the left side of the nasal bones, lateral maxilla, and mandibular ramus.

Two of the calvarial bone grafts and two of the iliac bone grafts will be covered with tissue guided regeneration material from Gore-Tex.

Two swine will be euthanized at one month, two months, four months, six months, eight months and twelve months to obtain specimens for histological studies.

Barium sulfate mixed with heparinized formalin will be infused after euthanasia to make neovascularization in the bone grafts identifiable radiographically.

Each bone grafts site will be physically measured for evidence of bone resorption or growth, and the measurements will be compared with the dimensions of the bone grafts measured at time of initial placement.

The titanium implants are of fixed length and will serve as markers for loss on maintenance of the bone graft heights as well as the above physical measurements.

**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:** Funding has been obtained for the materials for this protocol by Nobelpharma for the titanium implants, Howmedical of Albuquerque for the micro screws, and W. L. Gore and Associates for the tissue guided regeneration material. The freeze dried allogenic swine bone and their demineralized bone powder are being supplied by the Department of Anatomy, Medical College of Georgia. This protocol is to utilize the nine miniature swine presently housed at the Biological Research Service. There has been no change in the study periods, as this study is planned for assessment of one year specimens. The initial start is scheduled for Oct 93.

**MAJ Trent Filler has replaced MAJ Hanson as principal investigator.**

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/33A

STATUS: Ongoing

TITLE: Autologous Pericranium for Temporomandibular Joint Disc Replacement in Sheep

START DATE: Jun 93

ESTIMATED COMPLETION DATE: Aug 94

PRINCIPAL INVESTIGATOR: LTC Roland G. Gustafson

DEPARTMENT: DENTAC

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: MG Donovan, NC Dickerson

KEY WORDS: TMJ, discectomy

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**Study Objective:** (1) Determine the success of autologous pericranium as a temporomandibular joint disc replacement tissue utilizing histological assessments of the morphological changes of the pericranium at timed intervals.

(2) Compare condylar morphological changes in temporomandibular joints repaired with pericranial grafts and joints in which unrepaired discectomies are performed.

**Technical Approach:** (1) Fifteen domestic sheep will be used for this study. A control for a normal temporomandibular joint disc and condyle have been previously studied histologically.

(2) Under general anesthesia, each of the fifteen sheep will have autologous pericranium harvested via a bicoronal flap. An incision over the zygomatic arch and glenoid fossa will give access to the temporomandibular joint space. The TMJ discs will be excised bilaterally and the pericranium sutured to the anterior and posterior stumps of the TMJ disc attachments with non resorbable sutures unilaterally. The other temporomandibular joint will go unrepaired following its discectomy.

(3) Three sheep will be euthanatized at one month, two months, four months, six months, and ten months to obtain specimens for histological studies.

(4) The pericranium from each joint site will be studied for histological changes and fibrous adhesions.

(5) The condyles of each animal will be studied to assess any changes as a result of the autologous pericranium TMJ disc replacement. These will be evaluated radiographically and by histological sections.

**Progress:** To date we have operated on 14 of the 15 animals. Necropsies are to begin in Nov 93 in order to obtain histological results for this study.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/49A

STATUS: Completed FY93

TITLE: Evaluation of Alloplastic Material Polytetrafluoroethylene (PTFE) for Reconstruction of Orbital Floor Defects

START DATE: Sep 92

ESTIMATED COMPLETION DATE: Jun 93

PRINCIPAL INVESTIGATOR: MAJ Larry J. Hanson

DEPARTMENT: Dentac

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: M Donovan, R Gustafson

KEY WORDS: orbital floor defects

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**Study Objective:** Evaluate the alloplastic graft material Polytetrafluoroethylene (PTFE--GORTOX) for reconstruction of floor of orbit defects in preventing enophthalmos and restoring structural integrity and the histologic compatibility of the PTFE within the orbit over time.

**Technical Approach:** Ten sheep will be used for this study. Under general anesthesia a surgical defect of uniform size will be made in the orbital floor of each animal. One of the orbital floors will remain unrepaired at each time period to serve as a control for that time period. One millimeter soft tissue patch PTFE will be utilized for the reconstruction of the defect in three of the four orbits per each time period. Measurements to evaluate enophthalmos will be made prior to the making of the floor defect, after the defect is made, after repair, and at euthanasia to evaluate the stability of the reconstruction. Forced duction tests will be performed prior to development of the orbital floor defect, following reconstruction with PTFE, and at euthanasia. Histological sections through the orbital floor will be evaluated for signs of inflammation and foreign body reaction. Histologic evaluation of the structural integrity of the graft material will also be evaluated. Histological evaluation of the adjacent sinus mucosa, regional lymph nodes, and control lymph nodes from the lower extremity will be evaluated. Sinus mucosa will be biopsied for signs of infection/inflammation at the time of the original surgery.

**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 use of alloplastic graft materials for reconstruction of traumatic defects of the orbital floor is well documented. Many of the alloplastic materials presently being used have less than ideal biocompatibility and handling characteristics. A study to evaluate the efficacy of a medical grade expanded polytetrafluoroethylene (e-PTFE) sheet material for reconstruction of the orbital floor was undertaken. Defects of the orbital floor were created in ten domestic sheep and reconstructed with 1 mm thick e-PTFE sheet material. The surgical sites were evaluated for the development of enophthalmos and biocompatibility at two weeks, one, two, four and six month intervals. The results of this study indicate that the e-PTFE alloplastic reconstructive material has excellent biocompatibility, handling characteristics and prevented enophthalmos when used to reconstruct traumatic orbital floor defects.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/48

STATUS: Completed FY93

TITLE: Intradermal Hepatitis B Vaccination in Patients with Chronic Renal Insufficiency and End Stage Renal Disease (Monitor: LTC Gary Ripple)

START DATE: Jun 92

ESTIMATED COMPLETION DATE: Jun 93

PRINCIPAL INVESTIGATOR: MAJ Jeffrey R. Abrams

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: G Pisel

KEY WORDS: hepatitis vaccination, renal failure

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**Study Objective:** To demonstrate the efficacy of intradermal administration of hepatitis vaccine in hemodialysis patients.

**Technical Approach:** This is a prospective observational study. The investigators intend to demonstrate the efficacy of such a strategy in our dialysis patients and in patients with severe chronic insufficiency. Six hemodialysis patients (one a prior non-responder), and several patients (approx. 6-10) with chronic renal insufficiency will be vaccinated with intradermal Recombivax (recombinant vaccine) every other week and monitored for delayed type hypersensitivity (DTH) reactions. Vaccination will continue until the patient receives 5 doses or develops a DTH reaction. The literature cites no significant adverse reactions to such a regimen except for the possibility of persistent induration and discoloration at the site of inoculation. Bleeding at the site of inoculation might occur as a consequence of recent anticoagulation (dose would be given following the dialysis procedure). NOTE: Study changed to More than Minimal Risk with semiannual review and medical monitor assigned Jul 92.

**Semiannual Review (Apr 93):** To date, 11 patients have been enrolled. Five of the nine patients who completed the series of injections converted. The investigators found it difficult to follow up on patients who were dialyzed elsewhere so they have not recruited any more dialysis patients. All current dialysis patients at WBAMC have either been immunized or refuse to participate. Investigators have not aggressively pursued further enrollees but want about fifteen patients total. Because of personnel changes, the protocol was temporarily suspended, however, the investigators plan to enroll four more patients and complete the series by Jun 93.

**Progress:** Fourteen patients aged 22-71 (average age 51) with creatinine clearance less than 15 ml/min received 10 mcg of Recombivax intradermally every two weeks for up to five doses. Five patients had ESRD secondary to diabetes. Eleven patients were on dialysis at the time of the study. Seven patients (50%) converted after an average of 3.3 injections. The only complication of the injection was persistent dermal reaction at the injection site in some patients. No patient over the age of 65 converted. The conversion rate in patients under 65 was 7 of 9 (78%). Dermal reaction did not correlate with development of detectable antibody. Intradermal Recombivax at 10 mcg per dose produced detectable antibodies in 50% of our patients. Given the age and presence of kidney failure, this rate compares favorably with intramuscular injection and is less expensive.

LTC Gary Ripple replaced LTC Lane as medical monitor. LTC Lane PCS'd.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/41

**STATUS:** Ongoing

**TITLE:** Blood Pressure Control During Scheduled Conversion of Nifedipine XL to Amlodipine

**START DATE:** Sep 93

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** MAJ Jeffrey R. Abrams

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** L McConnell

**KEY WORDS:** amlodipine, hypertension

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**Study Objective:** (1) To determine if adequate blood pressure control can be maintained during a scheduled conversion of nifedipine XL to amlodipine (2) To determine if side effects are less common with amlodipine (3) To determine if adequate control of hypertension is less expensive with amlodipine.

**Technical Approach:** The study will be a prospective, open label trial that utilizes each patient as his or her own control. The incidence of adverse effects and adequate control of blood pressure will be the main parameters that are monitored.

**Progress:** Twelve patients entered the study. One patient felt his blood pressure was too high, complained of being nervous, and stopped taking his medication. Patient had no symptoms. Patient was withdrawn from the study.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/22

STATUS: Terminated FY93

TITLE: Influence of Endogenous and Exogenous Lipids on Pulse and CO-oximetry Measurements (Monitor: LTC Gary Ripple)

START DATE: Mar 92

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Gregory Becker

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: T Do, RC Johnson, G Mock

KEY WORDS: lipids, intralipid, oximetry

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**Study Objective:** To determine if intralipid infusion will influence CO-oximetry variables in critically ill patients; to determine if intralipid infusion will influence pulse oximetry in critically ill patients; to assess if endogenous hyperlipidemia is associated with artifactual changes in CO-oximetry measurements or pulse oximetry; and to determine if both four and six wavelength whole blood spectrophotometry is prone to lipid induced artifact.

**Technical Approach:** Twenty patients will be recruited as controls by the investigators for this study and informed consent will be obtained. Demographic data, a medical problem list, and medications will be recorded on the attached data sheet after a brief interview and chart review. Venipuncture will be performed by one of the investigators and specimens will be sent to the clinical lab with an accompanying requisition slip for a Lipid 2 profile, CBC, and Liver profile. Patients will not be used as controls if there are one or more of any exclusion criteria present (noted elsewhere) or if the lipid profile reveals a diagnosis of hyperlipoproteinemia. Radial artery puncture will be performed by one the investigators or a credentialed Pulmonary Service technician. Both a room air arterial blood gas analysis will be run and recorded on this sample as well as oximetry variables on both the IL-282 CO-oximeter and Radiometer OSM3 hemoximeter. The patient's room air pulse oximetry reading on a single pulse oximeter unit will be performed and recorded.

Forty consecutive patients in the intensive care units who are to receive Intralipid infusion will be recruited by the investigators and informed consent will be obtained from the patient or his/her next of kin or legal guardian. Exclusion criteria are listed elsewhere in this protocol. Demographic data, a medical problem list, and medications will be recorded on the attached data sheet after a brief interview and chart review. Immediately before an 8 hour infusion of Intralipid, baseline specimens will be obtained by the investigators (via venipuncture or aspiration of a specimen from an indwelling line) for a Lipid 2 profile, CBC, and liver profile; and a radial artery puncture (or aspiration of a sample from an indwelling arterial line) will be performed by the investigators and hand carried to Respiratory Care and the Pulmonary Lab for ABG analysis and whole blood oximetry on both the IL-282 CO-oximeter and OSM3 hemoximeter.  $F_iO_2$  will be recorded on the data sheet. Pulse oximetry using the same unit as in controls will be measured and recorded as well. All specimens and measurements except the baseline liver panel will be repeated midway during the infusion, immediately after, and the following morning. A liver panel will be obtained in order to assess whether those patients with liver dysfunction (who may not metabolize lipid particles as rapidly), if any, are more prone to lipid induced artifact in any of the measurements made.

Forty consecutive patients who have a new diagnosis of or who are about to undergo initial therapy for hyperlipo-proteinemia will be recruited by the investigators from the Internal Medicine Clinic and other ambulatory settings and informed consent will be obtained. Demographic data, a medical problem list, and medications will be recorded on the attached data sheet after a brief interview and chart review. Venipuncture will be performed by one of the investigators and specimens will be sent to the clinical lab with

an accompanying requisition slip for a Lipid 2 profile, CBC, and liver profile. Radial artery puncture will be performed by one the investigators or a credentialed Pulmonary Service technician. A room air arterial blood gas analysis will be run and recorded on this sample as well as oximetry variables on both the IL-282 CO-oximeter and Radiometer OSM3 hemoximeter. The patient's room air pulse oximetry reading on the same single pulse oximeter unit will be performed and recorded. All specimens and measurements will be repeated and recorded after telephonic arrangements are made for a repeat testing date after about 3 months of therapy.

Statistical analysis of the data using a SPSS/PC+ statistical program will be performed. Specific analysis will include, but not be limited to, the assessment of statistically significant differences in: (a) oximetry variables measured at the same time on the IL-282 vs. OSM3 hemoximeter in patients and controls; (b) determination of Hgb concentration by oximetry (4 or 6 wavelength) vs the hemoglobinometry method used in the clinical lab by Coulter Counter; (c) oximetry variables, blood gases, lipid levels, CBC values, or pulse oximetry measurements made before, during and after Intralipid infusion in critically ill patients; (d) oximetry variables and pulse oximetry in controls vs. patients with untreated hyperlipidemia; and (e) oximetry variables, blood gases, lipid levels, CBC values, or pulse oximetry measurements pre and post dietary and/or pharmacologic therapy for patients with endogenous hyperlipidemia.

**Amended Apr 92:** Study changed to More than Minimal Risk and amended to require informed consent from all patients.

**Progress:** After the last patient was entered into this study in August 1992, no further patients were entered. The protocol was terminated as the investigators become involved in other activities and all but one left WBAMC.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/08

STATUS: Completed

**TITLE:** A Study Investigating Safety and Duration of Effect of Isosorbide-5-Mononitrate in a Controlled-Release Formulation in Patients with Stable Effort Angina Pectoris (Monitor: LTC Moreno)

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Dec 92

PRINCIPAL INVESTIGATOR: MAJ Roger J. Belbel

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Pearl, TW Martin, T Do

KEY WORDS: Isosorbide-5-Mononitrate

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**Study Objective:** To determine the safety and effectiveness of Isosorbide-5-Mononitrate controlled release formulation. This is a long-acting medication designed to keep the coronary arteries open. It is taken by mouth once a day. This is the final stage of testing a new medication before it becomes available for general use. In previous testing in humans, it has been found to be both safe and effective.

**Technical Approach:** Twenty adult volunteers will be enrolled. All will have stable effort angina pectoris. Subject will undergo a medical history, physical examination, and laboratory screen including chest x-ray, electrocardiogram, urinalysis, and blood chemistries. Two treadmill exercise tolerance tests will be performed at five to ten day intervals before beginning medication with Isosorbide-5-Mononitrate. The patients will then be randomly divided into three groups. They will either take a placebo, 60 mg of Isosorbide-5-Mononitrate per day or 120 mg of Isosorbide-5-Mononitrate daily. Neither the patient nor the investigator will know which patients are taking which medications. Upon commencing the medication, graded exercise tolerance tests will be performed on the 14th, 28th, and 42nd days. At the time of each of these treadmill tests, the patient will undergo a physical examination including determination of weight, heart rate, and blood pressure. A resting electrocardiogram will also be taken at the time. The entire protocol is expected to accrue approximately 150 patients. It is estimated that William Beaumont will accrue 20 patients.

**Semiannual Review:** Apr 92 - project due to begin in May.

**Progress:** Study closed in Mar 93; material and medications returned to company. Five WBAMC patients had been enrolled; three completed the protocol.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/61

STATUS: Completed FY93

TITLE: Management of the Terminally Ill Patient in an Army Teaching Hospital

START DATE: Sep 92

ESTIMATED COMPLETION DATE: Nov 92

PRINCIPAL INVESTIGATOR: CPT Carlos E. Jimenez

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Lane, T Do

KEY WORDS: terminally ill

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**Study Objective:** (1) To examine the age, gender, race, history of end organ/malignancy diseases and underlying cause of death of the involved individuals. We will calculate averages and percentages when indicated to demonstrate a pattern/majority. (2) To determine if a DNR status was ever discussed (patient, family, both or neither) and decided during the hospitalization (first 24 hours and after). Also, we will determine if the patient had a living will prior to or during the hospitalization. (3) To examine hospital course in terms of duration, procedures performed, limitation of care, entrance into the seriously ill list, ICU admissions, and autopsies performed. (4) To determine how many of the patients were followed by any of the sub-specialty clinics in the Department of Medicine. (5) To determine any possible relationship among the DNR status (first 24 hrs and after 24 hrs) vs. invasive procedures, admission to the ICU, hospital days, limitation of care, and end organ disease/malignancy.

**Technical Approach:** This will be a retrospective chart review to include treatment master file, death certificate, autopsy report, narrative summary, admission history and physical and progress notes. The study will include about 150 patients who died during the study period. A specific data collection sheet will be created to retrieve the pertinent information in an organized fashion. Patient name and social security will not be presented in order to protect patient's confidentiality.

**Progress:** Study Objectives: Examine the mortalities within the Department of Medicine during the period from April 1991 to March 1992 with particular attention to demographic and therapeutic data. Evaluate whether there is a significant difference in hospital days, ICU admissions and heroic procedures between DNR orders written in the first 24 hours versus after 24 hours in terminally ill patients (documented end organ disease or active malignancy). Design: A retrospective chart review to include masterfile, death certificate, autopsy report, narrative summary, history and physical from admission or progress notes. Setting: William Beaumont Army Medical Center. Patients: 172 adult patients who died during the study period. Results: 172 charts were reviewed out of the 179 deaths reported within the Department of Medicine during study period. 121 (70%) were males and the total average age was 66.6 years. There were 110 (63%) terminally ill (TI) patients and 62 (56%) of these received a DNR order within the first 24 hours. The average hospital days, ICU admission and heroic interventions for the TI patients receiving DNR within the first 24 hours versus after 24 hours were 9.1, 26.7 ( $P < 0.001$ ), 25, 25 ( $P = 0.06$ ), and 10, 16 ( $P > 0.01$ ), respectively. Conclusions: When comparing terminally ill patients in terms of DNR orders instituted within the first 24 hours versus later during hospitalization, it was determined that there was a significant difference in respect to number of hospital days and heroic procedures performed. This suggests that the Patient Self-Determination Policy presently being instituted in our institution could lead toward a more compassionate management and at the same time reduce hospital costs.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/37

STATUS: Completed FY93

TITLE: Evaluation of the Night Float System (NFS)

START DATE: Aug 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: CPT Carlos E. Jimenez

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: PB Cannady, DM Omori, DS Berry

KEY WORDS: night float system

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**Study Objective:** To study the perceived benefits and potential problems associated with a night float system when compared to a traditional every-4-night call system.

**Technical Approach:** Self-administered questionnaire to be completed voluntarily and anonymously by residents and their significant others (selected questions), along with attending ward staff (selected questions) which will include questions about quality of patient care, housestaff emotional and physical well-being, medical education and quality of life for housestaff and significant others.

**Progress:** Study is completed. Results are scheduled to be presented at 1993 annual meeting of American College of Physicians.

**Abstract:** **Objective:** To study the perceived benefits and potential problems associated with a night float system (NFS) when compared to a traditional every fourth night call system. **Design:** Self-administered questionnaire (33 items) completed by *internal medicine residents and their significant others*, along with ward attending staff, regarding quality of patient care, medical education and quality of life for housestaff and significant others. **Results:** The response rates among the housestaff, attending and significant other groups were 19/25 (76%), 27/31 (87%) and 16/25 (64%) respectively. The housestaff and attending groups agreed that NFS has improved housestaff positive attitudes towards the residency program (95% & 70%) and has decreased housestaff fatigue (95% & 93%), but has not improved medical documentation (42% & 11%). However, while the housestaff group agreed that the NFS has resulted in more reading time (84%), decreased incidence of illness for the ward resident (84%), increased time spent on patient care (74%), decreased errors on orders by physicians (74%) and has not affected patient care by the lack of continuity (63%). The attending group significantly disagreed ( $P < 0.005$ ) with the above mentioned items (22%; 47%; 19%; 19% & 15%, respectively). Both the housestaff and significant other groups agreed the NFS increased time spent with family significant others (84% & 81%) and does not increase the incidence of marital discord (75% & 82%) or miscommunication (78% & 82%) between the NFS resident and significant others. **Conclusions:** The housestaff and their significant others prefer the NFS over the traditional every fourth night call system because it improves housestaff educational, interpersonal, emotional, and physical well-being without significantly affecting quality of patient care. On the other hand, attendings prefer the every fourth night call system over the NFS mainly because of the perception that the latter negatively affects certain aspects of patient care.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/16

STATUS: Terminated FY93

TITLE: Incidence and Clinical Significance of Adrenal Hemorrhage in Septic Shock (Monitor: LTC Moreno)

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Ray Johnson

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: G Becker, R Wolfgang, TP Baker

KEY WORDS: adrenal hemorrhage, septic shock

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**Study Objective:** To determine the relationship between acute adrenal hemorrhage, adrenal insufficiency and clinical outcome.

**Technical Approach:** Those subjects admitted to the critical care units who are eligible for entry will have baseline serum cortisol levels obtained followed by stimulatory assessment of the adrenals with a short cosyntropin stimulation test as previously described. The septic state will be treated with therapeutic modalities as deemed necessary by the primary care provider. Those subjects surviving the septic episode should undergo abdominal CT scanning with examination of the adrenals for evidence of hemorrhage. Non-survivors should undergo autopsy with adrenal examination for evidence of hemorrhage.

**Amendment (May 92):** Protocol upgraded to More than Minimal Risk and amended to require consent from all patients.

**Progress:** Principal investigator unable to enroll patients. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/54

STATUS: Ongoing

TITLE: Prospective Evaluation of Coccidioidomycosis in Human Immunodeficiency Virus-Infected Individuals Living in an Endemic Area

START DATE: Aug 91

ESTIMATED COMPLETION DATE: Aug 96

PRINCIPAL INVESTIGATOR: Lynn McNicol

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: N Aronson

KEY WORDS: Coccidioidomycosis, Human Immunodeficiency Virus

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**Study Objective:** To demonstrate whether coccidioidomycosis seen in HIV patients is reactivation disease or represents acute infection in an immunocompromised host. To assess the early predictive value for active coccidioidomycosis of the spherulin skin test, coccidioides complement fixation and immunodiffusion antibody studies and coccidioides antigen ELISA in the HIV infected population.

**Technical Approach:** This is a prospective descriptive study. Subjects will be obtained from individuals participating in the HIV natural history study 86-49 (non-active duty) and HIV infected active duty soldiers who are followed in the WBAMC Infectious Disease Clinic per AR 600-110. Completion date is dependent on number of patients enrolled and severity of their immunologic compromise. Estimated study duration is 5 years.

On entry, a complete geographic history will be obtained to assess travel to Cocci endemic regions (West Texas, Arizona, San Joaquin Valley in California). On entry and every 6 months thereafter, delayed hypersensitivity skin testing will be performed LAW DOD HIV staging. In addition, spherulin 1:100 (Berkeley Biologics) will be included in the battery which is already usual practice in cocci endemic regions. Chest radiograph will be obtained on entry and every 12 months which is current clinical practice during HIV staging. On entry and every 6 months, the following blood tests will be ordered: T cell subset by flow cytometry, quantitative immunoglobulins and SPEP, complement fixation Coccidioides antibodies (sent to Dr. Pappagianis' laboratory at UC, Davis), Coccidioidal precipitins (sent to FSH, TX), serum for coccidioidal antigen (research test) - will be frozen at -70° F initially. On entry and every 6 months, weight will be recorded. On entry and at every subsequent staging, patient will be clinically evaluated by history and physical examination to assess for presence of active coccidioidomycosis.

**Progress:** Sixty-nine individuals have been enrolled in this protocol to date. Unexpectedly, 18 of these individuals were lost to followup prior to completing at least two protocol evaluations and required six month followups have been more difficult than anticipated. Impacting events include the following:

- 1) Interim guidance reducing HIV staging requirements from every six months to "at least annually."
- 2) Extension of HIV TDRL reevaluation periods from once a year to every 18 months.
- 3) Early retirement and voluntary separations related to reduction of the active force.

Individuals lost to follow up prior to completing two stagings may have inadequate exposure to a cocci endemic area and we are therefore requesting that these enrollees not count against our 100 volunteer target.

**In order to improve follow up of participants departing the area, we will propose that they be given a prepaid postcard identifying their new home address, phone, treatment facility and physician. In addition, they will be encouraged to contact the WBAMC Infectious Disease Clinic annually. They will be advised that, should they ever receive a diagnosis of cocci, it would be important to inform the WBAMC Infectious Disease Clinic by sending a copy of the hospital summary or clinic note.**

**Protocol modifications detailed above will be submitted via amendment pending review and concurrence of the associate investigator.**

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/11

STATUS: Completed FY93

TITLE: Oxygen Saturation After Colonoscopy

START DATE: Dec 92

ESTIMATED COMPLETION DATE: Jul 93

PRINCIPAL INVESTIGATOR: CPT Martin Maldonado

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: T Landes, G Becker

KEY WORDS: oxygen saturation

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**Study Objective:** To determine if patients develop hypoxemia after colonoscopy and to determine if clinical criteria will predict which patients could develop hypoxemia after colonoscopy.

**Technical Approach:** One hundred unselected patients undergoing routine colonoscopy will be recruited to participate in this study. Informed consent will be obtained. Demographic data, medical history and medications will be recorded on the attached data sheet after a brief interview and chart review. After preparing the patients for colonoscopy, baseline oxygen saturation will be obtained before induction of conscious sedation. Oxygen saturation monitoring will be done during the duration of the colonoscopy and for 60 minutes after the completion of the procedure. Oxygen saturations will be recorded before the induction of conscious sedation, 2 minutes after induction of conscious sedation, every 10 minutes during the procedure and at time 0, 5, 15, 30, 45, and 60 minutes after completion of the procedure. No other oxygen saturations will be recorded unless SaO<sub>2</sub>

<90%. All colonoscopies will be performed by an experienced endoscopist using a fiberoptic colonoscope. The duration of the procedure and the doses of Meperidine, Diazepam, and/or Midazolam used before and during the colonoscopy will be recorded. Oxygen via nasal cannula will be provided if SaO<sub>2</sub> <90%. Statistical analysis will be performed on a computer program.

