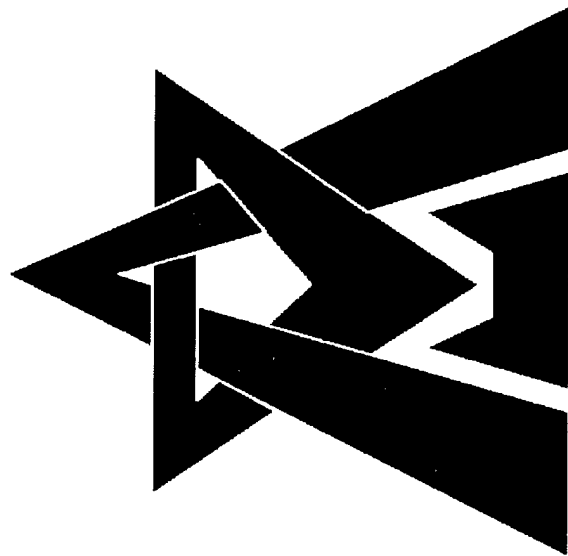


Madigan Army Medical Center
Department of Clinical Investigation

Annual Progress Report



Fiscal Year 1999

BEST QUALITY EXPECTED!

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13. ABSTRACT *(Maximum 200 words)*

This report covers all research protocols that were administratively or technically supported by the Department of Clinical Investigation, Madigan Army Medical Center, during FY 1999. Included in the individual reports are title, investigators, funding, objective, technical approach, and progress for FY 1999. Also included in the report are personnel rosters for the Department, funding information, and presentations and publications emanating from Madigan Army Medical Center during FY 1999.

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ANNUAL PROGRESS REPORT

30 SEPTEMBER 1999

DEPARTMENT OF CLINICAL INVESTIGATION

MADIGAN ARMY MEDICAL CENTER

TACOMA, WASHINGTON 98431

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Table of Contents

| | |
|---|-----|
| Introduction | 4 |
| Acknowledgements | 4 |
| Foreword | 5 |
| Special Dedication | 6 |
| Unit Summary | 7 |
| Committee Members | 10 |
| Madigan Research Day 1999 Proceedings | 12 |
| Introduction | 13 |
| First Annual Madigan Research Day Awards..... | 14 |
| Second Annual Madigan Research Day Awards..... | 15 |
| Military Unique Clinical Investigation..... | 18 |
| Scientific Approach To Managed Care | 23 |
| Keynote Lecture by COL Bonnie M. Jennings, AN..... | 28 |
| Special Award Presentation by Nancy Whitten..... | 29 |
| BG George J. Brown Mentor's Cube Presentation | 30 |
| Medical Education Research Session | 31 |
| Experimental Design Session | 37 |
| Case Report Session | 45 |
| Poster Session..... | 51 |
| Steger Award | 61 |
| Fellow's Research Award | 62 |
| Kenyon Joyce Award | 62 |
| Publications | 63 |
| Presentations | 68 |
| Detailed Summary Sheets Table of Contents..... | 73 |
| Index | 533 |

FISCAL YEAR 1999

DEPARTMENT OF CLINICAL INVESTIGATION
MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431

Introduction

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Institutes of Health, and Title 9, Subchapter A, Parts I, II, and III of the Code of Federal Regulations. The investigators adhered to Title 21, Part 50 of the Code of Federal Regulations and the recommendations from the Declaration of Helsinki in the performance of investigations involving human subjects.

Acknowledgments

I would like to take this opportunity to thank Nancy Whitten, Barbara Jones, Troy Patience, and Genie Hough for their effort, in the compilation, preparation, and editing of this publication.

Foreword

The continued expansion of scholarly activity at Madigan Army Medical Center (MAMC) during a time of unexpected loss, deployments, backfilling, and increased clinical productivity is a tribute to the commitment to excellence of the MAMC community of clinical investigators. Madigan experienced remarkable turnover in graduate medical education programs, house-staff assigned, and certified faculty yet produced new scholarly activity at historical levels simultaneous with increased patient contacts, care and service. Madigan Department of Clinical Investigation (DCI) supported 111 new research protocols, 85 completed protocols, 49 terminated protocols, 6 suspended protocols and 239 on-going protocols (289 staff protocols, 23 fellow protocols, 58 resident protocols, 8 intern protocols and 1 external protocols). IRB approved protocols involving 372 house-staff, 102 fellows, 116 residents, and 13 interns. The emphasis and priority for Military Unique Clinical Investigation continues to be increased. DCI has initiated outreach programs to teach the regulatory requirements for ethical conduct of research while providing pre-review and design support for our medical executives seeking to improve the quality of care through a more scientific approach to managed care.

The very important Graduate Medical Education mission at Madigan continues to receive strong support from DCI through leadership in curriculum development, medical education research, and the unique training opportunities available through the departmental programs (i.e. PALS, ATLS, etc.). The following number of interns, residents, fellows and faculty participated: "Introduction to Clinical Investigation Short Course" (55), and 'Surgical Training Protocols'; i.e., PALS and ATLS (68).

Madigan Research Day 1999 was held 1 April 1999 and offers the best benchmark available for the vigor of scholarly activity and clinical research at our institution, and within our region. Fifty-two abstracts were submitted and reviewed by subcommittees and 21 selected for podium presentations. This year we added 10 poster presentations. Moderators presented several additional presentations to focus the research efforts in the areas of Military Unique Clinical Investigation (LTC C. Ray Dotson, MS, Assistant Chief, DCI), Scientific Approach to Managed Care and Outcome Studies (Nancy N. Greenfield, Chief Quality Services), INFORM Course (Lori Loan, Chief, Nursing Research Service), Medical Education Research (COL Patrick Kelly MC, GME), Experimental Design (Dr. Katherine Moore, Ph.D., Senior Scientist, DCI), and Case Reports (COL Romeo Perez, MC, Chief, Ob/Gyn). The COL Patrick S. Madigan, M.D. Foundation and The Geneva Foundation supported the effort from conception to execution to include the Program Brochure, Open House, and recruitment of Judges.

BG Mack Hill's opening comments set the stage for the challenge and celebration of scholarly activity at MAMC. Four presentations were awarded Army Achievement Medals in the following areas: **Change of Practice** - CPT Laura L. Feider, AN for "Risk Factors for Nosocomial Pneumonia in the Intensive Care Unit" (Mentor: Mary McCarthy, RN, MN, Critical Care Nursing); **Discovery** - CPT Samuel S. Jang, MC for "Targeting Hearing Loss Prevention at the High Risk Populations" (Mentor: LTC Jeffrey D. Gunzenhauser, MC, Preventive Medicine); **Innovation** - CPT Eric Shry, MC for "Utility of Echocardiography in Asymptomatic Active Duty Service Members with Heart Murmur" (Mentor: MAJ Maureen Arendt, MC, Cardiology/Internal Medicine); **Interdisciplinary** - MAJ Brian Harrington, MC for "Evaluation of Clinical Standards Implementation at Madigan" (Mentor: COL Joseph Yetter, MC, Family Practice). The inaugural recipient of the Excellence in IRB Service Award ("Whitten Award") was presented to COL Ted Carter MC. The BG George J. Brown Mentor's Cube was presented to *COL William Cahill, MS*. The Madigan Research Day Proceedings were published in the U.S. Army Medical Department Journal (AMEDD Journal), and are included in this publication with the permission of the Editor, Bruce Nelson. In the AMEDD Journal "preface" Major General James B. Peake provided the following summation, "Shows the diversity and depth of ongoing scholarly activity at just one of the Army's Medical Centers". Madigan Research Day 2000 will be held 13 April 2000.

Special Dedication

Nancy J. Whitten

We mourn the loss of our extraordinary protocol specialist, guiding light, and powerful voice to assure the ethical conduct of research for our clinical investigation community. The DCI Conference Room will be dedicated in her name at Madigan Research Day 2000. And the Annual IRB Excellence Award will be named in her honor.



Message from COL James Lamiell MC; C, CIRO 9 Aug 1999

I am shocked and saddened to hear about Ms. Nancy Whitten's catastrophic loss...As you know, Ms. Whitten is the most senior ARMY CI Protocol Coordinator. She has served the Army and the Clinical Investigation community admirably for 24 years. I am grateful for her exemplary service...

COL James Lamiell MC

Unit Summary

A. Objective:

To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan Army Medical Center and its region.

B. Technical Approach:

All research, investigational and training activities within the Department of Clinical Investigation are conducted under the guidance of AR 40-7, AR 40-38, AR 70-25, AR 70-18, and HSC Reg 40-23. Careful monitoring of all approved protocols is conducted in order to assure strict compliance with the applicable regulations.