**Progress:** One hundred patients were entered. The study was completed in July 1993. Information from the study will be presented at the 1993 annual meeting of the American College of Physicians.

**ABSTRACT:** Desaturation by pulse oximetry during nonemergent colonoscopy is well documented, but the incidence of post-procedure desaturation has not been investigated. WE sought to assess the incidence, clinical predictors, and sequelae of post colonoscopy desaturation. Baseline clinical data was obtained in 100 patients undergoing nonemergency colonoscopy performed by experienced endoscopists. Baseline oxygen saturation was obtained by pulse oximetry prior to sedation, continuously during the procedure and for one hour afterwards. Intravenous sedation doses included (x±SE)meperidine (67.0±2.0 mg) and midazolam meperidine (2.9±0.1 mg) or diazepam (8.0±0.4 mg). Seventy-eight patients (78.0%) desaturated to < 90% during the procedure and 62 patients (62.0%) desaturated during post-procedure monitoring. Those patients with persistent desaturation received supplemental oxygen (2L/min via nasal cannula). Only four patients who did not desaturate during colonoscopy did so during post-procedure monitoring. Age, gender, history of cardiac or pulmonary disease, and dose or type of sedation used failed to be good predictors of post colonoscopy desaturation. Although no adverse effects or complications were noted during or after the colonoscopy, these results suggest that post colonoscopy desaturation is a common occurrence, but rarely leads to long term sequelae. Most patients with post procedure desaturation will have evidence of desaturation during colonoscopy. We suggest that high risk patients who desaturate during colonoscopy may benefit from post procedure monitoring.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/36

STATUS: Ongoing

TITLE: Effect of Heart Disease on the Hemodynamic Response to Supine Upper Extremity Exercise  
(Monitor: COL Davis)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Mar 93

PRINCIPAL INVESTIGATOR: CPT Timothy W. Martin

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Belbel, L Brenner

KEY WORDS: exercise, hemodynamics, cardiac catheterization

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**Study Objective:** Characterize and compare the hemodynamic response to supine upper exercise in patients with and without heart disease.

**Technical Approach:** Patients who require heart catheterization and do not have exclusion criteria will be identified and counselled by cardiology staff. Consenting patients will be brought to the catheterization laboratory in a fasting, mildly sedated state. From the femoral approach, a Swan Ganz catheter will be advanced to the right heart and a pigtail catheter will be advanced to the left heart. Resting pressure and flow measurements and blood samples will be obtained. The patient will then perform five to eight minutes of supine arm cycle exercise, during which rest measurements will be repeated. Based on the results of rest measurements, angiography, and other clinical information, patients will be categorized as normal or as having coronary artery disease, cardiomyopathy, or valvular heart disease. The response to supine upper extremity exercise will be compared among the groups.

**Progress:** Forty-five patients have performed supine armcrank exercise during cardiac catheterization. One patient suffered a CVA within several hours of catheterization and his case was reviewed. Reviewer felt complication was not directly related to protocol.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/16

**STATUS:** Ongoing

**TITLE:** Cardiopulmonary Response to Upright Exercise in Patients with Asymptomatic Valvular Aortic Stenosis and Patients with Aortic Valve Prostheses (Monitor: COL Weisman)

**START DATE:** Feb 93

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** MAJ Timothy W. Martin

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** R Belbel

**KEY WORDS:**

upright exercise, valvular aortic stenosis, aortic valve prostheses

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**Study Objective:** To determine the effect of valvular aortic stenosis and aortic valve replacement on cardiopulmonary exercise performance and the relationship between ECHO/Doppler measurements and cardiopulmonary performance in patients with valvular aortic stenosis and aortic valve prostheses.

**Technical Approach:** A total of 75 patients (ages 18-75) will be included in the study (25 with aortic stenosis, 25 with aortic valve prostheses, and 25 controls). Patients will undergo upright cycle exercise, 20 W/min increments, symptom-limited, followed by cool-down exercise with continuous monitoring of O<sub>2</sub> consumption, CO<sub>2</sub> production, tidal volume, anaerobic threshold, respiratory rate, heart rate, power, and blood pressure. Patients will be monitored for 10 minutes following the exercise test.

**Semiannual Review (Apr 93):** Protocol too new. Enrollment underway.

**Progress:** No response received from investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/22

STATUS: Completed FY93

TITLE: Fourth International Study of Infarct Survival (ISIS-4) (Monitor: LTC Moreno)

START DATE: Jun 91

ESTIMATED COMPLETION DATE: Aug 93

PRINCIPAL INVESTIGATOR: CPT Gregory Mock

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Bernheim, R Belbel

KEY WORDS: Infarct Survival, Captopril, Magnesium, Nitrate

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**Study Objective:** To obtain reliable assessment of the separate and combined effects on vascular mortality of adding three widely practicable treatments to the current standard treatments for a wide range of types of patient (high risk and low risk) with definite or suspected myocardial infarction.

**Technical Approach:** This will be an international, multi-center, partially double-blinded, partially placebo-controlled, randomized, prospective study. The three study treatments will be randomized in a "2 x 2 x 2 factorial" design. Each patient will be randomized between controlled-release mononitrate vs. placebo, captopril vs. placebo, and magnesium vs. open control. If, as hoped, a total of 40,000 patients is randomized, there will be about 5000 patients in each of the eight possible combinations of trial treatment. The eight possible combinations are: 1) nitrate alone, 2) captopril alone, 3) magnesium alone, 4) nitrate and captopril, 5) nitrate and magnesium, 6) captopril and magnesium, 7) nitrate, captopril, and magnesium, and 8) no trial treatment. Group sizes of 5000 may not be large enough to yield statistically reliable results. But, the factorial design makes the assumption that the effect of the other two trial treatments is equally distributed between the treatment of interest and its control due to the randomization. Therefore, if 40,000 patients are entered, each treatment will have 20,000 patients vs. 20,000 control subjects for data analysis.

**Amendment (Jun 92):** CPT Mock assumed PI responsibility 1 Jun 92 due to PCS of CPT Chapin (previous PI).

**Progress:** The first patient was enrolled in the ISIS-4 trial on 16 August 1991. From 16 August 1991 to 31 August 1993, a total of 35 patients were enrolled in the study. Nineteen patients ruled in for myocardial infarction by serial ECG changes and/or elevation of CPK enzymes. There were no in-house mortality among the enrolled patients. At least 10 of the patients with a confirmed diagnosis of myocardial infarction underwent a subsequent CABG or angioplasty. Fourteen patients were randomized to receive IV magnesium. No adverse effects were reported. The ISIS-4 study was a worldwide effort. There were over 58,000 patients entered into the study in over 1,000 hospitals. Preliminary results are available. The final results will be published in the near future in a major journal. ISIS-2 and 3 were published in *Lancet*.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 76/33

STATUS: Ongoing

TITLE: Diagnostic Adrenal Scanning with <sup>131</sup>I (NP59)

START DATE: Mar 76

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Albert J. Moreno

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: adrenal scanning

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**Study Objective:** To determine the usefulness of <sup>131</sup>I-NP59 in scanning of the adrenal glands. This agent will be used (1) as a screening test for detection of primary aldosterone tumor, Cushing's disease, adrenal cortical adenoma, or pheochromocytoma; (2) to image adrenals in patients who require adrenal venography and are allergic to contrast media; (3) to detect unilateral adrenocortical hypofunction - calcification, metastatic carcinoma, post-venography infarction, etc.; (4) to detect functioning adrenal remnant after adrenalectomy for Cushing's syndrome; (5) to aid in assessment of adrenocortical function in patients who have been on adrenocortical steroid therapy.

**Technical Approach:** Patients with clinical evidence of adrenal disease will be thoroughly evaluated by an endocrinologist. Following intravenous administration of <sup>131</sup>I-NP59, adrenal scanning will be performed after 7-10 days. The material will be obtained from the Nuclear Pharmacy, University of Michigan. The WBAMC radiopharmacist will perform sterility and pyrogenicity tests on the radiochemical to ensure that radiopharmaceutical standards are met prior to injection

**NOTE:** Project was erroneously terminated in Oct 84. Project reactivated in Sep 92 and folder was reconstituted to include required documentation.

**Progress:** Fourteen patients have been studied since this protocol was approved. No adverse effects noted.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/32

STATUS: Completed FY93

TITLE: Preoperative Evaluation Compared to Patient Outcomes: The WBAMC Experience for Vascular Surgery

START DATE: Apr 93

ESTIMATED COMPLETION DATE: Sep 93

PRINCIPAL INVESTIGATOR: CPT Robert W. Morse

DEPARTMENT: Medicine

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: PC Cannady, W Bowland, A Canfield, R Belbel, C Lauer

KEY WORDS: preoperative evaluation vascular surgery

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### Study Objectives:

(1) retrospectively review elective AAA repair and CEA cases at WBAMC and risk stratify patients based on established markers of CAD age>70, prior angina, prior MI, previous CHF, ventricular arrhythmias, diabetes mellitus, q waves on resting ECG. Evaluate outcomes based on these risk factors.

(2) Retrospectively evaluate radionuclide ventriculography and thallium results based on outcomes.

(3) Retrospectively review cases for perioperative cardiac events as defined by angina, CHF, MI, death, dysrhythmias.

(4) Attempt to validate a risk assessment protocol based on the above findings.

### Technical Approach: Retrospective records review.

**Progress:** The purpose of this study was to retrospectively review vascular surgery cases at an Army medical center for pre-operative historical and objective data, perioperative cardiac complications and attempt to (1) risk stratify patients using the Eagle criteria and evaluate predictive ability at our institution, (2) assess current non-invasive risk stratification testing based on outcome data, and (3) attempt to evaluate the current role of the Department of Medicine at our institution in pre-operative risk stratification. Currently, vascular surgery patients at our MEDCEN undergo a comprehensive non-invasive evaluation which variably includes; Standard GXT, Thallium GXT, MUGA, ECHO. Current literature commentary supports a combined clinical risk stratification utilizing historical markers of CAD followed by diagnostic evaluations in those individuals at intermediate risk for perioperative cardiac complications to determine need for cardiac revascularization prior to elective vascular surgery, such as that devised by Eagle et al. Twenty-two Elective AAA repair and 26 CEA cases at our MEDCEN were retrospectively reviewed and patients were risk stratified based on criteria, established by Eagle et al, which include Age > 70, prior angina, ventricular dysrhythmias, diabetes mellitus or Q waves on resting ECG and outcomes were evaluated based on these risk factors. Preoperative non-invasive testing results were evaluated based on outcome data. Cases were reviewed for perioperative cardiac complications as defined by Unstable Angina, Ischemic Pulmonary Edema, Myocardial Infarction or Cardiac Death. Primary results included an overall event rate of 22.7% among our AAA patients with 0% event rate of Unstable Angina, 18.2% event rate of Ischemic Pulmonary Edema, 9.1% event rate of Myocardial Infarction and 9.1% Death rate. Risk stratification by Eagle criteria revealed an event rate of 25% among patients with no clinical variables and an event rate of 21.4% among patients with 1 or 2 clinical variables. No patients with 3 or > clinical variables were identified. Non-invasive testing did not further risk stratify any of these patients. Only 27% of AAA patients had a Medical or Cardiology risk assessment. CEA patients had an overall event rate of 3.9% with this correlating with one Myocardial Infarction in a patient with 1 or 2 clinical variables. Overall event rate amongst this intermediate risk group was 5%. Due to the low CEA event rate statistical analysis was only possible on the AAA group. Chi square cross tabulation with

**Yates correction, when necessary, was performed. No clinical variable or non-invasive test was predictive of outcome for our group of patients. Primary conclusions included the following: (1) Eagle criteria was not predictive of outcome for our study group of 22 AAA patients, (2) non-invasive testing did not further risk stratify our group of study patients and was not predictive of outcome for our group of 22 AAA patients, and (3) for this group of study patients there clearly lacked an effective medicine/vascular surgery interactive risk stratification process.**

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/57

**STATUS:** Ongoing

**TITLE:** NSABP C-05: A Clinical Trial to Assess the Relative Efficacy of 5-FU + Leucovorin with or without Interferon Alfa-2a in Patients with Dukes' B and C Carcinoma of the Colon (Monitor: LTC Soisson)

**START DATE:** Sep 92

**ESTIMATED COMPLETION DATE:** Sep 94

**PRINCIPAL INVESTIGATOR:** MAJ Michael E. Nash

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** W Bowland

**KEY WORDS:** Dukes' B & C carcinoma

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**Study Objective:** This study will evaluate the relative effectiveness of 5-FU plus Leucovorin with and without alfa interferon in prolonging disease free and overall survival in patients who have undergone standard curative resection of Dukes' B and C carcinoma of the colon.

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

**Semiannual Review (Apr 93):** No patients entered to date.

**Progress:** No patients enrolled to date.

**DETAIL SUMMARY SHEET**

**DATE:** 1 October 93

**PROTOCOL #:** 93/36

**STATUS:** Ongoing

**TITLE:** The Effect of Meal Consumption Before Radionuclide Ventriculography (Monitor: LTC Algeo)

**START DATE:** Jul 93

**ESTIMATED COMPLETION DATE:** Jun 94

**PRINCIPAL INVESTIGATOR:** MAJ Elmer J Pacheco

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** A Moreno, G Turnbull, M Brodbeck, D Hokanson

**KEY WORDS:** meal radionuclide ventriculography

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**Study Objective:** To determine the effect of a standardized meal on the resting LVEF in patients with a normal LVEF.

**Technical Approach:** A retrospective and prospective study in which patients with a known normal LVEF derived through a MUGA performed at our institution and during a fasting state, will be asked to undergo a repeat study 45 min after the ingestion of a standardized meal totalling 700 cal, consisting of 50% carbohydrates, 30% fat, and 20% protein. This meal will consist of 4 oz orange juice, 8 oz 2% milk, 2 pieces of toast, 2 boiled eggs, 2 slices of bacon, 1 cup of coffee with sugar and non-dairy cream, and 1 banana.

**Progress:** Seven patients have completed protocol as per guidelines with deviations. No side effects have been reported. In patients who have completed both phases of the study (i.e., fasting and post-prandial MUGA), there seems toward increased LVEF post-prandially, although statistical analysis is pending.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/53

STATUS: Ongoing

**TITLE: Phase II Study of Interferon-Modulated Indium-111-Labeled b72.3 Monoclonal Antibody (MoAb) Scintigraphy in the Staging and Follow-Up of Breast Cancer Patients of Poor Prognosis (Monitor: MAJ Cadiz)**

START DATE: Nov 1993

ESTIMATED COMPLETION DATE: Oct 2000

PRINCIPAL INVESTIGATOR: MAJ Elmer J Pacheco

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: A Moreno, W Sippo, S Hetz, TH Nguyen, ME Nash, GG Turnbull, G Morgan

KEY WORDS: breast cancer, scintigraphy

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**Study Objective:** The use of human leukocyte interferon-alpha (HuIFN- $\alpha$ ) in this study would attempt to enhance the expression of a tumor-associated antigen (TAG-72) in breast cancer patients of poor prognosis. The sensitivity and specificity of Indium-111-labeled B72.3 MoAb against TAG-72 in this subset of patients will be compared to conventional bone scintigraphy during their initial staging and follow-up. An analysis of the poor prognostic factors (i.e. Aneuploid DNA content, high S-phase, high Ki-67 growth fraction, negative ER/PR status, low pS2, high EGF, high HER-2neu, high Cathepsin D level, and low p53 expression) will be performed so as to document their importance in the prediction of survival in this set of patients, as well as discerning which combination of these factors will more accurately predict outcome.

The Modified Scarff-Bloom-Richardson system will be compared to nuclear grading, with and without mitotic count in the histopathological assessment of the obtained tissues. Their effectiveness in predicting relapse will be defined.

**Technical Approach:** Details are too lengthy to list here. Protocol is on file in Department of Clinical Investigation.

**Progress:** Approval of grant is pending.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/13

STATUS: Terminated FY93

**TITLE:** A Double-Blind, Parallel, Multicenter Study Comparing the Efficacy and Safety of Intravenous Granisetron Hydrochloride (40 mcg/kg) with Oral Granisetron (1 mg bid) in the Prophylaxis of Nausea and Emesis Induced by Cisplatin-Based Chemotherapy (Monitor: MAJ Faucette)

**START DATE:** Feb 93

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** MAJ Robert Sheffler

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** D Beaudoin

**KEY WORDS:** Granisetron, nausea and emesis

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**Study Objective:** To compare the efficacy of a single dose of intravenous granisetron (40 mcg/kg) with oral granisetron (1 mg) given bid, over a 24 hour study period, in preventing acute nausea and emesis in patients receiving cisplatin-based chemotherapy and to assess the safety of granisetron given as either a single intravenous dose (40 mcg/kg) or an oral dose of 1 mg given bid, over a 24 hour period in patients receiving cisplatin-based chemotherapy.

**Technical Approach:** This is a randomized, double-blind, parallel group study in adult patients with malignant disease, who are naive to chemotherapy, and who are scheduled to receive cisplatin therapy at a dose of at least 60 mg/m<sup>2</sup>, administered alone or in combination with other chemotherapeutic agents. Eligible patients will be stratified by gender and randomized with equal probability to one of the following regimens:

**Intravenous Granisetron Group:**

- o One placebo tablet 60 min prior to chemotherapy, followed by
- o Granisetron 40 mcg/kg infusion 30 min prior to chemotherapy
- o One placebo tablet 12 hours after first dose of study medication.

**Oral Granisetron Group:**

- o One 1 mg (active) granisetron tablet 60 min prior to chemotherapy, followed by
- o Placebo (saline) infusion 30 min prior to chemotherapy,
- o One 1 mg (active granisetron tablet) 12 hours after first dose of study medication.

Observations will include the number of emetic episodes, the degree of nausea, and the frequency of antiemetic rescue. These observations will be made and recorded for the 24 hour post-chemotherapy period. A patient worksheet will be provided to the patient so that his/her response to study medication can be recorded.

**Semiannual Review (Apr 93):** Project placed on hold 18 Mar 93. IRB notified at April meeting. No patients enrolled.

**Progress:** This protocol was initiated pending approval of the agent for use by the FDA. Due to the approval of oral Zofran (Ondansetron) and some serious side effects of Granisetron, the study was withdrawn by the manufacturer and the protocol terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/22

STATUS: Terminated FY93

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

START DATE: Mar 89

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ David Slagle

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Sun, L McNicol

KEY WORDS: Health care workers, HIV, seroconversion

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**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:** Principal investigator has departed the institution and the associate investigators do not wish to continue the study. The protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/50

STATUS: Terminated FY93

TITLE: Centocor: HA-1A Efficacy in Septic Shock (CHESS Trial-Centocor Protocol #C0041T20, IND #2283)(Monitor: Dr. Hobretsch)

START DATE: Aug 92

ESTIMATED COMPLETION DATE: Jan 93

PRINCIPAL INVESTIGATOR: MAJ David Slagle

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Sun, W Lane

KEY WORDS: septic shock, CHESS

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**Study Objective:** The primary objective of this trial is to compare the effectiveness of 100 mg of HA-1A and placebo in reducing the 14 day all-cause mortality in patients with septic shock who have documented gram negative bacteremia. The secondary objective of this trial is to assess the safety of HA-1A in patients with septic shock, who have and do not have documented gram negative bacteremia.

**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.

**Amendment #1 (Sep 92):** Changed method of randomization.

**Addendum #1 (Quarterly Safety Summary)** presented at 19 Jan 93 IRB along with suspension letter. Enrollment suspended by Centocor on 18 Jan 93 until further notice due to an increased incidence of adverse effects.

**Semiannual Review (Apr 93):** Protocol terminated by manufacturer 15 Mar 93. No WBAMC patients enrolled. IRB notified at April meeting.

**Progress:** No patients have been enrolled at WBAMC. Study terminated by manufacturer in Mar 93.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/12

STATUS: Terminated FY93

TITLE: Evaluation of the Safety and immunogenicity of *Vibrio cholerae* Detoxified LPS-Cholera Toxin Conjugate Vaccine (Phase I) (Monitor: COL Cannady)

START DATE: Jan 93

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ David Slagle

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Sun, L Hobratch

KEY WORDS: LPS-cholera toxin conjugate vaccine

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**Study Objective:** The primary objectives of this protocol are twofold, to evaluate both the (1) safety and (2) immunogenicity of an investigational cholera vaccine composed of the detoxified lipopolysaccharide of *V. cholerae* 01 serotype Inaba. Safety will be determined by assessing clinical response to vaccination by observation. Immunogenicity will be evaluated by assaying for the presence of antibodies in the serum of individuals vaccinated with the protocol vaccine. This phase 1 study is not designed to gather information concerning efficacy.

**Technical Approach:** This study is a Phase I study only (safety and immunogenicity) of investigational vaccines composed of the detoxified lipopolysaccharide of *V. cholerae* 01 serotype Inaba. The objectives do not include a side-by-side comparison of our detoxified LPS conjugates with the whole cell cholera vaccine. We plan to characterize the serum antibodies elicited by these investigational vaccines with those elicited by the whole cell cholera vaccine. In this study a total of 75 healthy volunteers, age 18 to 45 years, will be randomly assigned to receive 2 doses of the following vaccines: (1) 25 volunteers will receive two doses (6 wks apart) of one conjugate cholera vaccine (lot 912); 25 volunteers will receive two doses (6 wks apart) of a second type of conjugate cholera vaccine (lot 913); 10 volunteers will receive two doses (6 wks apart) of unconjugated cholera vaccine (25 ug of detoxified LPS); 15 volunteers will receive two doses 6 wks apart of the standard parenteral killed whole cell vaccine. Note: Lot 912 uses cholera toxin (CT1) from Pasteur-Merieux Inst. (Lot 582) conjugated to detoxified LPS of *V. cholerae* strain 569B (classical Inaba); Lot 913 used cholera toxin (CT2) from Dr. Richard Finkelstein (Lot 3038) conjugated to detoxified LPS of *V. cholerae* strain 569B (classical Inaba). This Phase 1 study has limited objectives. The number of volunteers and the vaccines to be injected should provide sufficient information to verify if our laboratory standardization is predictive of their safety and if the immunologic properties of the detoxified LPS have been improved over that of the whole cell cholera vaccine. If we decide that the results of this Phase 1 study are satisfactory, then these data will be presented to the WRAIR Scientific Review Committee, as well as the NIH and FDA, as the basis of a request to proceed with additional clinical studies.

**Semiannual Review (Apr 93):** Study terminated; unit declined to participate.

**Progress:** Study terminated in Apr 93.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

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 Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: LB McNicol

KEY WORDS: HIV Natural History

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**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 service members. At the directive of the Secretary of the Army, all active duty HIV+ service members are to be clinically staged periodically.

**Progress:** MAJ Wellington Sun has replaced MAJ David Slagle as principal investigator; MAJ Slagle has ETS'd. Gregory Martin is no longer on staff and has been removed as an associate investigator.

A total of seven individuals with newly identified HIV infection were enrolled in this protocol during FY93. Four individuals are active duty military and three are dependent spouses of active duty soldiers. Six are male and one is female. Data collected using the clinical evaluation form, DA Form (temp) Ref: HQDA Ltr, DASG-PSP-D, 9 Apr 86, on each new enrollee is sent to the US Army HIV Data Systems upon completion.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**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 (Monitor: COL Cannady)

**START DATE:** Jul 89

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** MAJ Wellington Sun

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** LB McNicol, W Sun

**KEY WORDS:** Zidovudine, needlesticks

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**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.

**Semiannual Review (Apr 93):** No patients enrolled over the past year. Protocol should remain active so that AZT may be offered to healthcare workers who may sustain a significant needlestick injury with HIV-contaminated blood.

**Progress:** No patients have been enrolled over the last year.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/51

STATUS: Terminated FY93

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

START DATE: Jul 90

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RD Sierra, DC Slagle, R Weickmum, LB McNicol

KEY WORDS: cytokines, rGM-CSF

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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.

**Semiannual Review (Apr 93):** Study terminated due to FDA approval of study drug. No patients enrolled.

**Progress:** Study terminated in Apr 93 on semiannual review.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/05

STATUS: Ongoing

**TITLE:** Active Immunization of Early HIV Infected Patients with Recombinant gp 160 HIV protein Phase II Study of Toxicity Immunotherapy, in vivo Immunoregulation and Clinical Efficacy (Monitor: COL Cannady)

START DATE: Nov 90

ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: CE Davis (WRAIR), G Martin

KEY WORDS: Recombinant gp 160 HIV Protein, immunotherapy

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**Study Objective:** To conduct a Phase II trial of the recombinant HIV envelope glycoprotein gp160 candidate vaccine, in patients with early HIV infection (Walter Reed Stage I-II). Specific objectives include:

- 1) To continue to evaluate the immunogenicity and toxicity of this product;
- 2) To determine the parameters predictive of immunoresponsiveness; and
- 3) To determine the clinical efficacy of immunization with gp160 in the treatment of early HIV 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.

**Addendum:** Modifies eligibility criteria. Approved by Tri-Service HUC (26 Feb 91), WBAMC HUC/IRB (23 Apr 91) and WRAMC HUC.

**Amendments:** (1) Deleted recipe skin testing on Day 180 (typographical error); WBAMC IRB notified 16 Jul 91. (2) Day 210 tetanus immunization shifted to Day 240 and Day 210 visit deleted; WBAMC IRB notified 17 Aug 91. (3) Initiated Phase IIB; presented to IRB 21 Apr 92. (4) Booster vaccinations to be given at 2 month intervals; presented to IRB 21 Jul 92.

**Semiannual Review:** Apr 93. Six patients have completed 240 days with no clinical adverse effects noted. PI expects to enroll approximately 5 patients in Phase IIB.

**Progress:** The phase II study is ongoing. Currently, 12 patients are actively participating. No new patients were enrolled since last review (the study is closed to enrollment). There have been no adverse events. So far two patients have met the secondary end point and one has reached the primary end point, as defined by the protocol.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/65

STATUS: Ongoing

TITLE: Early Diagnosis of Tuberculosis Using Gene Amplification Techniques (GAT)

START DATE: Sep 92

ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: WF Nauschuetz, HM Gelston, TJ Casey

KEY WORDS: polymerase chain reaction, tuberculosis

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**Study Objective:** To compare gene amplification techniques with current culture methods in the diagnosis of tuberculosis.

**Technical Approach:** This protocol will consist of two phases. Phase I will be the validation phase and Phase II will be the prospective evaluation of clinical respiratory specimens. Sources will be consecutive specimens submitted to the WBAMC Mycobacteriology Lab as well as specimens from TB cases submitted to El Paso County Health Laboratory.

**Progress:** Thermocycles and oligonucleotide synthesizer are now available at WBAMC. We are still in the specimen collection phase, in cooperation with El Paso County Health District.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/01

STATUS: Ongoing

**TITLE:** Active Immunization of AZT-Treated HIV-infected Patients with Recombinant GP160 HIV Protein: Phase I/II Study of Immunogenicity Toxicity, and Effect in In Vivo Immunoregulation (Monitor: MAJ Raszka)

START DATE: Feb 93

ESTIMATED COMPLETION DATE: Dec 94

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: CE Davis, D Slagle, LB McNicol, G Martin

KEY WORDS: Recombinant gp 160 HIV Protein, immunotherapy

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**Study Objective:** To conduct a Phase I/II feasibility trial of the recombinant HIV envelop glycoprotein, gp160 candidate vaccine in patients who are HIV infected (Walter Reed Stage 1-5) and currently under treatment with AZT. Specific objectives include: 1)to evaluate the immunogenicity and toxicity of this product in HIV-infected individuals on AZT, and 2)to determine the parameters predictive of immune responsiveness.

**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.

**Semi-Annual Review (Apr 93):** Project has just received approval from HSC.

**Amendment (Jan 94):** Details are lengthy. Copy on file at DCI.

**Progress:** Five subjects have been entered into the study. MAJ William Raszka has replaced MAJ Wasserman as medical monitor. MAJ Wasserman has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/10

STATUS: Ongoing

**TITLE:** A Randomized, Blinded Evaluation of Two Doses of Stavudine (d4T) in Severely Immunocompromised Patients with HIV Infection who have Failed or are Intolerant of Alternative Antiretroviral Therapy (Monitor: MAJ Raszka)

**START DATE:** Nov 92

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** MAJ Wellington Sun

**DEPARTMENT:** Med

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** L Hobratsch

**KEY WORDS:** Stavudine (d4T), HIV

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**Study Objective:** The primary objective of this trial is to provide potentially effective antiretroviral therapy to patients with advanced HIV infection who are unable to take AZT or ddI. A second objective is to determine optimal dosing of this agent. Efficacy of this agent will be evaluated by measuring interval CD4 counts, interval p24 antigen levels, and measuring the time to onset of new AIDS-defining diagnoses.

**Technical Approach:** Sequential patients eligible for enrollment in this protocol will be randomized to receive one of two doses of d4T, determined by weight:

>60 kg.: 20 mg BID OR 40 mg BID

40-60 kg.: 15 mg BID OR 30 mg BID

<40 kg.: 10 mg BID OR 20 mg BID

Randomization will be performed by the manufacturer, and study drug will be shipped for each individual patient. Neither the principal investigator at WBAMC nor the patient will know the dosage supplied. Patients will complete a baseline assessment, will be monitored every two weeks for the first month, and then will be monitored monthly for as long as they continue on the study.

**Addendum #1, Quarterly Safety Summary** circulated to IRB 19 Jan 93

**Amendment #2** presented to IRB 16 Feb 93; **Adverse Event (WBAMC)** was also presented at this meeting. Patient withdrawn from study and study drug returned to company. The complication was one of the commonly reported complications of this therapy.

**Semiannual Review (Apr 93):** Two patients enrolled. One withdrew secondary to development of severe bilateral lower extremity peripheral neuropathy (currently treated with Pamelor/Tegretol/Percocet). One patient withdrew because he no longer desired anti-retroviral treatment. Currently, no patients are receiving d4T, however, the protocol should remain active for future patients.

**Progress:** MAJ Sun has replaced MAJ Slagle as principal investigator. MAJ Slagle has been deleted from the protocol. MAJ Raszka has replaced MAJ Wasserman as medical monitor. MAJ Wasserman has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/40A

STATUS: Ongoing

TITLE: Comparison of Subcutaneous and Nebulized Trimethoprim-sulfamethoxazole in the Prophylaxis of *Pneumocystis carinii* Pneumonia (PCP) in Rats

START DATE: Aug 93

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Med

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RA Harris, TP Baker

KEY WORDS: *Pneumocystis*, trimethoprim, sulfamethoxazole

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**Study Objective:** To determine if *Pneumocystis* pneumonia can be prophylaxed in rats using nebulized trimethoprim-sulfamethoxazole.

**Technical Approach:** This will be an animal experiment. Sixty Sprague Dawley rats will be divided into 3 groups of 20 rats. Group 1 will serve as control and receive nebulized D5W with 1% benzyl alcohol, the vehicle of trimethoprim-sulfamethoxazole. Group 2 will receive nebulized trimethoprim-sulfamethoxazole prophylaxis. Group 3 will receive twice weekly subcutaneous trimethoprim-sulfamethoxazole which has been shown to be 100% effective in preventing PCP in the rat.(25) Each rat will receive the same regimen of oral dexamethasone and tetracycline in the feed on Day 0 as per Hughes (26). On Day 4 nebulization will be delivered in the same manner to all rats in Groups 1 and 2 using a micronebulizer (Bird Corporation, Palm Springs, Calif). During administration of nebulization the rats will be attached to a plethysmograph to monitor ventilation. Dose administered will be estimated by method as outlined by Girard.(9) Group 3 rats will also receive subcutaneous trimethoprim-sulfamethoxazole on Day 4. Prophylactic drugs will be administered subsequently weekly from Day 4. All rats will be inoculated intra-tracheally with 0.2 ml of a  $2 \times 10^6$  trophozoite/ml solution on Day 6. Two sentinel rats from each group will be euthanized at weeks 2, 4, 5, 6 and 7 to monitor progress of infection. Plasma, lung and liver will be harvested from the sentinels and stored at -70°C to assay for drug levels. All euthanized sentinel rats and any rats dying during the experiment will be examined for evidence of PCP. PCP infection will be determined by special stains of lung tissue and described as either infected or not infected. Severity of infection will be graded according to the number of *Pneumocystis* cysts as per Girard et al(25). The experiment will last 8 weeks. All rats will be euthanized at that time and assayed for evidence of *Pneumocystis carinii* infection. Serum liver function tests, BUN, creatinine and complete blood count will be done. Liver and lungs will be examined histologically for any evidence of toxicity. Survival will be expressed by Kaplan-Meier plot.

**Progress:** Work on the study has not yet been initiated due to unavailability of equipment. We hope that the volume respirator will be purchased soon.

**DETAIL SUMMARY SHEET**

**DATE:** 1 October 93

**PROTOCOL #:** 92/64

**STATUS:** Completed FY93

**TITLE:** The Relationship of Health Beliefs and Self Efficacy to Adherence Levels in Men and Women Who Complete Phase II Cardiac Rehabilitation

**START DATE:** Sep 92

**ESTIMATED COMPLETION DATE:** Nov 92

**PRINCIPAL INVESTIGATOR:** MAJ Susanne Clark

**DEPARTMENT:** Nsg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** M Kaough, M May

**KEY WORDS:** Adherence levels between genders

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**Study Objective:** To increase compliance levels of positive cardiovascular health habits after completion of Phase II Cardiac Rehabilitation.

**Technical Approach:** This is a descriptive, correlational study. Ten men and ten women who have completed Phase II Cardiac Rehabilitation will be asked to complete questionnaires concerning health beliefs, self efficacy, and demographic data. Results will be compared to determine whether a significant difference exists between men and women in their health beliefs and self efficacy levels and if there is a relationship to adherence levels to positive cardiovascular health behaviors.

**Progress:** This pilot study consisted of a sample of 20 subjects who had completed Phase II cardiac rehabilitation at WBAMC. Ten were male and 10 were female. The purpose of this study was to see if there was a relationship between health beliefs and self efficacy levels to adherence levels to positive cardiovascular health behaviors in men and women who completed Phase II cardiac rehabilitation. Because of technical difficulties during data analysis, and because no significant differences between males and females were noted in the variables measured, this research study should be repeated using a larger sample size. Other areas to explore include research conducted on the specific nursing interventions utilized in cardiac rehabilitation programs to determine their effectiveness and research on individuals who refuse to participate in rehabilitation programs, comparing these results with those of individuals who agree to participate in the programs.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/66

**STATUS:** Ongoing

**TITLE:** Workload Management for Nurses in the Trauma Resuscitation Unit

**START DATE:** Jan 93

**ESTIMATED COMPLETION DATE:** Oct 94

**PRINCIPAL INVESTIGATOR:** MAJ Susanne Clark

**DEPARTMENT:** Nsg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** trauma resuscitation

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**Study Objective:** To develop an accurate tool to measure nursing workload in the Trauma Resuscitation Unit; to develop an accurate tool to measure trauma patient acuity in terms of nursing care hours; and to develop an accurate tool that can predict nurse staffing needs.

**Technical Approach:** This is a descriptive, exploratory study of all incoming trauma patients, "code 3" designated for the Trauma Unit beginning 1 October 1992 through 1 October 1993. We will use a specially designed Trauma Resuscitation Acuity Worksheet to calculate nursing care hours for each "code 3" trauma.

**Progress:** Twenty-eight charts have been considered; 16 have been discarded due to insufficient data. The investigators believe that they need to collect more data so that study results will be significant. Estimated completion for the project is Oct 94. MAJ Clark has replaced MAJ Terriquez-Kasey as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/67

STATUS: Completed FY93

**TITLE: Wearing of Duty White Uniform by Professional Nurse Managers Invites Condescension, Encourages Domination, and Affects Power**

START DATE: Sep 92

ESTIMATED COMPLETION DATE: Oct 92

PRINCIPAL INVESTIGATOR: CPT Patricia Gustafson

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: white uniform

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**Study Objective:** This research proposes to investigate how professional nurse managers feel their appearance in the duty white uniforms invites condescension, effects power, and encourages domination in the military health care setting at William Beaumont Army Medical Center. This research will also determine the validity of the tool.

**Technical Approach:** This will be a pilot study. It will be descriptive/exploratory in nature. Limitations: The lack of a preestablished tool reliability and a small sample return could limit the generalizations drawn from this survey. In addition, because this survey is based on subjects' feelings and perceptions, there are personal variables which cannot be controlled or documented.

**Progress:** The purpose of this study was to ascertain if professional nurse managers feel their appearance in the duty white uniform invites condescension, encourages domination or effects their power in the military health care setting at William Beaumont Army Medical Center. A convenience sample of 23 male and female nurse managers was received. The research tool was a self designed survey. The statistical procedure use for the data analysis was the Mann-Whitney "U" test. The research hypothesis, that professional nurses in management positions feel more empowered and at less of a disadvantage when they would dress in either the class "B" uniform or the Battle Dress Uniform (BDU), versus the duty white uniform, was supported. The support was strongest especially when the nurse managers were dealing with physicians and administrators.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/28

STATUS: Completed FY93

TITLE: The Effects of Skin Color on the Accuracy of Pulse Oximetry

START DATE: Mar 93

ESTIMATED COMPLETION DATE: Jul 93

PRINCIPAL INVESTIGATOR: LTC Charles B. Hauser

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: FD Kline, JW Lonczak, DW Kendrick, PJ Marinich, TL Wilson

KEY WORDS: skin color, pulse oximetry

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**Study Objective:** The objectives of this study are to determine whether skin color affects the accuracy of pulse oximeter oxygen saturation readings as compared to arterial oxygen saturation values. If discrepancies due to skin color exist, the data will be examined to determine the saturation values at which they are most pronounced. Further objectives are addition to the existing body of knowledge and provision of a baseline for further research. Practitioner enlightenment to the possible limitations of pulse oximetry as a monitor of oxygen saturation is a final goal.

**Technical Approach:** This study will utilize a non-experimental, ex post facto retrospective design. The statistical evaluation will be done in two phases. The Phase I hypothesis is that no difference exists in arterial oxygen saturation values when measured by ear pulse oximetry and arterial blood gas. Each participant will have an intra-operative blood gas drawn via arterial puncture. The SpO<sub>2</sub> determined by pulse oximeter will be simultaneously recorded. The test for validity involves the comparison of these independent and dependent variables within each group. The data collected in the light-skinned group during Phase I serves to reinforce the current research data. Since the dark-skinned group was not represented in the original data, a determination will be made whether conclusions drawn from research on light-skinned patients can be extended to this group (Guilford and Fruchter, 1973).

**Progress:** Fifty-one subjects were entered into the study. Eleven were excluded because of equipment problems, failure to meet study criteria, or failure to draw blood.

**Abstract:** Monitoring of oxygen saturation by pulse oximetry has become a standard of care during the intra-operative period. Despite this standard, little research has been done investigating the effects of skin color on the accuracy of oxygen saturation values. Many articles allege that darker skin color could affect the pulse oximeter's accuracy. The investigators' Phase I hypothesis is that no difference exists in arterial oxygen saturation values when measured by ear pulse oximetry and arterial blood gas. The Phase I hypothesis of the study is that skin color does not effect arterial saturation measured by pulse oximetry. ASA1 and ASA2 patients scheduled for routine surgery were used for this study. Following an interview with the study participant, an informed consent was obtained. The Munsell color system was used to assess skin color. Each participant had an intra-operative arterial blood gas drawn. The pulse oximeter oxygen saturation reading was simultaneously recorded. Forty patients were entered into the study, 20 dark skin and 20 light skin. The Mann-Whitney U Test was used to evaluate the data. The study demonstrated no significant difference between dark versus light skin for arterial oxygen saturation. There was no significant difference between dark versus light skin for pulse oximeter oxygen saturation. There was no significant difference between dark versus light skin for the difference between arterial oxygen saturation and pulse oximeter oxygen saturation. We studied the effects of skin color on the accuracy of pulse oximetry. We found in our study that there were no significant differences between dark and light skin in regard to pulse oximeter accuracy.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/35

STATUS: Ongoing

TITLE: Lack of Child Care Facilities at WBAMC: Impact on Nursing

START DATE: Jul 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Sarah N Lozano

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: None

KEY WORDS: child care WBAMC

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Study Objective: 1) Develop an index to measure level of child care problems.

2) Analyze and interpret collected data in order to evaluate the effect of child care problems on absenteeism of the nursing staff in the MCH Nursing Section at WBAMC.

3) Analyze and interpret collected data in order to evaluate the impact of not having a twenty-four hour child care center with facilities for employees' sick children on the absenteeism of nursing staff in the MCH Nursing Section.

Technical Approach: The primary data for this study will come from a demographic data survey, so the study design or research methodology for this study will be qualitative.

Progress: A total of 129 surveys were sent out; greater than 50 were returned. Investigator has begun tabulating responses.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/68

STATUS: Terminated FY93

TITLE: Nursing Effects on Mastectomy Patients' Perception of Self Esteem

START DATE: Oct 92

ESTIMATED COMPLETION DATE: Oct 92

PRINCIPAL INVESTIGATOR: LTC Patricia Lutz

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: H Harris, D Bray, N Bickford

KEY WORDS: mastectomy

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**Study Objective:** The objective of this study is to determine if there is a positive correlation between nursing support and the mastectomy patient's perception of self esteem.

**Technical Approach:** Patients will be assigned to either Group A (experimental) or Group B (control) dependent upon their ward assignment. Group A (6W nurses) will be given the handouts based on Maslow's Needs (Appendix A-F) which will be discussed during a 15-minute inservice. Group B (6E) nurses will not be inserviced and will not be given the handouts. When the patient is scheduled for surgery, the General Surgery Staff will send the patients to the Acute Surgical Clinic, where they will be asked if they will participate in the study. Patients who agree to participate will be given the Rosenberg Self-Esteem Tool (Appendix I) which will be turned over to the investigators. Surgery is normally scheduled 1-2 weeks later and patients are admitted to either 6E (Group B - control) or 6W (Group A - experimental) with one-to-one nursing care. Three days postoperatively, the same patients will again be asked to complete the Self Esteem Tool and will additionally be asked to complete the Gardner and Wheelers' Nursing Support Scale (Appendix H). The total nursing care given by all staff members will be evaluated. At the end of the proposed two week study, the data will be taken back to the University of Texas at El Paso, where one-way Analysis of Variance will be used to determine if nurses do have an effect on a patient's perception of self-esteem.

**Progress:** Student project. Only six patients were entered; one withdrew due to language barrier. There was insufficient data; project has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/08

STATUS: Completed FY93

TITLE: Cardiac Catheterized Patients' Perception of Nursing Support

START DATE: Dec 92

ESTIMATED COMPLETION DATE: Mar 93

PRINCIPAL INVESTIGATOR: MAJ Elizabeth Nufer

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: CK Ching

KEY WORDS: Nursing Support

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**Study Objective:** To describe what patients who receive cardiac catheterization education information perceive as supportive nursing care.

**Technical Approach:** This project utilizes a descriptive study obtaining subjects from various hospital sites. Potential subjects will be identified by the investigators on a daily basis by calling the respective units. Prior to approaching them, their charts will be reviewed for any of the exclusion criteria. These patients will be approached to participate in the study and have their signature on the consent prior to answering the Nursing Support Scale 52 item questionnaire and demographic sheet. The investigators may explain the scale if the patient has a question about it. It is permissible to have the questions read to the patient and a family member mark the questionnaire for them. Data will be analyzed using descriptive and nonparametric statistics.

**Progress:** Research has been completed and will be reported in CPT Ching's thesis.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/09

**STATUS:** Ongoing

**TITLE:** Assessment of Recalled Medical Reservists' Needs

**START DATE:** Dec 90

**ESTIMATED COMPLETION DATE:** Mar 94

**PRINCIPAL INVESTIGATOR:** MAJ Christine M. Piper

**DEPARTMENT:** Nsg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** stress, depression

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**Study Objective:** To determine the degree of adjustment difficulty that reservists are experiencing and to assess the needs for additional support measures and programs.

**Technical Approach:** This study will utilize an anonymous voluntary questionnaire. This is a pilot study to survey medical and medical support reservists who were called to active duty to support Operation Desert Shield while assigned or attached to WBAMC.

**Progress:** Data collection complete and analysis underway.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/37

**STATUS:** Ongoing

**TITLE:** Use of Awareness of Stressors to Manage Burnout in Department of Nursing Midlevel Managers

**START DATE:** May 92

**ESTIMATED COMPLETION DATE:** Mar 94

**PRINCIPAL INVESTIGATOR:** MAJ Christine M. Piper

**DEPARTMENT:** Nsg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** burnout, stress in nursing

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**Study Objective:** To identify current levels of burnout in midlevel nursing managers and work-related stressors and increase awareness of stressors in order to address staff burnout more effectively.

**Technical Approach:** This study will survey midlevel managers in Department of Nursing. Three instruments will be completed prior to an educational offering on burnout and stress management. Subjects will be asked to complete the same three instruments at 1 month, 6 months, and 2 year post workshop to identify any measured changes.

**Progress:** Data collection has been completed. Raw data will be analyzed by the statistical consultant of the Department of Clinical Investigation.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 88/65A

STATUS: Ongoing

TITLE: Pediatric Intubation Training Utilizing the Ferret Model

START DATE: Jul 88

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Anne Varner

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: L Tremper

KEY WORDS: pediatric intubation ferret

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**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 ferrets 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).

**Amendment Jun 93:** Feline model changed to ferret model. New principal investigator is MAJ Varner.

**Progress:** Two Pediatric Advanced Life Support (PALS) courses were conducted during FY93 which included two intubation training sessions supported by the Biological Research Service utilizing a total of 8 ferrets. A total of 32 students completed the courses. Course critiques indicated that the training was extremely well received and judged as "excellent" overall. The ferret model has performed superbly for neonatal intubation training and has shown to be extremely durable with no discomfort or after effects. The PALS course established at WBAMC is an important asset to the hospital and to the El Paso community. Quarterly courses are anticipated in the future.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 86/24

STATUS: Ongoing

TITLE: The Effect of Relaxation Therapy on Patients with Asthma

START DATE: Jan 87

ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: Helen Villegas

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Asthma relaxation therapy

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**Study Objective:** To measure the effects of relaxation therapy on asthma symptoms, frequency of pain 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 PEF. 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:** Twenty patients are enrolled. Due to unavailable time to complete the control group, the investigator has had to again postpone collecting data to coincide with experimental group from November 1993 through February 1994.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/41

STATUS: Terminated FY93

**TITLE:** Mixed Venous Oxygenation Saturation in the Critically Ill Patient: Normal Fluctuations, the Effects of Patient Care Activities, and the Effects of Circadian influence

START DATE: Jul 92

ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: CPT Linda S. Weaver

DEPARTMENT: Nsg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: mixed venous oxygenation

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**Study Objective:** The objectives of this study are (1) to determine the normal fluctuations of SvO<sub>2</sub>; (2) to determine the effects of routine patient care and other activities on SvO<sub>2</sub> levels; and (3) to determine the effects of circadian influence on fluctuations of SvO<sub>2</sub> and the effects of patient care activities on SvO<sub>2</sub>.

**Technical Approach:** The convenience sample will consist of 50 patients admitted to the MICU who require the placement of a pulmonary artery catheter for medical management. A fiberoptic pulmonary artery catheter capable of continuously monitoring SvO<sub>2</sub> will be placed by the medical resident caring for the patient. Each patient will be observed and SvO<sub>2</sub> will be monitored and recorded on a strip chart recorder during two data collection periods, 0400-0700 hours (Time Group 1 - TG<sub>1</sub>) and 1600-1900 hours (Time Group 2 - TG<sub>2</sub>). SvO<sub>2</sub> data will be recorded each minute for a 30 minute period of rest. An average SvO<sub>2</sub> (baseline) will be calculated. SvO<sub>2</sub> data for all patient care activities taking place during the remainder of the observation period will be recorded. SvO<sub>2</sub> data within each Time Group will be analyzed using descriptive statistics. SvO<sub>2</sub> fluctuations will be described as percent variation from baseline. Average fluctuation in SvO<sub>2</sub>, mean changes in SvO<sub>2</sub> with activity, and mean duration of change in SvO<sub>2</sub> with activity will be calculated for each data collection period and compared using an analysis of variance.

**Progress:** As of 1 September 1993, 3 oximetric swan gang catheters have been utilized in the medical intensive care unit. None of the patients have met the inclusion criteria. Investigator desires to resubmit a different study plan and methodology in a new protocol rather than an amendment.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/02

STATUS: Ongoing

TITLE: Cervical Density: A Longitudinal Study to Determine Normative Values in Pregnancy

START DATE: Nov 92

ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Philip Bayliss

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Cervical Density

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**Study Objective:** The objectives of this study are to establish normative values for cervical density during pregnancy in uncomplicated pregnancies.

**Technical Approach:** A longitudinal study of nulliparous and multiparous women will be conducted. Each patient will be followed monthly from entry until delivery with cervical measurements. The patients will be recruited into this protocol from the routine obstetrical clinics at WBAMC. They will undergo serial transvaginal ultrasounds beginning at 16 weeks of gestation and continuing every 4 weeks until delivery. The images obtained of the cervix will be captured into a graphic file format for the personal computer. These files will be analyzed using densitometry software to establish a density score for the cervix. These scores will then be plotted to establish normative values for specific gestational ages.

**Progress:** Total equipment was received in October 1993. Investigator will begin enrolling patients in late October 1993.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/03

STATUS: Ongoing

TITLE: Cervical Density Measured via Ultrasound: A Predictor of Risk for Preterm Delivery?

START DATE: Nov 92

ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Philip Bayliss

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Rosa

KEY WORDS: Cervical Density, Preterm Delivery

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**Study Objective:** The objective of this study is to measure cervical density and to determine if it correlates to either preterm labor or delivery.

**Technical Approach:** A prospective, pilot study of the measurement of cervical density by computer assisted ultrasonography will be conducted. Pregnant patients from the Dept. of OB/GYN will be recruited for enrollment in this study. Two groups will be established. The first will consist of patients with no identifiable risk factors for preterm delivery and the second group with one or more of these risk factors identified. Each patient will undergo an endovaginal ultrasound for cervical length and dilatation between 22-26 weeks of gestational age. Images of the cervix for each patient will be captured into a computer by a digitizing process. These images then will be analyzed for an estimation of density of the cervix. Pregnancy outcomes will be matched with the ultrasound data to determine if cervical density scores are predictive for preterm labor or birth.

**Progress:** Total equipment was received in October 1993. Patients will be enrolled beginning late October 1993.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/51

**STATUS:** Ongoing

**TITLE:** A Prospective Randomized Comparison of Tocolysis and Expectant Management after Mature Fetal Lung Studies (Monitor: LTC Soisson)

**START DATE:** Sep 93

**ESTIMATED COMPLETION DATE:** Sep 94

**PRINCIPAL INVESTIGATOR:** CPT Christopher Benson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** P Bayliss

**KEY WORDS:** tocolysis, mature fetal lung

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**Study Objective:** The purpose of this study is to determine the role of tocolytic therapy in preterm labor patients once fetal lung maturity has been established.

**Technical Approach:** This is a prospective and randomized study. All preterm labor patients with biochemical evidence of lung maturity will be randomized into a tocolytic or expectant management group. Maternal and neonatal outcomes will be compared.

**Progress:** As soon as clinical lab sends word that it is prepared to perform FLM testing, investigators will begin enrolling patients.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/24

STATUS: Ongoing

TITLE: Vaginal Hysterectomy; Morbidity with and without Injection of Epinephrine in the Vaginal Cuff

START DATE: May 91

ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: MAJ Phillip C. Brittain

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Soisson, C Hawley-Bowland, HC Crawford

KEY WORDS: hysterectomy, cuff injection

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**Study Objective:** To determine if vasoconstrictor use in vaginal hysterectomy increases the incidence of cuff infections and to determine if vasoconstrictor use significantly reduces blood loss during vaginal hysterectomy.

**Technical Approach:** Patients scheduled for elective vaginal hysterectomy will be prepared for surgery in the usual fashion. The cervicovaginal junction will be injected circumferentially in each patient with 10cc's of one of the solutions described below. All patients will be given similar antibiotic prophylaxis. Estimates of blood loss will be made in conjunction with operating room staff and anesthesia. Postoperative hematocrits will be drawn at similar intervals. Intravenous fluid replacements will be at a 3:1 ratio to estimated blood loss. Specific analysis of what constitutes a postoperative wound infection will be standardized; localized abscess, erythema, marked tenderness, temperature elevation, rising white blood cell count/increasing percentage of immature forms on peripheral smear, tissue necrosis, frank pus, temperature >38 c, negative chest x-ray, and negative cultures of blood and urine. Cuff closures will be standardized among surgeons in the study.

In a double blinded randomized fashion, the pharmacy at William Beaumont Army Medical Center will prepare and code the solution to be injected. The study group will be injected with a dilute solution of epinephrine (1:200,000) in sterile saline, and a control group with sterile saline. Only at the conclusion of the study will the code be broken and data analyzed.

**Progress:** Eighty patients have been enrolled. Recruitment is a little slower than anticipated. No problems with data collection on those enrolled. No adverse reactions have been noted thus far.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/47

STATUS: Ongoing

TITLE: The Clinical Management of Patients with Mild Dysplasia of the Uterine Cervix

START DATE: May 91

ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ Philip C. Brittain

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Solsson, C Hawley-Bowland, HC Crawford

KEY WORDS: Dysplasia (mild)

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**Study Objective:** To determine the incidence of HPV infection in young women with histologically proven mild dysplasia (CIN I) of the uterine cervix.

**Technical Approach:** Patients with dysplastic cervical cells detected by cytology will undergo standard colposcopic examination, colposcopically-directed biopsies of suspicious cervical lesions found during colposcopy, and endocervical curettage. Patients with the following clinical and pathologic characteristics will be considered for study entry: (a) histologically proven mild dysplasia (CIN I) of the ectocervix; (b) adequate colposcopic examination; (c) absence of dysplastic epithelium in the endocervical canal as proven by endocervical curettage. These patients will be thoroughly counseled about study entry. Samples from patients who elect to participate will undergo in-situ DNA hybridization to detect specific subtypes of HPV within cervical cells using the Vira-Type kit. Patients with even last digit SSN will receive standard therapy using cryotherapy or laser vaporization of the transformation zone of the cervix (Group A). Patients with odd last digit SSN will be assigned to the observation group (Group B). All study participants will be monitored every 3 months in the Gynecology Clinic using cervical cytology (PAP Smear), colposcopic examination, and colposcopically directed biopsies of suspicious lesions. All women will be followed for a minimum of 2 years. The sexual consorts of study group patients will be referred to the Male Dysplasia Clinic in the OB-GYN Clinic for Vira Type, colposcopy and colposcopically directed biopsies.

**Progress:** Thirty-three patients are enrolled. Investigator is having some trouble recruiting patients due to disclaimer that no pregnancy can occur for the two year duration of the study and to the fact that some are reluctant to enroll because of the possibility they will be randomized into the observation rather than treatment group.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/31

STATUS: Ongoing

TITLE: Loop Electrosurgical Excision Procedure Treatment for Dysplasia of the Uterine Cervix

START DATE: May 93

ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Phillip C. Brittain

DEPARTMENT: OB/GYN

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: GL Maxwell, AP Soisson, P Miles

KEY WORDS: Loop, Dysplasia, Cervix

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**Study Objective:** (1) To compare methods of preparation of the cervix prior to Loop Electrosurgical Excision Procedure (LEEP) in treatment of cervical dysplasia. Specifically, to determine if colposcopic visualization of the dysplastic lesion or the absence of staining by iodine containing solutions on dysplastic lesions is a more efficacious method of defining the full extent of the lesion prior to excision.

(2) To determine the success rate of treatment of cervical dysplasia with LEEP, based on cytologic analysis of surgical specimens.

**Technical Approach:** (1) Patients with dysplastic cervical cells detected by cytology from Pap smears will undergo standard colposcopic evaluation, colposcopically directed biopsies of suspicious cervical lesions, and endocervical curettage.

(2) Patients with the following clinical and pathologic characteristics will be considered for study entry: a) histologically proven dysplasia of the ectocervix, b) adequate colposcopic examination, c) proven absence of dysplastic epithelium in the endocervical canal by endocervical curettage.

(3) Patients with these characteristics will be thoroughly counseled about study entry.

(4) The patients enrolled in the study will be treated with LEEP using standard protocols. A paracervical anesthetic block will be performed with 10cc 1% xylocaine with 1:100,000 epinephrine. Loop electrosurgical excision will be performed with bipolar cutting/coagulation wire loops using a Valley Lab Electrosurgical generator unit and large wire loops when possible (for better specimen analysis)<sup>6</sup>. Patients will be randomized by pseudo number generation to colposcopy followed by LEEP or application of Lugol solution to the cervix followed by LEEP of the non-staining areas. Comparison will be made to LEEP specimens collected using Lugol's solution for demarcation of the cervical abnormal epithelium, on the principle that normal squamous epithelium contains enough glycogen to stain and dysplastic tissue does not. Neither of these preparation techniques, however, are foolproof and both false positive and negative areas may be highlighted. We seek to determine whether colposcopy/LEEP is more efficacious than Lugol/LEEP, the surgical margins will be evaluated by standard histopathologic techniques. Treatment success will be analyzed 3 months after therapy when colposcopy and cervical cytology is performed.

**Progress:** Enrollment has been slower than anticipated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/40

STATUS: Completed FY93

**TITLE:** Comparison of Azithromycin and Erythromycin in the Treatment of Cervical Chlamydial Infection during Pregnancy

**START DATE:** May 92

**ESTIMATED COMPLETION DATE:** May 93

**PRINCIPAL INVESTIGATOR:** CPT Mark R. Bush

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** C Rosa

**KEY WORDS:** chlamydia, azithromycin

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**Study Objective:** To compare azithromycin and erythromycin with respect to efficacy in eradicating cervical chlamydial infection and to compare the incidence and severity of side effects.

**Technical Approach:** Pregnant patients with positive cervical chlamydial culture will be invited to join the study. Informed consent will be obtained. The patient will be randomized to either treatment arm via a sealed envelope system. The treatment arms are: erythromycin 500mg QID x 7d or azithromycin 1 gram PO x 1. The patient will be given a one page side effect questionnaire at the onset of therapy (see enclosure 4). Both treatment arms will be recultured 14 days after completion of therapy. In the event that a patient cannot tolerate erythromycin 500mg QID dosing secondary to side effects, the regimen will be altered to 250mg QID, as is customary. If she continues to be intolerant she will be considered a treatment failure for erythromycin and offered azithromycin.

**Progress:** To compare azithromycin and erythromycin in regards to side effect profile, intolerance, and cure rate in a pregnant population with chlamydial cervicitis. Thirty women were randomized to receive either erythromycin 500 mg PO QID x seven days or azithromycin 1 gram PO x one dose. Questionnaires identifying the incidence of nausea, vomiting, diarrhea, abdominal pain, and anorexia were completed by all. All patients in the erythromycin group reported two or more of the above gastrointestinal side effects, while no patient in the azithromycin group reported side effects ( $p < 0.001$ ). Five out of the 15 patients (33%) in the erythromycin treatment arm were intolerant to the 500 mg QID dosing secondary to side effects compared to none in the azithromycin group ( $p < 0.025$ ), and the dose was lowered to 250 mg QID to complete the course. Repeat cervical testing demonstrated similar cure rates for both medications, 100% after azithromycin and 93% (14/15) after erythromycin ( $p = 0.85$ ). These data suggest that azithromycin is a viable treatment option in a pregnant patient who cannot tolerate erythromycin secondary to side effects and may in some cases be considered the treatment of choice.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 86/08A

STATUS: Ongoing

TITLE: Obgyn Bowel Training Utilizing the Pig Model

START DATE: Jul 86

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Carla G. Hawley-Bowland

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Surgical training in residency - GI

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**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 awoken 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 have been utilized for training in twelve operative episodes for FY93. Seven residents were trained in bowel surgical techniques. There were no operative complications.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 86/33A

STATUS: Ongoing

TITLE: OB/GYN Microsurgical Tubal Re-Anastomosis Training Utilizing A Rabbit Model

START DATE: Mar 86

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Carla G. Hawley-Bowland

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: M Wood

KEY WORDS: Tubal Re-anastomosis

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**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 awoken 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 in seven operative episodes. Seven residents were trained in microsurgical tubal reanastomoses. There were no operative complications. MAJ Michael Wood has replaced COL Cesar Rosa as associate investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 86/64A

STATUS: Ongoing

TITLE: Genitourinary Tract Surgery Training Utilizing a Pig Model and Comparing Stenting Technique

START DATE: Aug 86

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Carla G. Hawley-Bowland

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Surgical Training

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**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 consist of unilateral ureter resection and re-anastomosis. Upon completion of this procedure, the laparotomy incision will be closed and the animal awakened 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 administered 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 in 11 operative episodes. Eight residents were trained in bowel surgical technique. One pig had the complication of a stitch granuloma, abdominal adhesions, and a disrupted ureter from the previous operative episode. One pig had a post-operative death after the first episode of surgery, thought to be pulmonary edema.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/63A

STATUS: Ongoing

TITLE: Certification Training: Advanced Laser Laparoscopic GYN Procedures in the Porcine Model

START DATE: Sep 91

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Carla Hawley-Bowland

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Laser

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**Study Objective:** To provide training and certification of OB-GYN Surgery Staff in laser and non-laser laparoscopic and vaginal surgical procedures. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

**Technical Approach:** The ability to suture during laparoscopy greatly expands the indications for laparoscopic surgery and increases the confidence of the surgeon performing more difficult procedures. There will be two live animal surgical stations and one station where some procedures will be taught with inanimate tissue such as bovine tongue and uterus. After the skin is prepped, an insufflation needle will be inserted near the umbilicus and the abdomen will be filled and maintained with 15mm Hg pressure of CO<sub>2</sub>. The insufflation needle will then be removed and replaced with a trocar/cannula for introduction of the video laparoscope which will enable monitoring of the procedure on a video screen. Two to three additional trocars/cannulas will be placed for introduction of laparoscopic graspers, scissors, laser fibers, etc. Training will involve extracorporeal and intracorporeal suturing techniques of various urogenital tissue through the laparoscopic cannulas. The argon-beam and ND:YAG laser will be used to train in techniques of tissue coagulation and excision. Abdominal lymph nodes will also be excised laparoscopically. Training will be conducted on endometrial ablation and tumor excision procedures with lasers and electrocautery (roller-ball and large loop wire electrodes) via a hysteroscope. If difficulty is encountered with introduction of the scope through the vagina, the uterus will be exposed by laparotomy via a mid anterior suprapubic abdominal incision. Additional training for endometrial ablation and tumor removal will also be conducted with bovine uterus and bovine tongue, respectively.

**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:** Four pigs were utilized for the training of physicians (military and civilian) in FY93. There were no intraoperative complications. The pigs were euthanized at the end of the training.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/48

STATUS: Completed FY93

TITLE: Is Measurement of Antibody Excess Cost-Effective After Administration of Rh-Immune Globulin?

START DATE: Sep 91

ESTIMATED COMPLETION DATE: Oct 92

PRINCIPAL INVESTIGATOR: CPT George M. Kingsley

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: F Harlass

KEY WORDS: Rh sensitization, Rh prophylaxis

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**Study Objective:** To perform cost analysis of the post-administration immune globulin excess testing.

**Technical Approach:** Patients entering the OB system will have ABO/Rh?Prenatal Antibody screen upon entry and at 28 weeks gestation (current standard practice). At delivery, patients identified as Rhogam candidates will be assigned by the attending obstetrician as being Low Risk (no gross placental pathology; no manual placenta extraction; no evidence of placental accreta, increta or percreta, and no evidence of placental abruption or placental previa) or High Risk (one of the above placental factors being present) for fetal-maternal hemorrhage. Patients will continue to receive post-partum Rhogam. Immune globulin excess monitoring will continue. An analysis will be performed to evaluate the cost-effectiveness of the post-administration monitoring for the total population, and comparing the High and Low Risk groups. The following methods of post-administration monitoring will be compared: Leihauer-Betke, Fetal-dex, ELAT (enzyme linked antiglobulin test), flow cytometry, and Rosette test.

**Progress:** Rhesus (Rh) sensitization remains a significant source of fetal morbidity and mortality. Few recommendations exist regarding post-Rh immune globulin administration (IG) testing to assure adequacy of dosage. We prospectively evaluated 1,050 patients' risk factors for fetal-maternal hemorrhage. All women were tested for Rh status and all RH negative patients with Rh positive infants were administered 350 mcg of Rhogam. All IG recipients were retested for Anti-D antibody excess (signifying adequate coverage). Rhogam recipients with high and low risk classification were compared for incidence of insufficient coverage. Risk factors were identified in 20% of IG recipients. There was no difference in the percentage of high risk versus low risk patients with insufficient IG coverage. Therefore, risk factor identification for fetal-maternal hemorrhage is not accurate in identifying which patients will require additional IG. We recommend testing in all IG recipients.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/23A

STATUS: Completed FY93

TITLE: OB-GYN Genitourinary Tract Surgery Incorporating a New Ureteral Anastomotic Device

START DATE: Apr 92

ESTIMATED COMPLETION DATE: May 93

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Soisson, K O'Hair, P Miles

KEY WORDS: ureteral anastomosis

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**Study Objective:** The purpose of this study is to compare the efficacy of the UNILINK system, a microvascular anastomotic device, with standard suture techniques in the anastomosis of transected ureters.

**Technical Approach:** The first surgery will consist of bilateral ureter resection and anastomosis. The UNILINK will be utilized to complete a ureteral anastomosis on the ureter assigned by pseudo random number generation. The contralateral transected ureter will be repaired using suture in a standard repair. Permanent suture will be placed exactly 1 cm. proximally and distally to the anastomotic site to aid in identification at the second surgery. Upon completion of this procedure, the laparotomy incision will be closed and animal awakened from anesthesia. Intravenous pyelograms will be performed immediately following the procedure and repeated at 5 and 15 minutes. Postoperative care will be conducted in a standard fashion. After two weeks, a second laparotomy, and preoperative intravenous pyelogram, will be performed and the anastomotic site will be resected bilaterally at the suture markings. Tissue specimens will be fixed in formalin, imbedded in paraffin, and stored until histologic analysis. Histologic sections every 2 mm. (10 sections/specimen) through the lumens of the anastomotic sites will be performed by Dr. Miles. The cross sectional diameter of each lumen will be measured in serial sections of tissue in order to quantify healing. The anastomotic site repaired with suture will serve as a control against which to compare the UNILINK system.

**AMENDMENT (Jul 92):** Due to problems with pilot project, methodology was changed to include increased spatulation and the use a J-stent. Ten additional animals were approved for use with the stipulation that only 2-3 animals would initially be entered and results evaluated. The attending veterinarian will decide if the results warrant use of the remaining animals.

**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:** Ureteral injury is a complication of gynecologic surgery in approximately 1% of all cases. The anatomic site of the injury determines the type of operative repair. When an end-to-end ureteral anastomosis is required, interrupted sutures are usually employed. A prospective randomized animal study was performed to determine the efficacy of a new microvascular anastomotic device, the UNILINK system, in repairing transected ureters. Nineteen pigs underwent randomized anastomosis with the UNILINK system on one side and traditional anastomosis using suture on the contralateral side. A postoperative intravenous pyelogram (IVP) was performed immediately and two weeks later, prior to harvesting the anastomotic site at a second laparotomy. Patency rates for each type of anastomosis were compared microscopically, and the degree of

hydronephrosis was compared grossly and radiographically. The anastomotic repair using the *UNILINK* system did not significantly differ structurally or functionally from traditional suture repair.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/18A

STATUS: Completed FY93

TITLE: Tissue Glue as an Adjunct to Wound Healing in the Porcine Model

START DATE: Mar 93

ESTIMATED COMPLETION DATE: Jul 93

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Soisson, PC Brittain, P Miles, T Carey, RA Harris

KEY WORDS: tissue glue, wound healing

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**Study Objective:** The object of this protocol is to determine whether application of autologous fibrin adhesive improves wound healing and increases tensile strength in surgical incisions in pigs.

**Technical Approach:** A total of six (6) adult Yorkshire-cross domestic swine will be used in the study. Eight paramedian incisions perpendicular to the spine will be performed. Autologous glue, placebo, and standard closure techniques will be applied to the incisions as determined by random number assignment. Incisions will be evaluated for healing, tensile strength, and seroma formation at the conclusion of the experiment.

**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 prospective animal study utilizing six domestic swine was performed to investigate the potential of autologous fibrin glue (porcine fibrinogen as cryoprecipitate plus commercial bovine thrombin) to facilitate wound healing and reduce subcutaneous dead space and subsequent seroma formation in surgical wounds. Eight pairs of paramedian incisions were made on the back of each animal 3 cm lateral from the midline. The length (5 cm) and depth (1.5 cm) of each incision were exactly the same in each animal. One half of the incisions were closed using interrupted sutures (2-0 NYLON) and one half were closed in the same manner after adding fibrin glue to the subcutaneous space. All wounds were surgically excised on postoperative day seven. The entire incision and the subcutaneous tissues were harvested and cut into 1 cm strips perpendicular to the incision using a special cutting instrument. All tissues were snap frozen at  $-60^{\circ}$  F in a cryobath and stored at  $-70^{\circ}$  F. The tensile strength required to disrupt the surgical incision in each tissue strip was measured with an INSTRON tensiometer. The tensile strength was recorded in pounds per square inch (psi). Two hundred forty-seven specimens were analyzed; the mean tensile force required to disrupt the surgical incision was 0.13 psi (sd=0.17 psi). The mean tensile strength for 130 specimens from glued incision was 0.13 psi (sd=0.166 psi) compared with a mean tensile strength of 0.12 psi (sd= 0.17 psi) for 117 specimens that were not glued. Differences in the mean tensile strength between the two groups was not statistically significant using analysis of variance ( $P=0.5756$ ) or a two tailed students T test ( $P=0.577$ ). Although fibrin glue did not appear to facilitate wound strength we believe it does reduce seroma formation by obliterating surgical dead space and that it is safe to administer. Fibrin glue could have significant utility in certain high risk patients, such as obese women with endometrial cancer.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/39A

STATUS: Ongoing

TITLE: The Hemodynamic Response of Meconium Infusion in a Pregnant Sheep Model: Attempted Simulation of the Amniotic Fluid Embolism Syndrome

START DATE: Sep 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Soisson, PC Brittain, RA Harris, P Bayliss, M Kestner, J Galloway, P Miles

KEY WORDS: simulation, sheep, amniotic fluid embolism syndrome

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**Study Objective:** The purpose of this blinded prospective randomized controlled trial will be to study the effects of intravenous injection of meconium and amniotic fluid on hemodynamic function and subsequent cardiopulmonary pathology in the sheep model.

**Technical Approach:** A total of 16 pregnant sheep over 130 days gestation (corresponding to a near term human pregnancy) with a confirmed singleton fetus will be used to investigate the effects of intravenous infusion of meconium emboli. The pregnant sheep will undergo placement of a Swan-Ganz jugular catheter and carotid arterial catheter to evaluate the hemodynamic changes associated with infusion of the amniotic fluid specimens. Baseline hemodynamic measurements will be obtained one hour after placement of the Swan-Ganz and carotid catheters with the animal unanesthetized restrained in a standard sheep stanchion with head gate. Two samples of amniotic fluid will be used for injection: light meconium stained and thick meconium stained amniotic fluid. The animals will be divided into two groups according to the type of meconium stained amniotic fluid that will be infused (light or thick stained fluid): two animals will receive intravenous saline (control), two will receive unstained amniotic fluid, six will receive light meconium stained amniotic fluid, and six will receive thick meconium stained amniotic fluid. In the 12 animals that will receive meconium stained amniotic fluid, 2 will be infused with whole light meconium stained fluid, 2 will receive whole thick meconium stained fluid, 2 will receive the supernatant from light meconium stained fluid, 2 will receive the supernatant from thick meconium stained fluid, 2 will receive the precipitate from light meconium stained fluid, and 2 will receive the precipitate from thick meconium stained fluid. The investigator administering the solutions will be blinded to the identity of the infused substances. Following infusion into the venous system, hemodynamic parameters will be measured for the first hour after infusion. Doppler echocardiography will be used to determine cardiac ejection fractions at the time of infusion and at one hour post-infusion. After euthanasia has been performed, histologic sections from each animal's lung will be submitted to the pathology department for analysis and confirmation of amniotic fluid embolism. Data obtained before and after infusion of the various substances will be compared statistically.

**Progress:** Sheep have not yet arrived. As soon as they arrive, study will commence.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/55A

STATUS: Ongoing

TITLE: Repair of transversely incised anterior abdominal rectus fascia: Optimization of technique

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AP Soisson, PC Brittain, RA Harris, P Miles, T Scully

KEY WORDS: transversely incised rectus fascia

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**Study Objective:** The purpose of this prospective randomized study will be to determine the most effective method of closing transversely incised lower anterior abdominal rectus fascia.

**Technical Approach:** A total of thirty six rabbits will be used in the study. Each animal will be randomly assigned to one of three postoperative interval groups: one week, two weeks and four weeks. Four to five transverse abdominal incisions will be made on each animal under general anesthesia, each incision being 8cm in length, extending through the anterior rectus fascia. Six groups of fascial suture repair will be investigated using 0-Dexon: Group I, a continuous running suture with 1cm bites taken at 1cm intervals; Group II, a continuous running suture with 2cm bites taken at 1cm intervals; Group III, a continuous running suture with 1cm bites taken at 0.5cm intervals; Group IV, interrupted sutures involving 1cm bites taken at 1cm intervals; Group V interrupted sutures involving 2cm bites taken at 1cm intervals; and Group VI, interrupted sutures involving 1cm bites taken at 0.5cm intervals. Groups II and III will involve using a suture long enough to maintain a SL/WL of 4 as previously mentioned. All randomization will be performed using a pseudorandom number generating program.

Upon completion of the assigned postoperative period, each animal will undergo euthanasia as described in animal procedures. Each 8cm fascial incision will then be removed "in bloc" and subsequently trimmed into 8 separate 2cm x 1cm strips. Three strips representative of separate wounds from each of the six repair groups (total of 18) will be submitted for pathology analysis to compare the degree of necrosis associated with each repair technique. The remainder of the tissue specimens will be frozen in liquid nitrogen and stored until analysis of tensile strength.

Tensile strength will be determined using an Instron materials testing system located at Texas Tech in conjunction with William Beaumont's Department of Orthopedics. Each tissue specimen will be randomly assigned to one of two measurement groups: intrinsic wound strength determined after removal of suture and extrinsic wound strength determined with suture left in place. Tensile strength will be defined as the force needed to separate the tissue specimen at the incision.

**Progress:** Study has just begun; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/45

STATUS: Ongoing

TITLE: Vaginal 5-Fluorouracil Therapy in the Management of Human Papilloma Virus Infections of the Cervix Uteri (Monitor: MAJ Butterfield)

START DATE: May 92

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: CPT Peter Napolitano

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: A Soisson, C Hawley-Bowland, P Miles, P Day, D Smith

KEY WORDS: Cervix uteri, HPV, 5-fluorouracil

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**Study Objective:** To determine if 5-FU therapy is efficacious in eliminating HPV from the genital tract and to determine if 5-FU therapy will prevent the progression of HPV infections and minor associated cytologic abnormalities (kilocytotic atypia) to dysplasia.

**Technical Approach:** Patients will undergo HPV Profile, colposcopic examination, directed biopsies of suspicious lesions, and endocervical curettage (ECC). Patients with a positive HPV Profile will undergo Vira Type to further identify the subtype of the virus. Patients with a normal colposcopic examination or when directed biopsy and ECC excludes a dysplastic process will be counseled appropriately for study entry. Patients who elect to participate will be randomly assigned to one of two treatment regimens: Group A will be assigned to the observation only arm and will be followed closely with repeat cytology, HPV Profile, and colposcopic examinations every 3 months for six months. Group B will receive 5% topical 5-Fluorouracil cream (1/4 applicator) in the vagina every night for 7 nights. Following therapy, patients will be followed in the same manner as those in Group A.

**Adverse Event** presented to IRB Feb 93. Patient admitted for urinary retention secondary to labial erythema and edema for accidental contact with topical 5-FU cream. No adverse sequelae.

**Semiannual Review (Apr 93):** Currently, approximately 40 patients are enrolled and hopefully, approximately 10 more will be enrolled by 30 May 93 to complete the project. No preliminary results are available. One adverse event was reported to the Feb IRB.

**Progress:** Fifty patients have been enrolled with no documented adverse reactions. Follow up PAPs status post therapy are only now being performed. No early results are available. MAJ Butterfield has replaced LTC Rosa as medical monitor. LTC Rosa has PCS'd.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/69

STATUS: Completed FY93

**TITLE: Pregnancy After Failed Tubal Ligations: A Review of William Beaumont Army Medical Center's Experience**

START DATE: Aug 92

ESTIMATED COMPLETION DATE: Jul 93

PRINCIPAL INVESTIGATOR: CPT Peter Napolitano

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Rosa

**KEY WORDS: Failed Tubal Ligations**

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**Study Objective:** To make a comparison of prospectively collected cases in our registry to those collected system-wide by Health Services Command. We will evaluate any differences in intra-uterine versus ectopic rates, and if there are any associations with types of tubal ligations performed.

**Technical Approach:** This will be a retrospective review of the percentage of failed tubal sterilizations recorded in WBAMC's registry. A similar review of data retrieved from HSC's Statistics and Biometrics Section will be used to compare with that in the WBAMC registry.

**Progress:** This is a review of cases of failed tubal ligations diagnosed at William Beaumont Army Medical Center over the past three years. The data was prospectively collected in a registry of all patients with a positive pregnancy test and with documentation of a prior tubal ligation. Since 1989, 14 patients have been entered in the registry. Nine patients (64%) had ectopic pregnancies. During that period of time we had 4,038 deliveries. Reviewing the experience of other military hospitals, from data provided by the Epidemiology section at Health Services Command, during the years 1984 to 1988, the ectopic pregnancy rate in patients with failed tubal ligations was 35%. The reported incidence of ectopic pregnancy after tubal ligation ranges from 16 to 75%. Our data, although small in number, corroborates the increased likelihood of an ectopic pregnancy after a failed tubal ligation and thus the critical nature and importance of early management of this type of pregnancy.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/58

STATUS: Terminated FY93

TITLE: Gonadal Function After Vasectomy

START DATE: Nov 89

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL Cesar Rosa

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: N Dunn

KEY WORDS: Vasectomy, gonadal function

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**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:** Fourteen patients had initial GnRH stimulation test and had their vasectomies. Samples were stored in DCI deep freeze. Subjects went to ODS/S. Upon their return as the investigator was getting ready to do the post vasectomy GnRH injection, it was noted ;that the initial samples had been lost due to freezer malfunction and subsequent thawing of the samples for an undetermined period of time. Initial volunteers can no longer be used for the study. Principal investigator has PCS'd and does not wish to restart project. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/17

STATUS: Terminated FY93

TITLE: A Prospective Study of the Treatment of Functional Ovarian Cyst

START DATE: Jul 91

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL Cesar Rosa

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: KK Vu, F Hariass

KEY WORDS: Functional ovarian cyst

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**Study Objective:** To determine the effectiveness of oral contraceptives in the involution of benign ovarian cysts in a prospective, randomized fashion, comparing it with a population given placebo.

**Technical Approach:** Patients presenting to the Gynecology Clinic, who on examination are identified as having a suspected functional ovarian cyst, will be invited to join the study. If the patient accedes, randomization into an oral contraceptive versus placebo group will be performed. Prior to the initiation of medication, an endovaginal ultrasound will be performed by the Department of OB-GYN. The result of the endovaginal ultrasound will not affect the treatment of the patient. As a second arm to the study we will derive information which will indicate how effective is the physician's bimanual examination as compared to the endovaginal ultrasound in the identification and follow-up of these functional ovarian cysts. The patient will be followed for 8 weeks or two cycles with an examination both by bimanual examination and endovaginal ultrasound at the end of 4 and 8 weeks of treatment or placebo.

**Progress:** No patients were enrolled in FY93. Principal investigator and associate investigators have PCS'd. Department of Obstetrics and Gynecology does not wish to continue the study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/34

**STATUS:** Ongoing

**TITLE:** GOG #95/SWO6 #9047, Randomized Clinical Trial for the Treatment of Women with Selected Stage IC & II (A, B, C) and Selected Stage IA & IB Ovarian Cancer (Monitor: MAJ Nash)

**START DATE:** Oct 91

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** LTC Andrew Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** C Hawley-Bowland

**KEY WORDS:** ovarian cancer

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**Study Objective:** To determine if a short course of chemotherapy is more effective than intra-peritoneal radioisotope therapy in the treatment of early stage ovarian cancer and to determine the relative toxicity of each treatment.

**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.

**Semiannual Review:** Apr 93 - 1 patient enrolled. Patient randomized to P32 treatment arm and received therapy without complication.

**Progress:** Three patients are enrolled to date. No adverse reactions have been reported.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/67

STATUS: Ongoing

**TITLE: GOG #90, Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction followed by Vincristine, Dactinomycin and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors (Monitor: MAJ Nash)**

START DATE: Nov 91

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: ovarian germ cell cancer

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**Study Objective:** To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP) followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors. To evaluate the effect of BEP chemotherapy in patients with recurrent or progressive disease during or after previous non-cisplatin containing chemotherapy. To further investigate the relevant prognostic factors. To evaluate the acute and chronic toxicity of such chemotherapy, particularly in gonadal and reproductive function. To evaluate the effect of chemotherapy on menstrual status and reproductive function in patients in whom the uterus and one tube and ovary are preserved.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled to date.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/68

**STATUS:** Ongoing

**TITLE:** GOG #93, Evaluation of intraperitoneal chromic phosphate suspension therapy following negative second-look laparotomy for Epithelial Ovarian Carcinoma (Monitor: MAJ Nash)

**START DATE:** Oct 91

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** LTC Andrew Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** C Hawley-Bowland

**KEY WORDS:** ovarian epithelial cancer

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**Study Objective:** To evaluate the efficacy of P32 therapy in patients with no residual ovarian cancer and to evaluate the morbidity from intraperitoneal P32 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.

**Semiannual Review (Apr 93):** No patients enrolled.

**Progress:** One patient has been enrolled with no complications or adverse reactions.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/04

STATUS: Ongoing

TITLE: Protocol GOG # 99, A Phase III Randomized Study of Surgery VS. Surgery Plus Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma (Monitor: MAJ Nash)

START DATE: Nov 91

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: endometrial adenocarcinoma

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**Study Objective:** To determine if patients with intermediate risk endometrial adenocarcinoma, who have no spread of disease to their lymph nodes, benefit from postoperative pelvic radiotherapy. To evaluate how the addition of radiotherapy will alter the site and rate of cancer recurrence in those intermediate risk individuals.

**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.

**Semiannual Review (Apr 93):** No patients enrolled.

**Progress:** No patients enrolled.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/13

STATUS: Completed FY93

TITLE: GOG # 108, Ifosfamide (NSC # 109724) and the Uroprotector Mesna (NSC # 113891) With or Without Cisplatin (NSC # 11987) In Patients With Advanced, Persistent, or Recurrent Mixed Mesodermal Tumors of the Uterus (Monitor: MAJ Nash)

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Sep 93

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: mesodermal tumors, uterus

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**Study Objective:** To confirm reported high response rates of advanced or recurrent mixed mesodermal tumors of the uterus to Ifosfamide/Mesna; to determine whether the addition of Cisplatin to Ifosfamide/Mesna improves response rates or survival in patients with these tumors; and to determine the toxicity of Ifosfamide/Mesna with Cisplatin in patients with these tumors.

**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.

**Semiannual Review (Apr 93):** No patients enrolled.

**Progress:** GOG has completed the protocol. No patients were enrolled at WBAMC.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/14

STATUS: Terminated FY93

TITLE: GOG #104, SWOG - 8501. Intraperitoneal Cis-Platinum/Intravenous Cyclophosphamide vs. Intravenous Cisplatinum/Intravenous Cyclophosphamide in Patients with Non-Measurable (Optimal) Disease Stage III Ovarian Cancer (Monitor: COL Raymond Lundy)

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Undetermined

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: ovarian cancer (optimal)

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**Study Objective:** To carry out a Phase III randomized trial of intermediate dose intraperitoneal cis-platinum ( $100\text{mg}/\text{M}^2$ ) plus intravenous cyclophosphamide versus intermediate dose intravenous cis-platinum ( $100\text{mg}/\text{M}^2$ ) plus intravenous cyclophosphamide for optimal Stage III ovarian cancer. To evaluate the toxicities and complications of the two combination drug regimens. To determine in the setting of a prospective randomized trial if the human tumor clonogenic assay with a wide range of drug concentration testing can accurately predict pathologic complete response to two-drug combination therapy in the setting of systemic and intraperitoneal drug administration.

**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.

**Semiannual Review (Apr 93):** GOG closed the protocol. No WBAMC patients were enrolled.

**Progress:** Study terminated on semiannual review in Apr 93. No patients enrolled.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/30

STATUS: Ongoing

TITLE: GOG #122, Whole Abdominal Radiotherapy versus Circadian-Timed Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma (Monitor: MAJ Sheffler)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: endometrial carcinoma (advanced)

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**Study Objective:** To compare treatment outcomes (survival and progression free interval) and failure patterns in patients with stages III and IV endometrial carcinoma (< 2cm residual disease) treated with whole abdominal irradiation versus circadian-timed combination doxorubicin-cisplatin chemotherapy. To determine and compare the incidence and type of acute and late adverse events observed with the two treatment regimens.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled. MAJ Sheffler has replaced COL Lundy as medical monitor. COL Lundy has retired.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/31

STATUS: Terminated FY93

TITLE: GOG #121, A Phase II Trial of High Dose Megestrol (MEGACE) in Advanced or Recurrent Endometrial Carcinoma (Monitor: MAJ Cadiz)

START DATE:

Apr 92

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: endometrial carcinoma

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**Study Objective:** To determine the response rate and progression-free interval in patients receiving high dose megestrol acetate (Megace) for advanced or recurrent endometrial carcinoma. To determine the toxicity of high dose megestrol acetate in such patients. To determine if estrogen/progesterone receptor status is predictive of response.

**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.

**Semiannual Review (Apr 93):** Study closed by GOG. No WBAMC patients enrolled.

**Progress:** Study terminated in Apr 93 on semiannual review with no WBAMC patients enrolled.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/32

STATUS: Ongoing

TITLE: GOG #125, Extended Field Radiation Therapy with Concomitant 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes (Phase II) (Monitor: MAJ Sheffler)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: cervical carcinoma (metastatic)

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**Study Objective:** In this study, patients with cervical cancer who have biopsy confirmed para-aortic lymph node metastases will receive combination chemotherapy consisting of cisplatin and 5-FU intravenous infusion concomitantly with pelvic and para-aortic extended field radiation therapy. The objectives of this study are to assess progression-free survival and overall survival; sites of initial failure; and morbidity of the treatment.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled. MAJ Sheffler has replaced COL Lundy as medical monitor. COL Lundy has retired.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/33

STATUS: Ongoing

TITLE: GOG #107, A Randomized Study of Doxorubicin (NSC #123127) versus Doxorubicin plus Cisplatin (NSC #119875) in Patients with Primary Stage III and IV Recurrent Adenocarcinoma (Monitor: MAJ Cadiz)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: adenocarcinoma

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**Study Objective:** The major objective of this study is to determine whether the addition of cisplatin to doxorubicin offers significant improvement in the frequency of objective response, the duration of progressive free interval, and the length of survival as compared to doxorubicin alone.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled. MAJ Cadiz has replaced COL Lundy as medical monitor. COL Lundy has retired.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/34

STATUS: Ongoing

**TITLE:** GOG #109, A Randomized Comparison of 5-Fu Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy versus Radiation Therapy Alone in Selected Patients with Stages IA2, IB and IIA Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection (Monitor: MAJ Nash)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: cervical carcinoma

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**Study Objective:** To determine whether the combination of 5-fluorouracil (5-FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive pelvic lymph nodes, positive parametrial involvement or positive surgical margins following radical hysterectomy and lymph node dissection for stages IA2, IB, and IIA carcinoma of the cervix. To determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled to date.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/35

STATUS: Ongoing

TITLE: GOG #132, A Phase III Randomized Study of Cisplatin (NSC #119875) versus Taxol (NSC #125973) versus Taxol and Cisplatin in Patients with Suboptimal Stage III and IV Epithelial Ovarian Carcinoma (Monitor: MAJ Nash)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Apr 95

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: C Hawley-Bowland

KEY WORDS: epithelial ovarian carcinoma

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**Study Objective:** To determine the relative efficacy of regimens consisting of taxol, versus cisplatin and versus a combination of the two drugs in patients with suboptimally debulked epithelial ovarian cancer; to determine which of the three regimens contribute most favorably to progression free interval and survival; and to compare the incidence of audiology sequela and other toxicities from either of the three regimens.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** One patient has been enrolled with no adverse complications or reactions.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/51

**STATUS:** Ongoing

**TITLE:** GOG #114, Phase III Randomized Study of IV Cisplatin and Cyclophosphamide vs IV Cisplatin and Taxol vs High Dose IV Carboplatin followed by IV Taxol and Intraperitoneal Cisplatin in Patients with Optimal Stage III Epithelial Ovarian Carcinoma (Monitor: MAJ Sheffler)

**START DATE:** Sep 92

**ESTIMATED COMPLETION DATE:** Aug 97

**PRINCIPAL INVESTIGATOR:** LTC Andrew Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** epithelial ovarian carcinoma

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**Study Objective:** To compare recurrence-free interval, complete pathologic response, and survival between the standard regimen of intravenous cisplatin/cyclophosphamide and the two experimental regimens: (1) Intravenous cisplatin/taxol and (2) intraperitoneal carboplatin followed by intravenous taxol and intraperitoneal cisplatin in patients with optimal (<1 cm residual) Stage III epithelial ovarian carcinoma. To compare the toxicities and complications of the three treatment regimens. To correlate serial serum CA-125 levels with negative second look and recurrence-free interval.

**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.

**Semiannual Review (Apr 93):** One patient has been enrolled to date with no adverse side effects.

**Progress:** One patient enrolled at WBAMC with no complications or adverse events.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/52

STATUS: Ongoing

TITLE: GOG #135, Evaluation of Drug Sensitivity and Resistance with the ATP-Cell Viability Assay (ATP-CVA)

START DATE: Aug 92

ESTIMATED COMPLETION DATE: Aug 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: ATP-CVA

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**Study Objective:** a. To evaluate the correlation between the ATP-cell assay and patient response to chemotherapy in untreated primary epithelial ovarian carcinoma; to correlate laboratory results with the achievement of pathologic CR at time of second look surgery; to correlate laboratory results with progression-free survival; and to correlate single agent and combined agents in vitro studies with clinical outcome. Single drugs as well as drug combinations will be tested in vitro.

**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 enrolled to date.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/62

**STATUS:** Ongoing

**TITLE:** GOG #138, A Phase II Trial of Cisplatin and Cyclophosphamide in the Treatment of Extraovarian Peritoneal Serous Papillary Carcinoma (Monitor: MAJ Sheffler)

**START DATE:** Sep 92

**ESTIMATED COMPLETION DATE:** Oct 95

**PRINCIPAL INVESTIGATOR:** LTC Andrew P. Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** papillary carcinoma

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**Study Objective:** To determine the response rate, and response duration in patients with extraovarian peritoneal serous papillary carcinoma treated with a combination of cisplatin and cyclophosphamide.

**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.

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** No patients enrolled.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/63

STATUS: Ongoing

TITLE: GOG #134/NCCTG #92-61-51, A Phase III Trial of Taxol at Three Dose Levels and C-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma (Monitor: MAJ Sheffler)

START DATE: Sep 92

ESTIMATED COMPLETION DATE: Sep 97

PRINCIPAL INVESTIGATOR: LTC Andrew P. Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: ovarian carcinoma

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**Study Objective:** To determine if the dose of Taxol affects response rate, progression free interval or survival in patients with platinum-resistant ovarian cancer; to compare the toxicities of the three regimens; to compare the efficacy and toxicity of two dose levels of G-CSF (5 micrograms/kg/day versus 10 micrograms/kg/day) in patients who receive the highest Taxol dose (250 mg/m<sup>2</sup>); and to determine the relationship between peak Taxol plasma concentration and toxicity/response.

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

**Semiannual Review (Apr 93):** No patients enrolled to date.

**Progress:** One patient has been enrolled with no complications or adverse reactions.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/14

STATUS: Ongoing

TITLE: GOG #136, Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying Causes, Diagnosis, Prevention and Treatment of Ovarian Cancer

START DATE: Jan 93

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew P. Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: ovarian carcinoma

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**Study Objective:** To accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions; to provide a repository for long term storage of ovarian tumor, tissue, and serum. This material will be used in studies to better understand the molecular biology of ovarian tumors; and to make available, through the Cooperative Human Tissue Network (CHTN), tumor tissue and serum for proposed projects conducted by GOG Investigators (internal bank) and by researchers nationally (external bank).

**Technical Approach:** 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 been enrolled. There have been no adverse reactions.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/21

**STATUS:** Ongoing

**TITLE:** GOG #140, An Assessment of Age and Other Factors Influencing Protocol versus Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions

**START DATE:** Apr 93

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** LTC Andrew P. Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** epithelial ovarian cancer

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**Study Objective:** To assess the frequency at which patients with epithelial ovarian cancer are enrolled in prospective clinical studies at institutions participating in gynecologic oncology group protocols; to assess whether patient age affects enrollment in prospective gynecologic oncology group protocols; and to assess what demographic or clinicopathologic factors affect patient enrollment in prospective gynecologic oncology group protocols.

**Technical Approach:** 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 enrolled to date.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/26

STATUS: Terminated FY93

**TITLE:** A Randomized Study of Doxorubicin plus Cisplatin versus Circadian-timed Doxorubicin in Patients with Primary Stage III and IV Recurrent Endometrial Adenocarcinoma (Monitor: MAJ Sheffler)

START DATE: Feb 93

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: doxorubicin, endometrial adenocarcinoma

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**Study Objective:** To determine if circadian-timed doxorubicin-cisplatin chemotherapy offers significant improvement in the frequency of objective response, the duration of progression-free interval and the length of survival as compared to standard doxorubicin-cisplatin chemotherapy. To determine if there are any significant differences in toxicity between circadian-timed delivery of doxorubicin-cisplatin chemotherapy versus standard delivery of doxorubicin-cisplatin chemotherapy.

**Technical Approach:** 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 insufficient support personnel.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/42

STATUS: Ongoing

TITLE: GOG # 9207, Laparoscopic retroperitoneal lymph node sampling followed by immediate laparotomy in women with cancers of the cervix(Monitor: LTC Gormley)

START DATE: Oct 93

ESTIMATED COMPLETION DATE: Oct 98

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: laparoscopic, cancer of cervix

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**Study Objective:** To determine the adequacy of laparoscopic sampling of pelvic and aortic lymph nodes by immediate laparotomy in women with cancers of the cervix.

To obtain information of adverse effects and difficulties associated with laparoscopic sampling of pelvic and aortic lymph nodes.

**Technical Approach:** 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 enrolled to date.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/47

**STATUS:** Ongoing

**TITLE:** GOG # 143, Familial and Reproductive Factors in Ovarian Cancer

**START DATE:** Sep 93

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** LTC Andrew Soisson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** familial, reproductive, ovarian cancer

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**Study Objective:** 1.) Compute prevalence rates for cancer of the ovary, breast, colon, and uterus in first and second degree relatives of ovarian cancer cases.

2.) To identify that subset of multicas e families who would be candidates for linkage analysis studies in the companion GOG protocol 144.

3.) To estimate, by fitting major gene models to familial ovarian cancer incidence.

4.) To determine if established reproductive risk factors (parity, oral contraception (OC) use, tubal ligation) alter risk in women with a positive family history.

5.) To collect and store a blood sample from each participant in the study for storage and subsequent gene analysis frequency.

**Technical Approach:** 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 enrolled to date.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/48

**STATUS:** Ongoing

**TITLE:** GOG # 144, Molecular Genetic Analysis of Ovarian Cancer Families

**START DATE:** Sep 93

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** LTC Andrew Solsson

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** genetic, ovarian cancer families

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**Study Objective:** 1.) To determine the frequency of chromosomal rearrangements in women with familial ovarian cancer.

2.) To identify genetic markers linked to familial ovarian cancer.

3.) To identify deletions or rearrangements that signal the site of the mutation.

**Technical Approach:** 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 enrolled to date.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/30

STATUS: Ongoing

TITLE: Angiogenesis as a Histopathological Prognostic Feature for Uterine Cervical Dysplasia and Invasive Carcinoma

START DATE: Apr 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: CPT Joel Webb

DEPARTMENT: OB/GYN

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: L Maxwell, P Brittain, A Soisson, T Casey

KEY WORDS: Angiogenesis Histopathological

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**Study Objective:** To determine if microvessel counts in cervical cone biopsy specimens of patients with cervical dysplasia correlates with the histologic grade of dysplasia and to determine if microvessel counts in hysterectomy and biopsy specimens in patients with invasive cervical cancer correlate with other known prognostic factors and with survival.

**Technical Approach:** (1) All patients with cervical dysplasia who have undergone a cone biopsy at William Beaumont Army Medical Center in the past 3 years will be identified by review of operative logs; (2) All patients with invasive cervical cancer who have undergone cervical biopsy or hysterectomy in the past 3 years at William Beaumont Army Medical Center will be identified by review of the operative and pathology logs; (3) Histologic sections from the patients cone biopsy, cervical biopsy, or hysterectomy contain the dysplastic lesion or carcinoma will be prepared using standard techniques from paraffin embedded tissues; (4) Two slides from each patient will be prepared. One slide will be stained with hematoxylin-eosin to grade the tumor and the dysplastic lesion. One slide will be stained with anti-factor eight antibody to count the number of vessels in the following fashion: (a) Each slide will be de-paraffinized and rehydrated utilizing standard techniques; (b) Tissues will be stained with anti-factor 8 antibody to highlight microvessels using a standard immunoperoxidase technique; (c) The area of highest neovascularization will be determined by Doctor Casey and subjectively graded on a scale from 1-4+, individual microvessels will be counted on a 200X field (20X objective lens and 10X ocular lens); (d) Microvessel counts will be compared with degree of dysplasia for patients with preinvasive disease and with other prognostic factors and survival in patients with invasive carcinoma.

**Progress:** Sixty subjects have been enrolled in the study. We are in the process of analyzing the data and we estimate completion within the next few months.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/54

STATUS: Ongoing

TITLE: Vaginal Operative Delivery in Modern Obstetrics

START DATE: Sep 93

ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: CPT Joel Webb

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: P Bayliss

KEY WORDS: vaginal delivery, forceps

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**Study Objective:** To review data in the current literature to determine whether forceps delivery is a safe and viable alternative to cesarean deliveries in certain labor situations.

**Technical Approach:** Retrospective review of data in obstetrical literature.

**Progress:** Study has just begun; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/30

STATUS: Completed FY93

TITLE: Accupressure Bracelets: An Effective Treatment for First Trimester Nausea and Vomiting of Pregnancy

START DATE: Aug 91

ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: CPT Gary Wharton

DEPARTMENT: Obgyn

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: DL Gehlbach

KEY WORDS: Accupressure bracelets, Nausea, Vomiting of pregnancy

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**Study Objective:** To investigate whether the use of an accupressure 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 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:** The object of this prospective study was to evaluate the efficacy of acupressure bracelets in controlling morning sickness. Thirty pregnant women were recruited for study entry, meeting the following criteria: 1) were in first trimester of pregnancy, 2) had no evidence of organic causes of symptoms, 3) were married, 4) were more than 18 years of age, 5) had symptoms for greater than seven days. Twelve women were treated with standard diet modifications, four were treated with diet modification and a placebo bracelet, and fourteen received diet modification and an acupressure bracelet. Treatment success was evaluated subjectively with a questionnaire to assess severity of symptoms and objectively by analysis of weight and blood pressure changes, and the presence of ketonuria. Multiple statistical tests failed to show any difference in the subjective or objective degree of nausea and vomiting in the three groups. We believe that this study suggests that acupressure bracelets are not effective in preventing nausea and vomiting of pregnancy.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/28

**STATUS:** Ongoing

**TITLE:** Evaluation of Phenobarbital in the Prevention of Intraventricular Hemorrhage in the Very Low Birth Weight Infant (<1500gms or 32 Weeks)

**START DATE:** Oct 91

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** CPT Gary C. Wharton

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** FE Harlass

**KEY WORDS:** Intraventricular hemorrhage, Phenobarbital

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**Study Objective:** To retrospectively compare WBAMC records where the current standard of care includes phenobarbital administration to any mother suspected or imminently delivering an infant 15gms or less, to those of R. E. Thomason General Hospital (RETGH), where the current standard of care does not include this administration. Through this comparison, an attempt will be made to demonstrate that such administration is beneficial in reducing the incidence and severity of intraventricular hemorrhage in this population as previously suggested.

**Technical Approach:** This will be a retrospective case controlled analysis of maternal and infant records. WBAMC's experience will be controlled with the experience at RETGH.

**Progress:** Data collection is complete. Tabulation and analysis of data is set to begin. Rough draft of the final report will follow, with a projected completion date of January 1994.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/19

**STATUS:** Ongoing

**TITLE:** Management of Inflammatory Cytologic Abnormalities Detected by Papanicolaou Smears: A Randomized, Prospective Study

**START DATE:** Feb 93

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** CPT Gary C. Wharton

**DEPARTMENT:** Obgyn

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** C Hawley-Bowland, J Webb

**KEY WORDS:** inflammatory cytologic abnormalities, Papanicolaou smears

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**Study Objective:** To prospectively evaluate the efficacy of three therapeutic regimens of metronidazole versus a control, on the course of inflammatory cytologic abnormalities.

**Technical Approach:** 400 female Patients will be randomized into 4 groups using a sequential randomizing system. These groups will consist of: Group A: Metronidazole 500mg po bid x 7 days; Group B: Metronidazole 2gms po x one dose; Group C: Metronidazole gel (0.75%) 5gms intravaginally bid x 5 days; Group D: Control, no treatment

**Progress:** We need to enroll approximately 40 more patients before having an adequate number. We will then analyze the data. We expect to finish early next year.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/45

STATUS: Terminated FY93

TITLE: Comparison of Two Techniques of Estrogen Receptor Assay in Breast Cancer

START DATE: Nov 89

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: CPT Thomas P. Baker

DEPARTMENT: Path

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: TH Nguyen, G Bell, S Army

KEY WORDS: Estrogen receptor assay, breast cancer

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**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 semiquantitative 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 femtomoles (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 than 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 Path Lab. 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: The research protocol, as written, will yield no potentially publishable data, as several articles along the same line have been published in the past four years. An amendment made to the protocol approximately one and a half years ago will also no longer provide any publishable data, since two articles concerning the same clinic followup have been published in the past year. At this time, CPT Baker is considering submitting a protocol utilizing immunohistochemical markers on breast tissue and their prognostic significance; the proposed protocol would utilize the approximately 50 cases of paraffin imbedded and frozen breast tissue collected for present protocol. Present protocol has been terminated.**

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/47A

STATUS: Ongoing

TITLE: *The Effect of Bovine TSH on Hemoglobin Proportions in Adult Rats*

START DATE: Jul 92

ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: MAJ Jack T. Pearson

DEPARTMENT: Path

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Critz, D McKell, J Enriquez, KM Brady, T Baker

KEY WORDS: hemoglobin

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**Study Objective:** Test bovine TSH's effect on rat hemoglobin chromatogram patterns.

**Technical Approach:** Phase I: In this phase five adult animals and the litter from one timed pregnancy will be used to gain familiarity with the procedures to be used in this protocol (and described below); cardiac puncture, intraperitoneal injection, performance and preparation of chromatography.

Phase II: This phase will be used to repeat Gilman and Datta's chromatograms. However rather than classic liquid chromatography, this project will utilize HPLC. Twenty adult rats and the litters from 6 timed pregnancies will undergo cardiac puncture. The specimen will be chromatographed. The chromatograms will be compared to establish the previously observed difference in the adult and neonatal pattern and subsequently compared to Gilman and Datta's work.

Phase III: In this phase, 10 adult rats will each be dosed with different concentrations of bovine TSH. After one week, a cardiac puncture will be performed and the specimens tested for T3 RIA and T4 levels. The dose producing a level of hyperthyroidism which is three times normal will be chosen for phase IV.

Phase IV: In this phase, 20 adult animals will have an intraperitoneal injection of bovine TSH. The control group will also consist of 20 adult animals and will receive an injection of sterile normal saline. Each week a cardiac puncture will be performed and the specimen chromatographed.

**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).

Amended Sep 93, approved Sep 93: Deleted T Casey, added T Baker as associate investigator. Deleted K O'Hair, added R Harris as attending veterinarian. Changed completion date to Jun 94.

Amended Jan 94, approved Jan 94: Phase IIb, IIIb amended. Copy on file at DCI. Number of rats required increased from 75 to 142.

**Progress:** Six rats have been used. Phase I of the project has taken longer than initially anticipated, however, is near completion. The procedure for chromatography has been completely worked out and preliminary chromatograms on adult and neonatal rats confirm Gilman and Datta's observation of consistent differences in the chromatograms of adult versus neonatal rats. Additionally, all members of the project have become proficient in the animal procedures to be used later in the study. Currently, Phase II is scheduled to begin in November.

**Requested modifications are of sufficient magnitude to warrant reconsideration by the AUC; protocol will be reevaluated.**

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/01

STATUS: Ongoing

TITLE: Retrospective Analysis of the Association between Attention Deficit Disorder and Central Auditory Processing Problems

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: COL Alva W. Atkinson

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Dennis, MC Knott, D Penow

KEY WORDS: ADD, CAPP

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**Study Objective:** Two hypotheses will be addressed: (1) Central auditory processing problems (CAPP) occur in high frequency (>20%) among patients diagnosed with Attention Deficit Disorder (ADD) and (2) the incidence of CAPP in ADD will be represented equally among the subtypes of ADD (ADD with hyperactivity and ADD without hyperactivity).

**Technical Approach:** The medical records of patients assessed by Developmental Pediatrics Clinic for ADD and by Audiology and Speech/Language Clinics during 1989-1990 will be reviewed. Data will be collected for age, grade, diagnoses, auditory and language evaluation results. Specifically, data from the audiologic assessment data from the SCAN (central auditory processing battery) will be collected. From the language evaluation, the overall receptive and expressive language assessments (normal, mild moderate, or severe) and the TOKEN test results will be noted. Data will be studied for frequencies and association using descriptive and simple comparative statistics. The investigators consider this a pilot study which will potentially be the basis of a prospective, more tightly controlled large study.

**Progress:** COL Atkinson has replaced MAJ Sierra as principal investigator. MAJ Penow has been added as an associate investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/04

STATUS: Ongoing

**TITLE: Adolescent Females with Hirsutism and/or Menstrual Abnormalities Suggestive of Polycystic Ovarian Syndrome or Late Onset Congenital Adrenal Hyperplasia**

START DATE: Nov 90

ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne E. Cuda

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: RL Svec

**KEY WORDS: Hirsutism, Menstrual abnormalities, Polycystic Ovarian Syndrome, Congenital adrenal hyperplasia**

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**Study Objective:** To prospectively follow patients with the complaints of hirsutism and/or menstrual abnormalities using standard of care. The data collected from these patients will be collated and compared to previous studies in an attempt to clarify prior research and work out a more streamlines approach.

**Technical Approach:** Females presenting to the Adolescent Clinic with complaints of hirsutism and/or oligomenorrhea and amenorrhea will be eligible for the study. Patient must be two years past menarche. Patients will sign an informed consent which will allow data collected during their care to be used in a study. Diagnostic work-up and treatment will be according to the accepted standard of care. We propose to combine several approaches to the work-up of these complaints in order to elucidate more information concerning the differences and similarities between patients falling into a particular diagnostic category.

**Progress:** Twenty-five subjects were enrolled into study. Investigator is finalizing report of results.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/35

STATUS: Terminated FY93

TITLE: A Double-Blind Randomized Trial of Low Dose Captopril in Adolescents with Insulin-Dependent Diabetes Mellitus

START DATE: Jul 91

ESTIMATED COMPLETION DATE: Jun 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne E. Cuda

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Svec

KEY WORDS: Captopril, Adolescent insulin-dependent DM

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**Study Objective:** To examine adolescent diabetics with persistent microalbuminuria to determine if use of an ACE inhibitor can reduce microalbuminuria.

**Technical Approach:** On entry into the study, 3 specimens for microalbuminuria and a 24-hour urine specimen for protein and creatinine will be obtained. The mean of the 3 microalbuminuria samples will be used to determine persistent microalbuminuria. If abnormal, the subject will be eligible to participate in the study. Baseline HgA1C, CBC/diff, TFTs, renal functions, and ophthalmology exam will also be documented. Patients will be randomized using a random numbers table into treatment or placebo groups. This will be double-blinded. The treatment group will be started on Captopril at 0.1 mg/kg/dose twice daily. The placebo group will receive similar tablets twice daily. At the end of six months, the groups will cross over and complete the remaining six-month period. Subjects will be followed every 6-8 weeks with measurement of blood pressure, microalbuminuria, HgA1C, renal panel, and 24-hour urines. Compliance with the medication will be followed by counting pills. The treatment period will be 12 months for each subject. Following treatment period, subjected will return in 6-8 weeks for measurement of blood pressure, HgA1C, and microalbuminuria. Results will be analyzed using the paired Student t test.

**Progress:** There were an insufficient number of study subjects. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/24

STATUS: Ongoing

TITLE: Dietary Treatment of Hypercholesterolemia in Adolescents

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne Cuda

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Rupp, MM Beverly

KEY WORDS: hypercholesterolemia (adolescent)

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**Study Objective:** To identify whether adolescents are a group that will need more therapy or a modification of the currently recommended therapy for hypercholesterolemia.

**Technical Approach:** A flyer will be available at the Adolescent Medicine Clinic front desk which will explain the study to interested adolescents and their parents. If an individual is interested in participating, he/she will be given a laboratory slip for a non-fasting serum cholesterol and triglyceride level and will be asked to provide a phone number.

If the serum cholesterol is greater than 200 mg/dl, the patient will have a fasting lipid profile. Should the level return at greater than 170 mg/dl but less than 200 mg/dl, the individual will be contacted and asked to repeat the test. If the mean of the two tests is greater than 170 mg/dl, the individual will have a fasting lipid profile. Should the individual persistently show cholesterol levels greater than 170 mg/dl or LDL-cholesterol levels greater than 110 mg/dl, he will be asked to make an appointment with either Dr. Cuda or Dr. Rupp, or to set up a time when he can be counselled by Ms. Beverly.

At the appointment the adolescent will fill out a questionnaire covering age, sex, family history of cardiovascular disease, current address and phone number, and prior diet modification for cardiovascular disease. Weight, height, and blood pressure will also be obtained.

The patient will then be randomized into treatment or non-treatment groups. The treatment group will receive counselling on the Step I diet as recommended by the AHA. The treatment group will be followed up in six months and undergo repeat serum lipid and lipoprotein testing. The non-treatment group will be followed up in six months with repeat blood testing. Should the patient have persistent hypercholesterolemia at follow-up then they will be counselled for the Step I diet and followed clinically.

**Progress:** Approximately 800 subjects were entered into study. Principal investigator is completing report of results.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/43

STATUS: Completed FY93

TITLE: Age of Menarche: A Risk Factor for Osteoporosis

START DATE: May 92

ESTIMATED COMPLETION DATE: May 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne E. Cuda

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Rupp, A Rodriguez, G Turnbull, A Moreno

KEY WORDS: osteoporosis

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**Study Objective:** To correlate age at menarche with bone density in adolescent females.

**Technical Approach:** 200 adolescent females, ages 13-21, who are at least 2 years post menarche will be asked to volunteer for the study. If the eligibility criteria are met, then they will fill out a short questionnaire, complete a dietary survey for calcium intake, and undergo dual-photon absorptiometry of the lumbar spine and proximal femur.

**Progress:** The effect of the timing of puberty on peak bone mineral density in females is unknown. Age at menarche, as a marker for pubertal development, also represents the establishment of the cyclic production of hormones. Cyclic hormonal production has an anabolic effect on bone mineral density (BMD). To determine the relationship between age at menarche and BMD, we measured BMD in four sites by dual-photon absorptiometry in 27 healthy adolescent girls at varying ages at menarche. A younger age at menarche was significantly associated with a greater BMD at the femoral neck,  $P=0.0274$ . When the patients were grouped according to age, there was a significant negative association between age at menarche and BMD at the femoral neck,  $P=0.04$ , and at the trochanter,  $P=0.0003$ . When each age of menarche was examined independently, there was a strong association between age and BMD at the femoral neck,  $P=0.025$ , and at the trochanter,  $P=0.03$ . The younger the age at menarche, the greater the BMD in the femoral neck and the trochanter. These findings suggest that the timing of puberty is an important determinant of peak bone mass. Since the peak BMD is achieved in late adolescence or early adulthood, adolescent females with significantly delayed menarche may be at increased risk of osteoporotic fractures as they approach menopause.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/07

STATUS: Ongoing

TITLE: Adolescent Risk Factors: Can We Predict the Presence of Activated HPV Oncogenes E6 and E7

START DATE: Nov 92

ESTIMATED COMPLETION DATE: May 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne E. Cuda

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Rupp, C Dillon, J Foley, W Nauschuetz

KEY WORDS: adolescent risk factors; HPV oncogenes

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**Study Objective:** To find the incidence of HPV, the incidence of activated HPV oncogenes and identify possible cofactors of activation in our population.

**Technical Approach:** The pap paddle and cytobrush used in routine gynecological examinations and then disposed of will be tested for HPV and activated oncogenes. The swab used in gonorrhea cultures on males with urethritis will also be tested prior to disposal. Urine samples from males will also be tested prior to disposal. Results will be correlated from data on risk factors normally maintained in charts. 200 female and 50 male patients, ages 13-21 years, will be studied.

**Progress:** We have successfully amplified HPV DNA from cervical specimens in another research protocol. We will continue the DNA testing on these 250 specimens collected from adolescent males and females. Within 60 days we will begin in situ amplification of E6 and E7 mRNA.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/88

STATUS: Ongoing

TITLE: Incidence of *Corynebacterium Haemolyticum* Pharyngitis in an Adolescent Clinic

START DATE: Oct 89

ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: CPT Christopher Dillon

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: M Weisse

KEY WORDS: *Corynebacterium Haemolyticum* Pharyngitis, Adolescents

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**Study Objective:** The incidence and seasonal variation of *corynebacterium haemolyticum* 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 haemolyticum* takes 48-72 hours for adequate growth. Those plates with growth suspicious for *Corynebacterium haemolyticum* 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 haemolyticum* 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.)

**Amendment (Jan 93):** Added CPT Dillon as new PI (MAJ Weisse became the associate); deleted Martinko and Wittler as associates; changed completion date to Nov 93; changed number of subjects to 1000; updated the DA 5303-R; and changed the funding paragraph.

**Progress:** To date, over 350 throat cultures have been plated for *corynebacterium haemolyticum* without any recovery of the organism. However, this may be due to a seasonal nature of the infection. We will continue the investigation for one complete calendar year to discover if this seasonal variation exists. The assays have been retested against the control and are functional.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/45

STATUS: Ongoing

TITLE: Up-Front Intensive 6-MP/Methotrexate VS Up-front Alternating Chemotherapy for Acute Lymphoblastic Leukemia in Childhood. POG: 9006 (Monitor: MAJ Sheffler)

START DATE: Jul 93

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Kelly Faucette

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: J Swaney

KEY WORDS: methotrexate leukemia

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**Study Objective:** Our objective is to continue this patient on the randomized trial on which he was started at WRAMC. The objective of this study is to compare, in a randomized trial of children with Acute Lymphoblastic Leukemia (ALL) who are at a higher risk for relapse, the efficacy and toxicity of A: 12 early intensive courses of IV methotrexate (MTX) plus IV 6-mercaptopurine (6-MP) vs. B: 12 early intensive courses of alternating intensive chemotherapy combinations (6-MP/MTX), VM-26/Ara-C, vincristine/ prednisone/ PEG-L-asparaginase/ daunomycin/ Ara-C.

In addition the study is designed to determine if RBC methotrexate/folate levels can be correlated with sites of relapse and event-free survival.

**Technical Approach:** In summary the protocol is designed to test a potentially more successful method of achieving remission, and maintaining a complete remission until a cure is achieved in a large number of high risk pediatric patients with ALL. Multiagent chemotherapy will be given using standard drugs, but changing the effective oral 6-MP to an IV form to achieve better and more standard drug levels, and drug kinetics, to potentially increase cell kill and effectiveness of therapy. In addition alternating Daunomycin and VM-26, which share some mechanism of cell kill may increase ultimate cell kill and thus survival per the Goldie-Coldman hypothesis.

**Progress:** We continue with one patient in remission in the WBAMC arm of this protocol. The patient remains stable with no significant side effects. Should another child be diagnosed with leukemia and fit the criteria for the study, we would anticipate enrolling him/her as well.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/06

STATUS: Ongoing

TITLE: Perceived Susceptibility to Harm During Adolescence

START DATE: Oct 89

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: COL John D. Foley

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: LD Cohn

KEY WORDS: Risk taking behavior

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**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:** All data collection has been completed. Poster presentations of some of the study data were made at the American Psychological Society Meeting in Toronto in August 1993. An article is in draft status for submission for publication.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/88

STATUS: Terminated FY93

TITLE: Seasonal Occurrence of Adolescent Health Risk Indicators

START DATE: Jan 91

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL John D. Foley

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Health risk indicators

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**Study Objective:** To determine if certain indicators of health risk behaviors by adolescents show a seasonal pattern of occurrence.

**Technical Approach:** Data will be collected retrospectively from outpatient and inpatient clinical records of information previously recorded in the course of providing appropriate medical care for patients. No identification of individuals by name will be necessary. Data from the previous 2-3 years will be utilized as available. Major areas of focus will be sexuality, substance use, and psychologic problems.

**Amendment (May 92):** Seven revisions have been made to the original study design: (1) Adolescent subjects, ages 15-20, will complete a survey designed to assess their perceived likelihood of encountering 21 illnesses and undesirable life events; (2) Subjects will complete a questionnaire designed to assess if teenagers hold stereotypes of individuals who are victims of illness (e.g., AIDS) and injury (e.g., car accidents); (3) Adolescents (ages 15-20) will be administered a revised version of the Survey of Health Behaviors which includes 9 questions addressing issues of sex and also includes one item assessing steroid use among the respondents' friends; (4) Adolescents (ages 15-20) will complete a questionnaire designed to assess adolescent stereotypes of teen parents. Participants will be shown a 3" by 3" color picture of a teenage girl sitting next to a young child (caption for one-half of the subjects will indicate the child is a baby sister and "sister" will be deleted for the other half). After viewing the photo, all teens will be asked to give their impressions of the target character using a rating scale; (5) Adolescent subjects will complete a task assessing their understanding of uncertainty terms (e.g., probably, possibly, might); (6) Approximately 100 physicians and nurses will complete a task identical to the task described in #5 to determine if physicians, nurses and adolescent patients attribute different meanings to words commonly used to convey the likelihood of health outcomes; (7) Every other subject recruited into the study will be asked to return to the clinic to complete the survey forms a second time. Re-testing will occur between 1-4 weeks after the initial session. The plan remains the same with the exceptions of the following: 100 physicians and nurses will be recruited into the study; adolescents participants will be recruited from Pediatrics and Pediatric Orthopedics; Medical Staff participants will be recruited from Pediatrics and Surgery.

**Progress:** Principal investigator has determined that lack of seasonal variation in risk indicators precludes further study.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

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: Nov 95

PRINCIPAL INVESTIGATOR: MAJ S Gwynne Geddie

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: G Handel, GL Maxwell, M Schydlower, J Enriquez

KEY WORDS: Newborn, Drug Affected

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**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.

**Amendment #1 (Sep 90):** Added new associate investigators and amended para 7d and 7g.

**Amendment #2 (Nov 91):** Changed PI to CPT Knight; deleted associate investigators Gordon & Valerie Bell, Howard Oaks & Ingrid Chamales; added LTC Rosa, MAJ Jesse and Dr. Handel as associate investigators. Amendment extended study completion date to Oct 92 and added R.E. Thomason General Hospital (RETGH).

**Amendment #3 (Sep 92):** Added CPTs Murphy and Maxwell as associates; added another paragraph to status; changed Plan to read: Due to the recently initiated "early discharge" policy for selected newborns at WBAMC, difficulties in obtaining sufficient uncontaminated urine specimens (non-invasively) have arisen and make this source for analysis of illicit drugs impractical. Collection of meconium specimens from newborns at WBAMC is much easier than obtaining uncontaminated urine specimens (non-invasively). WBAMC DCI currently has the technical ability to analyze meconium specimens for illicit drugs and their metabolites; changed 7.d to incorporate previously approved changes (Amendments #1 & #2); amended Duration of Study read: Through October 1992 or until 400 paired maternal urine/neonatal meconium specimens have been obtained; added references (4) and (5).

**Progress:** This study has been on hold due to PCS's of several investigators and the difficulty in getting samples analyzed. MAJ Geddie has assumed responsibility as principal investigator and will try to work out problems with the samples and will try to get study back on track within the next few months.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/22

STATUS: Ongoing

TITLE: The Effect of Epidural Anesthesia on Parturient Temperature and Its Relationship to Neonatal Evaluations

START DATE: May 93

ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: CPT Ana C. Hodges

DEPARTMENT: Peds

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: SW Jesse, GA Meneffee, EJ Bollerup, SG Geddie

KEY WORDS: Epidural anesthesia; parturient temperature

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**Study Objective:** To investigate the effects of epidural analgesia on maternal temperature in labor and subsequently on newborn temperature and outcome, specifically sepsis evaluation and/or treatment.

**Technical Approach:** Prospective, non-randomized, non-blinded evaluation. All infants will have been vaginally delivered. All patients will be chosen for inclusion based on a calendar time period.

**Maternal Groups:** I: Controls: Primiparous females, singleton fetus, no epidural or other anesthesia/analgesia. II: "EPI": Primiparous females, singleton fetus, epidural anesthesia administered in active labor under current WBAMC OB/GYN standard of care. No IV analgesia. III: "IV": Primiparous females, singleton fetus, active labor, IV analgesia as per WBAMC OB/GYN standard of care.

All infants born to above parturients will be evaluated and treated per current WBAMC/NICU guidelines. Information recorded will include interval temperatures, physical exam status, positive/negative sepsis evaluation and hospital course.

Comparison will be made of parturients' temperatures within and between maternal groups; neonates will be compared for temperature, positivity/negativity of sepsis evaluation and hospital course within and between maternal groups.

Statistical analysis will include ANOVA, which may be used to compare intrapartum temperatures between maternal groups. Student's t-test will be used to compare maternal temperatures at the time of delivery between maternal groups, as well as initial neonatal temperatures between maternal groups. An odds ratio will be used to compare the relative risk of a neonate requiring a sepsis evaluation between maternal groups as it applies to maternal temperature.

**Progress:** MAJ SG Geddie has been added as an associate investigator. Research is ongoing with continuing data collections. No conclusions have as yet been drawn. We will continue to collect data and will meet with a statistician for analysis. Our plan is to complete data collection by Dec 93 or Jan 94. We would like finish abstract and paper in time for submission to fall 1994 national/regional meetings.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/29

STATUS: Ongoing

TITLE: Small Bowel Carcinoma in Children

START DATE: May 93

ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: CPT Ana Hodges

DEPARTMENT: Pediatrics

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: K Faucette, TM Reyna

KEY WORDS: Bowel Carcinoma

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**Study Objective:** To determine through retrospective use of charts of patients with small intestinal carcinoma, the presentation and results of the varied modalities of treatment. Knowing that the overall numbers of cases are relatively small, it would require a review of multiple centers to accomplish any meaningful study. Additionally, since chemotherapy and radiation therapy are not without significant morbidity in growing and developing children, any study that might safely limit their usage would reduce these complications in this population.

**Technical Approach:** A retrospective analysis of all cases of small intestinal carcinoma registered within the military tumor registry system will be conducted. The cases will be studied for mode of presentation, demographic data, treatment instituted, outcome, and followup. This will be compared with similar findings in adult literature.

**Progress:** Data collection from military tumor registry is complete. Literature search is underway. We anticipate completion of abstract and manuscript in spring 1994 for proposed submission to appropriate fall 1994 pediatric specialty meetings.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/09

STATUS: Ongoing

TITLE: Oral versus Intravenous Antibiotic Therapy for Febrile Urinary Tract Infections

START DATE: Nov 92

ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: CPT Michael Hunt

DEPARTMENT: Peds

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: ML Weisse, AJ Moreno

KEY WORDS: urinary tract infections

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**Study Objective:** To determine whether oral antibiotics are equal in efficacy to intravenous antibiotics in treating febrile UTIs.

**Technical Approach:** All patients with febrile UTI's will be admitted to the pediatric inpatient service. After parental consent, the patient will be assigned randomly (table of random numbers) to oral or intravenous antibiotic therapy. The oral antibiotic is augmentin dosed 30-40 mg/kg/day div q 8 hours. The intravenous antibiotics are ampicillin 100mg/kg/day div q 6 hours and gentamicin 6-7.5 mg/kg/day div q 8 hours. The temperature of the patient will be followed until afebrile for twenty-four hours, and the urine until sterile. The urine and organism will be saved for study.

**Amendment (IRB Jan 93):** (1) Added COL Moreno as associate; (2) added "To ensure patient safety, each patient will have a urinary ultrasonogram and a Tc-DMSA (Tc- dimercapto-succinic acid) renal scan after admission to the ward." to end of STUDY DESIGN; (3) amended ANALYSIS of RISKS and BENEFITS to SUBJECTS and RISKS to those CONDUCTING RESEARCH to read: All patients will benefit by having the UTI treated under continuous observation by the Pediatric staff and house staff, laboratory support by a medical center, and the rapid availability of urological consult if necessary. A urinary ultrasound will be done to rule out the possibility of urinary obstruction; (4) amended FOLLOW-UP PROCEDURES to read: Each patient will have a renal ultra sonogram performed by the radiology department to rule out obstruction within eighteen hours of admission. A Tc-DMSA will be performed by the Nuclear Medicine Department to assess kidney involvement. Urine cultures will be repeated after completion of antibiotic therapy, and the patient will have follow up with house staff continuity clinics in consultation with Pediatric Infectious Disease Department; (5) amended FUNDING IMPLICATIONS to read \$3700.00 (Nuclear Imaging); \$1000.00 (TDY for presentation at scientific/clinical meetings); \$300.00 (Reprints); TOTAL \$5000.00.

**Progress:** To date, seven patients have been entered into the study. Approximately 10 patient's parents refused to have their children entered. The data to date indicate that oral antibiotics will sterilize the urine in the same period that intravenous preparations perform. Two patients who were given oral augmentin continued to have fever spikes beyond 36 hours, but no longer than 48 hours. One patient on intravenous antibiotics had fever spikes for 72 hours. Both groups had sterilized urine within 24 hours.

The challenge so far is encouraging parents to enter their children into the study and to motivate the pediatric staff and house staff to consider the protocol. Some medical professionals choose the intravenous route of treatment because of the ease to admit and no consent to obtain. This study encounters difficulty in obtaining frequent urine samples by nursing staff.

CPT Scott Sheets and MAJ William Raszka have been added as associate investigators.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 88/61A

STATUS: Terminated FY93

TITLE: Neonate Emergency Procedure Training in the Rabbit and Guinea Pig Model

START DATE: Jul 88

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Steven W. Jesse

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

**KEY WORDS:** *Emergency procedures, Pediatric training*

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**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:** Principal investigator departed WBAMC without arranging for continuation of study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/92A

STATUS: Terminated FY93

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: Terminated

PRINCIPAL INVESTIGATOR: MAJ Steven W. Jesse

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Breastfeeding, Enteral Absorption of Human IgG, Human IgG

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**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 1g/kg 10% HlgG 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:** Principal investigator departed WBAMC without arranging for continuation of this study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/49

STATUS: Ongoing

TITLE: A Comparison Study of Midazolam and Pentobarbital Versus Pentobarbital Alone in the Effective Sedation of Children for Non-Invasive Imaging (Monitor: MAJ Rubin)

START DATE: Sep 93

ESTIMATED COMPLETION DATE: Aug 94

PRINCIPAL INVESTIGATOR: CPT Michelle B. Kravitz

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: K Faucette

KEY WORDS: midazolam, pentobarbital, sedation, children

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**Study Objectives:** To compare the use of midazolam combined with pentobarbital vs the use of pentobarbital alone to sedate children for non-invasive imaging.

**Technical Approach:** This will be a prospective, double-blinded comparison study. All patients admitted for sedation between September 1993 and August 1994 who do not meet the exclusion criteria (see 6g) will be enrolled. The patient's age and weight will be entered in the computer and pharmacist alerted that the patient is a sedation study participant. The pharmacist will then send a darkened syringe containing either 0.1mg/kg midazolam or an equal volume of normal saline. The contents of the syringe will be injected intravenously following an initial dose of 2mg/kg of pentobarbital. An additional dose of pentobarbital will then be added (in increments of 25mg or 1mg/kg, whichever is less) until adequate sedation is achieved. Pentobarbital is given initially to all patients to best blind the study. Mixing of the two agents in one syringe cannot be done secondary to incompatibility and precipitation of versed with pentobarbital.

The sedating physician will fill out a questionnaire on each patient sedated by study protocol. This will include the following:

- 1) Name of patient.
- 2) Age of patient.
- 3) Medications patient takes at home.
- 4) Prior history of failed sedation and if so, drugs used to sedate at that time.
- 5) Imaging study needed/why study needed.
- 6) Study drug number (assigned by pharmacy to allow us to find out which drugs were used to sedate patient).
- 7) Dose of additional pentobarbital required.
- 8) Whether repeat sedation was required (defined as additional pentobarbital or other agent administered after pt left ward). Any mitigating factors, such as delay by MRI or CT in commencing study, will also be noted here.
- 9) Time to onset of sleep.
- 10) Duration of sedation.
- 11) Length of time until awake enough for discharge.
- 12) Side effects noted.

**Progress:** Project is new; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/29

STATUS: Completed FY93

TITLE: Retrospective Evaluation of Resting, Peak Exercise and Simulated Altitude Electrocardiograms of Young Black Males

START DATE: Mar 92

ESTIMATED COMPLETION DATE: Jun 93

PRINCIPAL INVESTIGATOR: COL William Pearl

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: electrocardiogram

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**Study Objective:** To determine if subjects with Sickle cell trait have different electrocardiographic responses to exercise and hypoxia than healthy controls.

**Technical Approach:** Review of electrocardiograms already obtained on fifty-two Black male basic trainees between 17 and 21 years of age.

**Progress:** Twenty-five healthy black men between 17 and 21 years of age were evaluated. Their resting and exercise electrocardiograms were recorded at simulated sea level and at a simulated altitude of 4,000 m. Sea level exercise caused a reduction in the amplitudes of R waves and a lowering of J points. Exercise at a simulated altitude of 4,000 m caused a lowering of the J point in several leads and a reduction of the R wave amplitude in lead aVF. Hypoxia caused a reduction in the amplitudes of the T waves and a lowering of the J points in several leads. These effects of exercise and altitude, to a great extent, eliminated the appearance of "early repolarization," which is very common among young black men.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/52

**STATUS:** Ongoing

**TITLE:** Retrospective Comparison of the Electrocardiograms of Subjects Having Sickle Cell Trait and Controls

**START DATE:** Sep 93

**ESTIMATED COMPLETION DATE:** Mar 94

**PRINCIPAL INVESTIGATOR:** COL William Pearl

**DEPARTMENT:** Ped

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** IM Weisman

**KEY WORDS:** electrocardiogram, sickle cell trait

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**Study Objective:** To determine whether subjects with sickle cell trait have different electrocardiograms than controls.

**Technical Approach:** Review of electrocardiograms already obtained on subjects having sickle cell trait and controls.

**Progress:** Project has just begun; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/40

STATUS: Ongoing

TITLE: Measles Immunity in New Housestaff

START DATE: Jun 91

ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: M Schydlower

KEY WORDS: Measles immunity, medical interns

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**Study Objective:** To determine the prevalence of immunity to measles in a group of health care workers, who are also young adults; to ensure immunity of new housestaff associate investigators; and to be cost-effective in immunizing new housestaff.

**Technical Approach:** A questionnaire will be administered to newly arriving interns at WBAMC to determine their past history with respect to measles infection. Immunization records will be reviewed to assess the number and timing of immunizations to measles. Sera will be drawn on each new intern for determination of individual immunity using ELISA.

**Progress:** Data is ready for evaluation. MAJ Raszka has replaced CPT Ramsey as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/25

STATUS: Ongoing

TITLE: Prevalence of Hypogammaglobulinemia in Children with Recurrent/Persistent Otitis Media

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Jul 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: hypogammaglobulinemia, Igb deficiency

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**Study Objective:** To determine the prevalence and extent of IgG deficiency in otitis prone children.

**Technical Approach:** Patients meeting the criteria below will have the study explained to them, and after informed consent is obtained, blood will be drawn for 1) complete blood count with differential, 2) quantitative immunoglobulin A, E, G, M, and 3) immunoglobulin G subclasses. If patient has an acute infection with fever at the time of clinic visit, the tests will be drawn at the next visit that the patient is seen and the acute infection is resolved.

Children 1 to 10 years of age presenting to pediatric clinic with history of 3 episodes of acute otitis media in the preceding 6 months, or duration of serous effusion  $\geq$  3 months after an episode of acute otitis media, will comprise the study population.

All patients will be followed by the principal investigator and the lab results explained. Treatment options/considerations based on clinical and laboratory evaluations will be discussed and most appropriate and acceptable therapy will be implemented.

**Progress:** Sixty patients have been enrolled to date. So far 10 patients have been detected with mild subclass deficiencies. No profound hypogammaglobulinemia has been noted. MAJ Weisse has departed. MAJ Raszka has assumed duties as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/12

STATUS: Ongoing

TITLE: Incidence of Occult Urethral Human Papilloma Virus (HPV) Infection in Sexually Active Adolescent Males

START DATE: Mar 92

ESTIMATED COMPLETION DATE: Feb 94

PRINCIPAL INVESTIGATOR: MAJ Richard Rupp

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: S Cuda, W Nauschuetz

KEY WORDS: HPV (Adolescent)

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**Study Objective:** To find the incidence of HPV infections in sexually active adolescent males and to possibly explore the feasibility of screening males for occult disease.

**Technical Approach:** The study will include approximately 100 males presenting to the Troop Clinic or the Adolescent Clinic, who are found on routine health screening to be sexually active or with complaints secondary to sexual activity. Sexually active males choosing to participate will be asked to provide a first morning urine. Participating sexually active males presenting with urethritis also will have an additional urethral swab done. These specimens will be tested using HPV DNA detection techniques. Virapap and Viratype kits are sensitive to as little as  $10^2$ -  $10^3$  viral particles which can be as few as 100-200 infected cells. The physician will obtain information including patient's age, age at onset of sexual activity, race, prior STDs, number and sex of partners, and whether the patient is circumcised. All patients will have a follow-up appointment to be counselled on positive and negative results. The subjects will be offered testing for other STDs (i.e., HIV, RPR, gonorrhea, chlamydia).

The data should help delineate the epidemiology of occult HPV in sexually active adolescent males. Condylomata are extremely rare in males of this age. With the high rates of infection found in adolescent females it is likely there is a high rate of occult HPV infections in males. From this data, it may be possible to make conclusions about the usefulness of male HPV screening tests. Knowledgeable about his HPV status, a patient will be able to make informed decisions about risky sexual behavior that may protect him and his partners.

**Progress:** Specimen collection is complete, with a total of seventy-five. We are awaiting results from DNA/PCR Lab.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/15

**STATUS:** Completed FY93

**TITLE:** Physiologic Response to Video Games in Adolescents

**START DATE:** Jan 92

**ESTIMATED COMPLETION DATE:** Jan 93

**PRINCIPAL INVESTIGATOR:** MAJ Richard Rupp

**DEPARTMENT:** Ped

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** K Ramsey

**KEY WORDS:** video games

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**Study Objective:** To show if there are possibly adverse physiologic cardiovascular changes while playing the video game Tetris and to see if these changes are more pronounced in novices vs. veterans of the game.

**Technical Approach:** Adolescent patients will play video games while their blood pressure and pulse are monitored in the clinic. No concerns for safety in the study due to the low incidence of seizures and the low risk of tendinitis since subjects will not be playing for extended time periods. Two subjects will participate in each session. Subjects will take turns playing Tetris for 10-minute periods.

**Progress:** Many adolescents spend a significant amount of their time playing video games. This study examined the effect of video games on the heart rate and blood pressure of these teens. Seventeen adolescents were monitored before, during and after a ten minute period of play by a dinamap pulse and blood pressure machine. The teens did not experience any change in pulse, diastolic pressure, systolic pressure, or mean blood pressure at any time during the study. Video games do not have any direct adverse effects on the cardiovascular status of adolescent players.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/55

STATUS: Ongoing

TITLE: Parents' Opinions about Disorders of Vigilance in their Children with Attention Deficit Disorder

START DATE: Aug 91

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: LTC Robert Sayers

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: AW Atkinson

KEY WORDS: Primary Disorder of Vigilance (PDV)

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**Study Objective:** Through the use of a parent questionnaire, determine the incidence of symptoms of Primary Disorder of Vigilance (PDV) in a population previously diagnosed with Attention Deficit Disorder (ADD) or being evaluated for ADD. Furthermore, this project will seek to differentiate this symptom cluster (PDV) as either a unique diagnosis or a subtype of ADD.

**Technical Approach:** The Developmental Pediatric Clinic at WBAMC follows approximately 180 patients with the diagnosis of ADD. Patients who are taking medication for ADD are seen in clinic at least every three months and parents come in for a brief interview on progress and refill every month. During one of these routine follow-ups, the parent will be asked to complete a questionnaire which addresses the major criteria for PDV for both the child and his/her parents. These criteria are taken directly from the article "Primary disorder of vigilance: A novel restlessness, and sleepiness" by Weinberg describing this "new" disorder.

**Progress:** The first portion of the study done by Dr. Richardson (former principal investigator) involved parents of children with attention deficit disorder who were being treated at WBAMC. The parents answered a questionnaire concerning their children's symptoms of primary disorder of vigilance (PDV). In this first sample, data was obtained on 130 children, with 31 having symptoms of this disorder. The next phase of the study is to prospectively look at children referred for developmental disabilities for any clues in the children and in their parents (since this is described as an autosomal dominant condition) for PDV. So far, 70 patients have been entered into the data base. We are comparing diagnoses of ADD with hyperactivity to see if PDV corresponds with any particular subgroup of ADHD, any particular behavior or mood disorder and/or with any particular learning dysfunction. At this time, we are preparing for our first statistical evaluation on the prospective data base. Total number of patients need is estimated to be 100-120.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/58

**STATUS:** Completed FY93

**TITLE:** Emergency Use of Erwinia Asparaginase for Treatment of Acute Lymphocytic Leukemia (Patient R.G. 3076)

**START DATE:** Aug 92

**ESTIMATED COMPLETION DATE:** Dec 92

**PRINCIPAL INVESTIGATOR:** Dr. Jerry Swaney

**DEPARTMENT:** Ped

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** lymphocytic leukemia

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**Study Objective:** To increase the response rate of acute lymphoblastic leukemia (LLL).

**Technical Approach:** Patient developed an allergic reaction to asparaginase produced by Escherischia coli. Erwinia asparaginase is to be substituted for the E. coli-based produce for the remainder of the protocol (18 of 20 doses).

**Progress:** Patient received 18 intramuscular injections of Erwinia Asparaginase without problems. There were no allergic complications.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 53

**PROTOCOL #:** 92/59

**STATUS:** Ongoing

**TITLE:** Emergency Use of Erwinia Asparaginase for Treatment of Acute Lymphocytic Leukemia (Patient C.H. 3759)

**START DATE:** Aug 92

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** Dr. Jerry Swaney

**DEPARTMENT:** Ped

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** lymphocytic leukemia

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**Study Objective:** To increase the response rate of acute lymphoblastic leukemia (ALL).

**Technical Approach:** Patient developed an allergic reaction to asparaginase produced by Escherichia coli. Erwinia asparaginase is to be substituted for the E. coli-based produce for the remainder of the protocol (18 of 20 doses).

**Progress:** Patient relapsed. Indications for initial use are the same on required re-induction.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/23

STATUS: Completed FY93

TITLE: Emergency Use of Erwinia Asparaginase (Patient S.K. 1539)

START DATE: Feb 93

ESTIMATED COMPLETION DATE: Jul 93

PRINCIPAL INVESTIGATOR: Dr. Jerry Swaney

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: acute lymphoblastic leukemia

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Study Objective: To increase the response rate of acute lymphoblastic leukemia (ALL).

Technical Approach: Patient developed an allergic reaction to asparaginase produced by *Escherichia coli*. *Erwinia asparaginase* is to be substituted for the *E. coli*-based product to be given in 9 doses of 3400 units each.

Progress: Patient received doses as dictated by protocol.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/62

**STATUS:** Ongoing

**TITLE:** Medical Experience of The Third Armored Cavalry Regiment During Operations Desert Shield and Desert Storm

**START DATE:** Aug 91

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** MAJ Glenn M. Wasserman

**DEPARTMENT:** Ped

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** B Martin, H Oaks, H McAdoo, R Harvey, B Merrill, C Hyams

**KEY WORDS:** Gulf Crisis, Persian Gulf Crisis, military medicine

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**Study Objective:** The aim of this project is to review and analyze the military, medical experience of first and second echelon medical units attached to a forward line unit (The Third Armored Cavalry Regiment) during Operations Desert Shield and Desert Storm.

**Technical Approach:** Data will be obtained primarily from retrospective review of preventive medicine disease surveillance data, self-completed questionnaires (Fourth Squadron), stool culture and ova & parasite analysis, and after action reports. There will also be anecdotal reports and data from the medical troop commander, dentist, acting psychiatrist and a physician assistant.

**Progress:** Manuscript is currently under review.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/39

STATUS: Terminated FY93

TITLE: A Randomized, Placebo Controlled Study of Immunoglobulin Therapy for Patients with Symptomatic Hypogammaglobulinemia (Monitor: MAJ Raszka)

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Martin E. Weisse

DEPARTMENT: Ped

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: B Veit, L Tremper, D Beaudoin

KEY WORDS: Immunoglobulin

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**Study Objective:** To determine if oral gammaglobulin effects clinical improvement and increased immunoglobulin levels in patients with symptomatic hypogammaglobulinemia.

**Technical Approach:** Patients who meet study criteria and are enrolled into the study will be randomly assigned to one of two groups. One group of patients will receive a gammaglobulin preparation by mouth, at a dose of 50 mg/kg per dose twice weekly for three months, then will be crossed-over to receive a placebo (orange juice) on the same dosage schedule for an additional three months. The second group will receive the placebo for the first three months, and be crossed over to receive the gammaglobulin preparation for the second three months. We intend for the study to be a randomized, double blind, placebo controlled trial. The dose of gammaglobulin we will use is equivalent to 400 mg/kg per month (the usual dose of intravenous gammaglobulin is 300-400 mg/kg every 3-4 weeks). Serum IgG peak and trough levels will be monitored monthly for the six month study period.

**Progress:** No differences were noted between placebo and treatment groups. Principal investigator terminated project.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/38

STATUS: Ongoing

TITLE: T-lymphocyte (CD4) Counts in Patients with Diagnosed Tuberculosis or Other Mycobacterial Disease Who Are Not Infected with the Human Immunodeficiency Virus

START DATE: Jan 94

ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: COL Arthur Morton

DEPARTMENT: PrvMed

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Lundy, MA Escobedo, K Pearl

KEY WORDS: T-lymphocyte counts tuberculosis mycobacterial

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Study Objective: (1) If T-lymphocyte (CD4) cell counts are depressed in patients with mycobacterial disease.

(2) If T-lymphocyte (CD4) cell counts predict treatment success in patients with mycobacterial disease.

Technical Approach: Study Design:

(1) Criteria for initial enrollment of subjects:

(a) Anti-tuberculosis drug naive

(b) Mycobacterial disease suspected because of a "positive" acid-fast smear of a clinical specimen

(c) Anti-Human Immunodeficiency Virus drug naive.

(d) Patients who present at the El Paso Health and Environmental District or at WBAMC for care.

(2) The initial evaluation will include the following:

(a) A specially designed questionnaire which requests information about: Name, social security number (or another number used for tracking purposes), age, sex, ethnic origin, country of birth, months of residence outside of the U.S., months of residence in the U.S.; history of cough, fever, sweats, weight loss, hemoptysis; prior tuberculosis treatment: IPT, BCG, multiple drug therapy; and AIDS risk factors: multiple sex partners, sex with men, IVDU, frequent blood transfusions, tissue transplants; and other immunosuppressing factors: end-stage renal disease (dialysis), diabetes mellitus (uncontrolled, insulin dependent, or non-insulin dependent), low body weight (less than 80% of ideal), previous partial or complete gastrectomy, regular alcohol use, regular steroid use, cancer, leukemia, cancer chemotherapy, cancer radiation therapy, or regular cyclosporin use.

(b) A serum HIV antibody test.

(c) Sputum or other clinical specimens for culture and sensitivity at days 0,1,2, 30, 90, and 180.

(d) A single Posterior-Anterior x-ray study of the chest will be done at day 0 and will be interpreted by the principal investigator. Each study will be classified into one or more of the following categories:

- [(1)] No evidence of past or present tuberculosis.
- [(2)] Evidence of healed primary tuberculosis (Ghon lesions or calcified hilar lymph nodes).
- [(3)] Infiltrates associated with hilar adenopathy suggestive of an active infectious process consistent with a diagnosis of non-cavitary pulmonary tuberculosis, mycobacterioses, or Pneumocystis Caranii pneumonia.
- [(4)] Cavitation consistent with a diagnosis of active pulmonary tuberculosis.
- [(5)] Pleural thickening with or without pleural effusion consistent with a diagnosis of pleural tuberculosis.
- [(6)] Multiple lesions consistent with a diagnosis of miliary tuberculosis.
- [(7)] Other significant abnormalities of the lung which may or may not be associated with tuberculosis.
- [(8)] No evidence of chronic obstructive lung disease (COLD).
- [(9)] Generalized pulmonary congestion consistent with a history of smoking or other chronic inflammatory lung diseases.
- [(10)] Increased lung volume consistent with a diagnosis of early COLD.
- [(11)] Increased lung volume with decreased markings consistent with a diagnosis of moderately advanced COLD.
- [(12)] Severely increased lung volume, decreased markings, and bleb formation suggestive of advanced COLD.

(e) Each film will also be interpreted by a radiologist for evidence of other pulmonary abnormalities such as lung cancer, enlarged heart, degenerative changes in the thoracic spine, etc.

(f) A tuberculin skin test by the Mantoux method using 5 tuberculin units (0.1 ml.) of Purified Protein Derivative (PPD).

(g) A physical examination which will include measurement of height and weight, examination for and evaluation of a scar suggestive of BCG vaccination and for lymphadenopathy.

(h) A complete blood count.

(i) A Westergren Erythrocyte Sedimentation Rate.

(j) A serum ALT (SGOT) test.

(3) A T-lymphocyte (CD4) cell count below 400 cells per cubic millimeter will be considered to be evidence of a significantly depressed count. These patients will be referred to physicians of their choice for further evaluation.

(4) This study design parallels the routine evaluation done by physicians when evaluating patients for evidence of disease caused by the various members of the family *Mycobacterium*. Additional studies not normally included in the routine evaluation will include the demographic and historical information questionnaire, a T-lymphocyte (CD4) cell count and a HIV test. All patients will be reevaluated at 30, 90, and 180 days. At the time of the subsequent evaluations, the T-lymphocyte (CD4) cell count, HIV test, and sputum or other clinical specimens will be obtained for direct microscopic examination for acid fast bacilli and culture will be repeated.

(5) Since there is a long lead time required to obtain mycobacterial culture results and since there is a 6 week to 6 month "window" period between the time of HIV infection and a "positive" HIV serum antibody test, all patients suspected of having a disease caused by a member of the *Mycobacterium* family will be eligible for initial enrollment. Subjects who are subsequently found to be infected with HIV or who do not receive a final clinical diagnosis of mycobacterial disease will be excluded later.

**Progress:** Volunteer agreement is being translated into Spanish. Once completed, study will commence.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 91/10

**STATUS:** Ongoing

**TITLE:** Assessment of Risk Factors for HIV Infections Among Active Duty U.S. Army Personnel with Documented Recent HIV-Antibody Seroconversion

**START DATE:** Feb 91

**ESTIMATED COMPLETION DATE:** Jan 96

**PRINCIPAL INVESTIGATOR:** Karlyn K. Pearl

**DEPARTMENT:** PrvMed

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** AR Morton, H Rodriguez

**KEY WORDS:** HIV seroconversion

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**Study Objective:** To assess demographic and behavioral determinants associated with new HIV infections. Incident cases are the only population which allow us to investigate important features of the current HIV infection epidemic. Risk factors and their relative significance as determinants of HIV infection will be assessed by comparing medical, demographic, and behavioral histories of active duty personnel recently infected with HIV with histories of individuals who have not seroconverted over a similar time period.

**Technical Approach:** The study will be conducted using a case-control design. A case will be defined on the basis of HIV-Ab seroconversion (positive Western blot in duplicate). Controls will be randomly selected HIV-Ab negative active duty personnel at the same posts where cases occur, and will be matched to each case on: Age (+/- 2 yrs), race/ethnicity, grade category (junior enlisted, senior enlisted, officer), and length of service in the Army. Two controls will be recruited for each case. Controls must have been tested negative for HIV-AB no earlier than three months before the positive test date of their matched case. Based upon standard methods for determining required sample sizes in a case-control study and the expected number of HIV-AB seroconverters, a 2-year study period is anticipated. All active duty personnel with confirmed HIV-AB seroconversion will be eligible for inclusion in this study. Cases will be identified each month by review of the USAHDS data base. Physicians in charge of the HIV testing and evaluation programs at posts from which cases are reported will be contacted by WRAIR and asked to invite incident cases to participate in this study. This study is designed to ensure strict confidentiality. All links between name, social security number, or other identification and study numbers are destroyed after the interviews are completed at the study site.

**Progress:** Phase II equipment has not yet arrived. We anticipate enrolling patients in this phase beginning Jan 94.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 8771A

**STATUS:** Ongoing

**TITLE:** Emergency Procedures Laboratory (Carpine Model)

**START DATE:** Jul 87

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** MAJ Ronald Liss

**DEPARTMENT:** PCCM

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** Emergency procedures laboratory

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**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.

**Technical Approach:** Cricothyroidotomy, venous cutdown, chest trauma management, and peritoneal lavage procedures will be accomplished in accordance with training manuals for each procedure.

**Progress:** Investigator failed to respond to requests for annual input. No training sessions were conducted in the past year.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/19A

**STATUS:** Ongoing

**TITLE:** Emergency Life Support Training for Paramedics in the Small Ruminant (Ovine or Caprine) Animal Model

**START DATE:** Jan 92

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** MAJ Ronald Liss

**DEPARTMENT:** PCCM

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:**

**KEY WORDS:** emergency life support

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**Study Objective:** This training will enhance the paramedics' capabilities of administering emergency lifesaving procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest trauma management.

**Technical Approach:** The emergency life support training program is designed for paramedics who are primarily responsible for providing first echelon care to the critically injured patient. Procedures taught will be according to the American College of Surgeons (ACS) Committee's Advanced Trauma Life Support Course. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations. Students then rotate through animal laboratories associated with the lecture content previously presented. The animal laboratory allows 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 laboratory is approximately 2-3 hours per cycle. Each animal station will consist of one instructor and four to five students.

**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:** Investigator failed to respond to requests for annual input.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/50

**STATUS:** Ongoing

**TITLE:** The Application of Civilian Pre-Authorization Standards to Inpatient Admissions in a Military Treatment Facility

**START DATE:** Jul 93

**ESTIMATED COMPLETION DATE:** Jan 94

**PRINCIPAL INVESTIGATOR:** COL Lou A. Popejoy

**DEPARTMENT:** Region

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** R Szykowski, JJ James

**KEY WORDS:** Pre-authorization standards, inpatients admissions

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**Study Objective:** To disprove the hypothesis that civilian healthcare industry pre-authorization program can be effectively applied in a military treatment facility to reduce inpatient expense.

**Technical Approach:**

**Phase I:** A study of a small sampling of previously admitted patients. Outpatient chart information on randomly selected cases will be evaluated by experienced civilian peer review nurses using Interqual screening criteria. Subsequently, civilian practicing specialists will review copies of the entire inpatients chart of the same admission episodes.

**Phase II:** The same peer review evaluation and subsequent physician review of the inpatient chart on concurrent, contemporary admissions. The sample size is estimated at approximately 25 admission from each of the major inpatient departments.

**Phase III:** Peer review nurse evaluation for pre-authorization approval of 100% of admissions during a 3-4 month period of time and selective physician review of inpatient charts of these same admissions. A coincident training and education module for providers will be instituted.

**Progress:** Project has just begun; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/39

STATUS: Terminated FY93

TITLE: Metamemory Functioning in Alcoholics

START DATE: Nov 91

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL AI K. Morris

DEPARTMENT: RTF

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: PH Marshall, JD Gold

KEY WORDS: metamemory functioning

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**Study Objective:** Metamemory refers to one's ability to make predictions about one's memory functioning. Alcoholics often report difficulties with memory. This study will determine to what extent these difficulties are related to metamemory.

**Technical Approach:** Subjects will first sign the informed consent form. They will then take the short intelligence test and fill out the biographical survey. They will then complete the FACT RETRIEVAL test.

**Progress:** Principal investigator departed WBAMC without arranging for continuation of study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/37A

STATUS: Terminated FY93

TITLE: Certification Training: Lasers in Urology in the Porcine Model

START DATE: Jun 91

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL Warren Bowland

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: FL Diaz-Ball

KEY WORDS: Laser training, Urology

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**Study Objective:** To provide training and certification of Urological Surgeons in laser cystoscopic procedures. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

**Technical Approach:** 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. **Surgical Procedure:** A cystoscope will be introduced through the urethra into the urinary bladder. Methylene blue 2% in N saline will be infused in to various regions of the urinary bladder mucosa for training with the ND:YAG laser and other lasers, such as the CO<sub>2</sub>, Argon, or KTP. Laser surgery training will include techniques from the external urethral os to the urinary bladder and possibly the ureters. If difficulty is encountered with introduction of the cystoscopy via the urethra (since the urethral os is up to 4 cms inside the vagina, anteriorly) the urinary bladder will be exposed by laparotomy via a mid anterior suprapubic abdominal incision. Urethral laser procedures can then be conducted by retrograding the cystoscope through the bladder neck. If larger vesicular tumors are required for laser excision or vaporization training, segments of the rectus muscle will transplanted into the bladder mucosa acutely. The bladder will then be closed with 3-0 dexon. Training is scheduled for a maximum of six (6) WBAMC surgeons and ten (10) Sierra surgeons.

**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 associate investigator, COL Diaz-Ball, has retired from the military. The principal investigator does not wish to pursue the protocol and it has been terminated.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/17A

**STATUS:** Ongoing

**TITLE:** The Prevention of Pigmented Gallstones with Oral Chenodeoxycholate in a Hereditary Anemia Mouse Model

**START DATE:** Aug 93

**ESTIMATED COMPLETION DATE:** Indefinite

**PRINCIPAL INVESTIGATOR:** CPT George Broughton

**DEPARTMENT:** Surg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** B Hammaker, T Baker, J Barker

**KEY WORDS:** Pigmented Gallstones

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**Study Objective:** This study will assess the efficacy of oral chenodeoxycholate (CDCA) in the prevention of pigmented gallstones in a mouse model with hereditary hemolytic anemia.

**Technical Approach:** Thirty (30) female WBB6F1 +/- mice will be irradiated and have bone marrow transplants from nb/nb mice (mice with gene that results in hemolytic anemia). The mice will be numbered for identification. Mice will be fed without CDCA for the first two months at WBAMC to become acclimatized and conditioned. They will then be started on CDCA therapy for the next ten months. The drug will be administered at a dose of 10 mg/kg of body weight Monday through Friday. Saturday and Sunday will serve as a drug holiday. Thirty other mice will serve as the placebo control group, and will receive similar husbandry as the study group for the duration of the study. At monthly intervals, liver function panels will be performed on each animal. The animals will be weighed at weekly intervals and the drug dosed accordingly. At the conclusion of the study, the animals will undergo laparotomy for bile collection and gallstone harvest. The bile will be quantitatively and qualitatively analyzed. The anesthetized animals will be euthanized by intracardiac exsanguination. The gallbladder and liver will be removed for histopathologic study.

**Progress:** COL Reyna has retired and has been removed as associate investigator. Due to the temporary transfer of CPT Broughton, the protocol has been in a standby status awaiting his return. The DCI attending veterinarian, MAJ Harris, has assured coordination of the protocol and has initiated procurement of required supplies. Upon CPT Broughton's return, the one year experimental phase will be initiated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/12A

STATUS: Completed FY93

TITLE: Combat Trauma Surgery Using a Portable contact Nd-(YAG) Laser

START DATE: Feb 89

ESTIMATED COMPLETION DATE: Completed

PRINCIPAL INVESTIGATOR: CPT Anthony J. Canfield

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: J McPhail, MJ Snyder, S Carey

KEY WORDS: Laser training, Surgery

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**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:** Conventional and laser repair of liver and spleen injuries were compared in a controlled study using the porcine model. Sixteen pigs were randomly placed in either the laser or conventional group. Injuries were made with a stellate clamp, producing a standardized injury in both the liver and the spleen. The laser repair was performed with a Nd(YAG) laser, using non-contact technique, and also with a new through-glass compression technique not yet described. Operative time, blood pressure, weight change, hematocrit change, depth of liver necrosis, and blood loss were measured. The operative time ( $p < 0.01$ ) and the drop in hematocrit were significantly less in the laser group ( $p < 0.01$ ). The depth of necrosis was the same for both groups. We found that the laser techniques provided faster repair of liver and spleen injuries with less blood loss. Lasers may have an application in repair of traumatic injuries.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/27A

STATUS: Ongoing

TITLE: Limb Lengthening by Intramedullary Distraction in a Sheep Model; Phase I - Physiologic Feasibility

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: COL Randolph L. Copeland

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: P Day, P Holzkecht, D Scales, T Baker

KEY WORDS: intramedullary distraction, limb lengthening

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**Study Objective:** This testing should demonstrate the feasibility of lengthening a long bone via an intramedullary device in an animal model. The initial phase of the project will be to demonstrate the physiologic potential for adequate new bone to form around an indwelling rod during the process of distraction. Subsequent phases of research would include the practical testing of a prototype indwelling device. Ultimately, a clinical trial in human patients is the goal in the last phases of development. In the process of using the progressive leg lengthening procedure we hope to learn more about the basic physiology of tissue response to stretch. We want to monitor the potential complications, especially infection, which frequently complicates the use of multiple wire external fixators.

**Technical Approach:** This phase of the research will involve the placement of an intramedullary rod into a long bone of the test animals. The rod initially will be interlocked only at one end. Sufficient room will be allowed at either end of the bone to facilitate application of a standard Ilizarov type fixation device. An osteotomy of the bone will be performed at a location well be outside of the isthmus of the bone so as not to be at the site of minimum diameter and maximum reaming damage to the canal. Lengthening will then be performed after a latency period of 5 days. The distraction will be at a rate of 1 mm per day. The goal of lengthening will be 15% of the measured length of the target bone.

The initial study will involve four test subjects. At the end of distraction, two of the animals in the series will continue with the Ilizarov device. The other two animals will have a subsequent completion of the transverse interlocking screws through the intramedullary rod, followed by removal of the external fixator. At the end of 30 days from cessation of lengthening one of the animals from each group will be euthanized and the limb harvested. The other two animals will be processed at 60 days providing there is evidence on radiographs of substantial new bone formation, otherwise delays of 3 week intervals will be added until at least three cortices demonstrate bridging bone on radiographs.

**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).

**Amendment (May 93):** CPT T Baker has been added as an associate investigator. MAJ Richard Harris has replaced MAJ O'Hair as attending veterinarian. Estimated completion has been extended.

**Progress:** This protocol has been somewhat delayed but is progressing. We have completed two animal subjects. Some technical difficulties were encountered but we believe the final results will be acceptable. The first animal developed a premature consolidation of the osteotomy site which required a repeat osteotomy. The second animal experienced a mechanical failure of the rod mechanism but the bone united in spite of the

relative loss of support. We attribute the failure to mechanical strain related to the placement of the rod, which did not penetrate deep enough to the distal canal. These problems contribute valuable lessons for future endeavors. Mechanical problems with the specimen saw in Pathology caused the most recent delay in our progress. This machine is now operational and the specimens are processing.

We anticipate shortening the proposed protocol from four animals to the current two. This decision will be based upon the final results of the microscopic examination. Clinically, the osteotomy sites healed very rapidly in spite of the presence of the intramedullary rod. The remainder of the protocol is to try the same procedure, but to leave the Ilizarov external device in place longer plus the rod to see if healing would take place more quickly. It is hard to imagine the bone healing any faster, since it appeared to heal as fast as historical controls with Ilizarov devices alone. Secondly, this would extend the use of the external fixator into a period of increased risk of pin tract problems, which is undesirable if it can be avoided.

We are currently searching for a source to develop and manufacture the internal lengthening device, is the ultimate goal of this research.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/17

STATUS: Terminated FY93

TITLE: Early Fracture Dating by Magnetic Resonance Imaging (MRI)

START DATE: Mar 92

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: CPT Darryl Cuda

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: G Momii

KEY WORDS: fracture dating (MRI)

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**Study Objective:** To attempt to accurately date fractures 10 days old or less by MRI

**Technical Approach:** The initial design will be to study 15 otherwise normal active duty males or females (ages 18-30 years) who will undergo daily T1 and T2 MRI for the first 10 days post fracture. Only fractures of major long bones will be studied for ease of imaging and only two individuals will be studied simultaneously. One radiologist will evaluate all studies.

**Progress:** Due to the virtual closure of the WBAMC Trauma Unit and the introduction of newer technology for fracture care, there has been only one patient who met the criteria for entry into the study. The majority of patients with long bone fractures are now treated by early open reduction and internal fixation, eliminating them from the study. Due to the lack of study patients, the study has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/26A

STATUS: Terminated FY93

TITLE: Artificial Substitutes for the Urinary Bladder in the Porcine Model

START DATE: May 90

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: COL Fernando Diaz-Ball

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: L Maldonado

KEY WORDS: Bladder Substitute, Continent Urinary Diversion

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**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 euthanize 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:** The principal investigator has retired and did not arrange for continuation of study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 90/42A

STATUS: Ongoing

TITLE: Fiberoptic Endoscope Cholecystectomy in the Porcine Model

START DATE: Oct 90

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Bowland, S Carey, AJ Canfield, D Eastman, S Bodney

KEY WORDS: Fiberoptic Endoscope Cholecystectomy

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**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<sub>2</sub>. 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:** LTC Hetz replaces COL Bowland as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/13A

STATUS: Ongoing

TITLE: Resident Training in Laparoscopic and Open Stapling Techniques

START DATE: Mar 91

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Bowland

KEY WORDS: Laparoscopic training

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**Study Objective:** The objectives are to teach the surgical staff and residents proper thoracic and abdominal laparoscopic procedures utilizing stapling instruments and suturing techniques and proper open stapling techniques utilizing the multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers.

**Technical Approach:** Both video laparoscope and open surgical training techniques will be conducted in the porcine model. The experimental design is such that one or both of the techniques will be conducted on each animal. When both laparoscopic and open techniques are utilized, the laparoscopic techniques will precede the open procedures. The determination of the techniques to be conducted will be done at the time of the training session and will be dependent upon the knowledge and expertise of the residents and staff being trained. After anesthesia induction, the following procedures will be conducted:

(1) Video laparoscopic - Abdominal: cholecystectomy, gastrectomy, small bowel resection, nephrectomy, hysterectomy, splenectomy and partial hepatectomy. Thoracic: esophagectomy, pulmonary resections and vagotomies will be performed utilizing the various stapling instruments and liga clips.

(2) Laparotomy (Open) - Abdominal: A midline incision from the xiphoid process to the pubis will be made. Then a multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers will be utilized to complete end-to-end, side-to-side colon and small intestinal anastomosis. Additionally, anastomosis will be completed between portions of the small intestine; from the small intestine to stomach and colon; and between the colon and rectum. Transection of the stomach, colon and small intestine will also be performed. Pulmonary: Transection of pulmonary tissue, bronchi, pulmonary arteries and veins will be performed utilizing the various instruments through an intercostal incision.

**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:** LTC Hetz replaces COL Bowland as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/15A

STATUS: Ongoing

TITLE: Certification Training: Advanced General Surgery Laser Laparoscopic Procedures in the Porcine Model

START DATE: Apr 91

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Bowland

KEY WORDS: Laser laparoscopy training

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**Study Objective:** To provide training and certification of General Surgery Surgeons in laser laparoscopic cholecystectomy, hernia repair, and appendectomy. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

**Technical Approach:** 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 and maintained with 15 mm Hg pressure of CO<sub>2</sub>. A trocar/cannula will be placed near the umbilicus for introduction of the video laparoscope which will enable monitoring of the procedure on a video screen. Two to three additional trocars/cannulas will be placed for introduction of laparoscopic graspers, scissors, laser fibers, etc. The cystic duct and artery will be bluntly dissected free, double ligated or clipped, and transected. The gallbladder will be dissected free from the liver bed by sharp, blunt, electrosurgical and laser techniques. Once free from hepatic parenchyma, the gallbladder will be approximated to the body wall, decompressed and pulled through one of the central trocar puncture sites.

Other advanced laparoscopic procedures will include hernia repair and appendectomy. Laparoscopic cannulas will be repositioned as necessary for subsequent procedures to enable visualization and tissue manipulation. Hernia repair- A defect will be created in the internal inguinal ring by sharp and blunt technique. Subsequently, the created hernia will be repaired by laparoscopic suture and stapling techniques. Appendectomy - The distal cecum will be isolated and mobilized. The distal segment will then be resected and closed by laparoscopic suture and stapling techniques. The appendage will be approximated to the body wall with large graspers and removed through a central puncture site.

Training is scheduled for six (6) WBAMC surgeons and ten (10) Sierra surgeons.

**Amendment (AUC Approved Apr 91)** increased the number of training sessions, animal requirements and resource requirements to accommodate training of 32 physicians.

**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:** LTC Hetz replaces COL Bowland as principal investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 88/64A

STATUS: Terminated FY93

TITLE: Microvascular Anastomosis of the Rat Femoral Vessels

START DATE: Nov 88

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Jeffrey R. Keim

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Microvascular anastomosis

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**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:** Principal investigator relocated without making arrangements to continue project. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/18A

STATUS: Ongoing

TITLE: Advanced Trauma Life Support Training in the Small Ruminant (Ovine or Caprine Animal Model)

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Mark S. Kestner

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: W Bowland

KEY WORDS: ATLS training

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**Study Objective:** This training will enhance the physicians' capabilities of administering advanced trauma life support procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest and abdominal trauma management.

**Technical Approach:** The Advanced Trauma Life Support (ATLS) training program is designed for physicians who are not primarily responsible for managing the critically injured patient on a day to day basis. 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 student 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 day affair with one instructor and up to five students assigned to each 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:** This training protocol is given at the center two to four times a year. Eight sheep were used for training in FY93.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/01A

STATUS: Terminated FY93

TITLE: *The Effect of Fibrin Sealant on Skin Graft Inhibition of Wound Contraction in the Porcine Model*

START DATE: Feb 93

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: LTC Michael Kulungowski

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: J Ortiz

KEY WORDS: Adhesive tissue, Wound healing, Fibrin sealant

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**Study Objective:** Our objective is to determine if fibrin sealant fixation of skin grafts augments their ability to inhibit wound contracture in the porcine model. Theoretically, if the fibrin sealant fixation of skin grafts allows for the inhibition of wound contracture in the animal model, this could be applied to the human patient in a later study.

**Technical Approach:** Six domestic swine will be utilized. Prior to each surgical procedure, anesthesia will be induced and surgical sites will be prepped. During surgery, four pairs of full thickness skin grafts will be made. A comparison of graft contracture of fibrin sealant treated grafts versus untreated grafts will be made between each pair of wounds. Graft site areas will be quantified every three days postop to day 28 using standardized photography or video digitization into a computer graphics program for analysis. For a period of 48 hours after recovery, the animals will be caged individually and allowed free access to food and water. Afterwards, they will be group housed. Evaluations will not be conducted on wounds showing evidence of infection, excessive hemorrhage or poor coaptations. The surface area of each original graft at day zero will be considered 100% and subsequent determinations will be reported as a percentage of the initial size. Contraction rates of each group will be compared statistically.

**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 investigator relocated without making arrangements for continuation of protocol. Project has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/02A

STATUS: Terminated FY93

TITLE: The Effect of Fibrin Sealant on Breaking Strength of Incisional Wounds in the Porcine Model

START DATE: Feb 93

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: LTC Michael Kulungowski

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: JE Ortiz; PL Day

KEY WORDS: Fibrin sealant

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**Study Objective:** To determine if fibrin sealant enhances wound healing as evaluated by wound breaking strength and histological evaluation of tissue in the animal model (i.e., fibroblast proliferation, angiogenesis, etc.). Should fibrin sealant prove efficacious in the animal model to promote wound healing, this could be utilized in the human patient in a comparative study to evaluate wound healing and thus promote the strength of the wound.

**Technical Approach:** Six domestic swine will be utilized. Prior to each surgical procedure, anesthesia will be induced and surgical sites will be prepped. During the initial surgery, four pairs of surgical incisions will be made. A comparison of fibrin sealant versus normal healing will be made between each pair of wounds. One pair of wounds will be harvested from each animal at day 7, 14, 21, and 28 post wounding. Breaking strengths and histological analysis of paired wounds will be determined. For a period of 48 hours after recovery, the animals will be caged individually and allowed free access to food and water. Afterwards, they will be housed together. Evaluations will not be conducted on wounds showing evidence of infection, excessive hemorrhage or poor coaptations. Adhesiveness of each group will be compared statistically.

**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 investigator relocated without making arrangements to continue project. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 91/11A

STATUS: Terminated FY93

TITLE: General Surgery Department Vascular Surgery Training Program Utilizing the Porcine Model

START DATE: Jan 91

ESTIMATED COMPLETION DATE: Terminated

PRINCIPAL INVESTIGATOR: MAJ Carl G. Lauer

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Vascular surgery training

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**Study Objective:** This training is designed to teach General Surgery resident physicians the basic operative skills required to perform vascular surgery.

**Technical Approach:** The exercise will concentrate on developing the surgeon's ability and confidence in handling vascular tissues, sutures, and prosthetics. Survival and non-survival procedures will be performed on each animal.

(1) The first animal will undergo transection and primary re-anastomosis of the aorta and vena cava. It will be recovered for 7 to 14 days, then undergo placement of a peripheral (femoral) PTFE A-V fistula. The abdomen will be re-explored, and the original aortic and vena caval anastomosis will be examined. The animal will then be euthanatized while the animal is still under anesthesia.

(2) The second animal will undergo placement of an interposition Dacron sleeve graft of the aorta. It will be recovered, and in 7 to 14 days it will undergo formation of bilateral femoral Brescia fistulae. The abdomen will then be re-explored, and the aortic graft examined. The animal will then be euthanatized.

(3) The third animal will undergo placement of a peripheral (femoral) PTFE A-V fistula. It will then undergo laparotomy and formation of a portocaval shunt. It will then 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:** Principal investigator relocated without making arrangements to continue project. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/27

STATUS: Completed FY93

TITLE: Patella Implant Size and Positioning: A Clinical Review and Radiographic Analysis

START DATE: Apr 93

ESTIMATED COMPLETION DATE: Sep 93

PRINCIPAL INVESTIGATOR: MAJ T. Scott McGee

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: R Bagg, MG Anderson, ME Reid, RA Espinosa, RB Gustilo, I Guloy

KEY WORDS: Patella Implant

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**Study Objective:** To determine if (1) the smaller sized patella implant is correlated with fewer post-operative problems;(2) alignment is significantly improved (also assessing the indications for intraoperative lateral release); (3) pain is decreased, and/or (4) instability is lessened.

**Technical Approach:** A retrospective review of all TKA patients over the last 2-3 years (50 patients approximately will be followed up with a standardized knee society rating score and radiographic evaluation of patella positioning.

**Progress:** The most frequent complication of total knee joint prosthetic replacement is malfunction of the patella femoral mechanisms. The incidence of patella femoral malfunction may be related to the size of the prosthetic component chosen to resurface the patella. WE tested this hypothesis by examining the outcome achieved in 115 knees in 96 patients who had been followed for more than two years post operatively. All knees were evaluated by the Knee Society Scoring System and the Knee Society Function Score. the patients were also evaluated as to their ability to rise from a chair and to climb stairs. The knees were divided into three groups: Group I had extra small patellar components, Group II small and Group III medium patellar components. There were no significant differences in the groups except for the post operative stair climbing ability, which was more impaired in the extra small patella group.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 93/56

**STATUS:** Ongoing

**TITLE:** The Use of Marcaine in the Prevention of Post Operative Pain in the Laparoscopic Cholecystectomy Patient

**START DATE:** Oct 93

**ESTIMATED COMPLETION DATE:** Oct 94

**PRINCIPAL INVESTIGATOR:** CPT James Reid

**DEPARTMENT:** Surgery

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** SP Hetz, JH Chiles

**KEY WORDS:** marcaine, pain, laparoscopic cholecystectomy

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**Study Objective:** This study will determine if the duration of the procedure, the anesthesia of the diaphragm and the anesthesia of the surgical site reduce post operative pain.

**Technical Approach:** The study will be a single center, double-blind study which will be prospective in nature.

**Progress:** Project has just begun; no data to report.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/46

STATUS: Completed FY93

TITLE: Familial Hirschsprung's Disease: Study of a Texas Cohort

START DATE: Apr 92

ESTIMATED COMPLETION DATE: Nov 92

PRINCIPAL INVESTIGATOR: LTC Troy M. Reyna

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: Hirschsprung's Disease

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**Study Objective:** To increase the awareness of the pediatric community of the occurrence of sporadic familial Hirschsprung's.

**Technical Approach:** A case report of a seven-week old male infant will be presented with constipation secondary to Hirschsprung's upon workup and evaluation. Study will include his relation to the cohort mentioned above which spans four generations and includes six proven/suspected cases of Hirschsprung's.

**Progress:** Clinical observations suggest the Hirschsprung's Disease (HD) is considered a sex-modified multifactorial trait. Inheritance within the same family is recognized but rare. A single family in Texas has had the occurrence of HD in nine members, with classic biopsy-proven HD in six members, two of which were dizygotic twins. This family pedigree spans five generations, with a variable spectrum of expression. There was one death related to HD. Six children underwent surgical correction, except one considered to have ultrashort HD which responded to non-operative conservative measures. Studies of isolated cohorts of HD such as this family and others listed in the literature may better assist in the understanding of inheritance patterns of this disease and may prove extremely useful in gene localization experiments. The inheritance pattern in this family strongly suggests the possibility of inheritance as an autosomal dominant with a variable penetrance.

## DETAIL SUMMARY SHEET

**DATE:** 1 October 93

**PROTOCOL #:** 92/54

**STATUS:** Terminated FY93

**TITLE:** Evolutionary Trends and Results of Cholecystectomy Laparoscopic versus Open in a Residency Teaching Program

**START DATE:** May 92

**ESTIMATED COMPLETION DATE:** Terminated

**PRINCIPAL INVESTIGATOR:** LTC Troy M. Reyna

**DEPARTMENT:** Surg

**FACILITY:** William Beaumont Army Medical Center

**ASSOCIATE INVESTIGATORS:** F Tapia

**KEY WORDS:** cholecystectomy

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**Study Objective:** To document changing trends in the training of residents in the treatment of gallbladder disease and the safety and efficacy of these techniques.

**Technical Approach:** A retrospective evaluation of this institution's results with laparoscopic cholecystectomy will be studied. Cases will be evaluated upon the level of expertise of both attending surgeon and the resident performing the case with regard to operative results and complications. A learning curve will thus be constructed and trends assessed to best determine the optimal implementation of this new surgical technique in a surgical training program.

**Progress:** Principal investigator departed MEDCEN without making arrangements to continue study. Protocol has been terminated.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/55

STATUS: Completed FY93

TITLE: Spectrum of Colorectal Injuries in Children: A Ten Year Review

START DATE: Aug 92

ESTIMATED COMPLETION DATE: Nov 92

PRINCIPAL INVESTIGATOR: LTC Troy M. Reyna

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: B Hammacker

KEY WORDS: colorectal injuries

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**Study Objective:** To document changing trends in the management of colorectal injuries in pediatric patients when contrasted with adult techniques and to assess any trends in evolution of techniques over the last decade of advancing trauma management. Also noted will be the differences in epidemiology between adult and pediatric injuries to this organ.

**Technical Approach:** A retrospective clinical evaluation of all records of pediatric patients admitted to CONUS medical facilities for the last ten years with a diagnosis of colorectal injuries will be undertaken. Charts will be collected, blinded with analysis of data from the admission physical exam, operative report(s), narrative summary, and autopsy report, if applicable.

**Progress:** Pediatric colo-rectal injuries and their management are rarely described in the trauma literature. A retrospective review of 22 cases of pediatric colo-rectal injuries treated over the past ten years were evaluated by age, sex, mechanism, outcome, and severity using the penetrating abdominal trauma index (PATI). There were 15 males and 7 females, with an age range from 1 to 15 years old. Thirty-six percent of the injuries resulted from child abuse; 32% from blunt trauma, and 32% from penetrating trauma. The average age of children abused was five years old, while the average age for blunt and penetrating trauma was nine years old. In the four patients with PATI scores greater than 25, one patient died in the operating room (PATI score of 45), and three patients lived, one with complications. The average length of hospital stay was 12 days (range of seven to 15 days) for the three patients that survived. We concluded that colon and rectal injuries are relatively infrequent. A significant percentage were secondary to child abuse, and a high index of suspicion should accompany the investigation of colon and rectal injuries in the younger age group. A comparison of adult versus pediatric injury severity would require a larger pediatric population with PATI scores greater than 25.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 93/24

STATUS: Ongoing

TITLE: Pediatric Thyroidectomy: Complications and Strategy

START DATE: Jan 93

ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: LTC Troy M. Reyna

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS:

KEY WORDS: thyroidectomy

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**Study Objective:** To determine by retrospective analysis of charts of children undergoing thyroid surgery; what mistakes or acts of omission contributed to the reported complications. Through this study the authors would hope to arrive at a recommended technique for surgical management of thyroid disease in children that optimally treats malignant and benign processes with minimal morbidity.

**Technical Approach:** A retrospective analysis of all cases of surgically-treated thyroid disease in CONUS will be conducted. The cases will cover the twelve year period 1980-1992 and . Evaluated will be detailed demographic data, including pathology, type of operation, results, and complications. Analysis will include study of operative reports with regard to documentation and visualization of all parathyroid glands and appropriate-sided recurrent laryngeal nerves and other pertinent anatomical structures.

**Progress:** Principal investigator is in the process of writing final abstract and manuscript.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/25A

STATUS: Ongoing

TITLE: Vascular Changes Associated with Stress Reaction of Bone in the Rat

START DATE: May 89

ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: JM Uhorchak

KEY WORDS: Stress reaction, bone

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**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:** After multiple failures, we have finally solved the problem of specimen preparation for sectioning. Previous efforts to embed the specimens in various plastics resulted in the production of numerous artifacts which distorted the histologic details of the cleared specimens. However, by thoroughly dehydrating with

propylene oxide and then embedding them in low-viscosity embedding media, a complex epoxy. This process is time consuming but produces excellent specimen samples which can be sectioned with the Buehler Isomet diamond wafering blade and stained with Coles' Hemoloxylin and Eosin.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 89/70A

STATUS: Ongoing

TITLE: Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model

START DATE: Nov 90

ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: CPT Charles Whitlow

DEPARTMENT: Surg

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: MF Rhodes, M Kestner

KEY WORDS: Tracheal reconstruction, Tracheal prosthesis

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**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 patent 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 over 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. prosthesis length
- Group II - 4 cm. prosthesis length
- Group III - 5 cm. prosthesis length
- Group IV - 6 cm. prosthesis length

The grafts in these animals will be evaluated at intervals of 4 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 luminal 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:** Thirteen rabbits were used in FY93. Improvements in surgical technique have greatly enhanced the success rate for these implants. Problems with stenosis and infection, both of a chronic nature, remain as complications. Principal investigator CPT Canfield has departed WBAMC and is now deployed in Somalia. CPT Charles Whitlow has assumed duties as principal investigator. MAJ Mark Kestner has been added as an associate investigator.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 92/11A

STATUS: Ongoing

TITLE: Emergency Life Support Training for Combat Medics in the Small Ruminant (Ovine or Caprine) Animal Model

START DATE: Jan 92

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: 2LT Hector Vega

DEPARTMENT: ADA

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATORS: J Walls

KEY WORDS: emergency life support

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**Study Objective:** This training will enhance the combat medical aidman's (Medic's) capabilities of administering emergency lifesaving procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest trauma management.

**Technical Approach:** The emergency life support training program is designed for medics who are responsible for providing first to third echelon care to the critically injured patient (echelon 1- self & buddy aid; echelon 2- combat lifesaver; echelon 3- medical specialist). Procedures taught will be according to the American College of Surgeons (ACS) Committee's Advanced Trauma Life Support Course. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations and a written examination. Students who successfully complete lecture and examination requirements, then rotate through animal laboratories associated with the lecture content previously presented. The animal laboratory allows 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 laboratory is approximately 2-3 hours per cycle. Each animal station will consist of one instructor and no more than four to five students.

**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 animals were utilized in FY93. The new PI has coordinated with MAJ Harris, DCI, to conduct a full training program for enhancement of emergency skills for combat medics on a quarterly basis in FY94.

## DETAIL SUMMARY SHEET

DATE: 1 October 93

PROTOCOL #: 88/52A

STATUS: Ongoing

TITLE: Combat Trauma Life Support Procedure in the Sheep Model

START DATE: Oct 88

ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: 2LT J. Walls

DEPARTMENT: 3ACR

FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Montes

KEY WORDS: Life support, Combat trauma

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**Study Objective:** To train Physician's 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 include:

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 87 combat medics and physician's assistants completed the ATLS training program under this protocol in FY93. After action reports and critiques indicated that this training was very well received and judged as extremely valuable in familiarizing emergency medical personnel in actual hands-on life saving techniques.

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