C. Staffing:

| <u>Name</u> | <u>Rank</u> | <u>MOS</u> | <u>Title</u> |
|------------------------|-------------|------------|---|
| Hume, Roderick F., Jr. | COL | 60J9A | Chief, DCI |
| Dotson, Carroll Ray | LTC | 71A67 | Asst Chief, DCI; Chief, Research Administration Service |
| Norlund, L. Lewis | MAJ | 75C64 | Chief, Laboratory Animal Resources Service |
| Rossignol, Todd M. | CPT | 71B67 | Chief, Research Operations Service |
| Carpenter, Steven W. | SFC | 91T4H | NCOIC |
| Ngala, Vickie R.* | SFC | 91T4R | Senior Animal Care NCO |
| Collins, Sherri L. | SGT | 91T20 | Senior Animal Care Sergeant |
| Chapman, Tiffany D. | SGT | 91T20 | Animal Care Specialist |
| Williams, Iridiana** | SGT | 91K20 | Medical Laboratory Specialist |
| Long, Brett W. | SPC | 91T10 | Animal Care Specialist |
| Fogleman, Sandra D. | SPC | 91T10 | Animal Care Specialist |
| Matej, Louis A. | GS11 | 00644 | Medical Technologist |
| Wright, James R. | GS11 | 00644 | Medical Technologist |
| DeHart, Mary Jo | GS11 | 00644 | Medical Technologist |
| Bullock, Jeff M. | GS11 | 00644 | Medical Technologist |
| Patience, Troy H. | GS09 | 1530 | Statistician (Medicine) |
| Whitten, Nancy J.*** | GS09 | 1087 | Research Protocol Specialist |
| Kaeo, Curtis K. | WG07 | 4749 | Maintenance Worker |
| Hough, Eugenia R. | GS06 | 0318 | Secretary/Steno |
| Jones, Barbara A. | GS05 | 0303 | Clinical Research Associate |

* Retired, ** Detailed out, ***Deceased

Staffing Summary:

| | Authorized | Required | Assigned |
|-------------|------------|----------|----------|
| Officers - | 4 | 10 | 4 |
| Civilians - | 8 | 12 | 8 |
| Enlisted - | 8 | 12 | 5 |

D. Funding FY 99

FY 99 Funding Worksheet

b. FUNDS (cumulative Fiscal Year 1999).

| | | | |
|---|------------|--------------|---------|
| OMA Total: | | \$ 617,600 | (total) |
| Civilian Payroll: | \$ 506,900 | | |
| Operations: | \$ 99,000 | | |
| CEEP: | \$ 6,000 | | |
| TDY | \$ 2,200 | | |
| Print/Publications | \$ 2,500 | | |
| Contracts | \$ 1,000 | | |
| Grants USAMRDC: | | \$ - | (total) |
| Grants Federal (PI): | | \$380,343 | (total) |
| Grants Nonfederal: (include grants from all intermediaries) | | \$ 80,086 | (total) |
| Grants (GRAND TOTAL): | | \$ 460,430 | (total) |
| MEDCASE: | \$ - | | |
| Military Payroll: | \$ 387,656 | | |
| Other Non-OMA | \$ - | | |
| Non-OMA Total: | | \$ 387,656 | (total) |
| | | \$ 1,465,686 | (total) |

E. Progress

During FY 99, there were 379 active protocols that received administrative and/or technical support during the year. Of these, 239 are presently ongoing, 6 are in a suspended status, 85 were completed, and 49 were terminated. The principal investigator distribution was as follows: 289 staff protocols (includes 151 group oncology protocols), 58 resident protocols, 23 fellow protocols, 8 intern protocols and 1 Weed Army Community Hospital protocol. There were 111 new protocols.

There were 65 publications in nationally recognized journals and 61 presentations at regional or national medical association meetings.

F. Fellowship/Residency Program Support

Fellowship/Residency programs supported by DCI: 21 residencies and 5 fellowships, they are: *Residencies:* Emergency Medicine, Family Practice, General Surgery, Internal Medicine, Neurology, Obstetrics and Gynecology, Occupational Therapy, Ophthalmology, Oral and Maxillofacial Surgery, Orthopaedic Surgery, Otolaryngology, Pathology, Pediatrics, Pediatric Psychology, Pharmacy, Physician Assistance Program (Emergency Medicine & Orthopaedics), Podiatry, Preventive Medicine (Public Health), Radiology, Transitional Year, and Urology.

Fellowships: Developmental Pediatrics, Faculty Development (Family Practice), Geriatrics, Maternal-Fetal Medicine, and Urogynecology.

116 protocols involving 111 residents

102 protocols involving 23 fellows

Other training programs supported by DCI:

Training protocols: Department of Surgery: 3
 Department of Emergency Medicine: 2
 Special Forces: 1

Other protocols supported:

Weed Army Community Hospital protocol

G. Committee Members

Clinical Investigation Committee

Katherine H. Moore, Ph.D.

Chairman

Chief or delegated representative of:

Department of Emergency Medicine

Department of Family Practice

Department of Medicine

Department of Nursing

Department of OB/GYN

Department of Pathology

Department of Pediatrics

Department of Radiology

Department of Surgery

Pharmacy Service

Physical Medicine & Rehabilitation Service

Department of Clinical Investigation

Biochemistry Section, DCI

Lab Animal and Resources Service, DCI

Medical Statistician, DCI

Microbiology Section, DCI

Research Administration Service, DCI

G. Committee Members (cont'd)

Human Use Committee
Katherine H. Moore, Ph.D.
Chairman

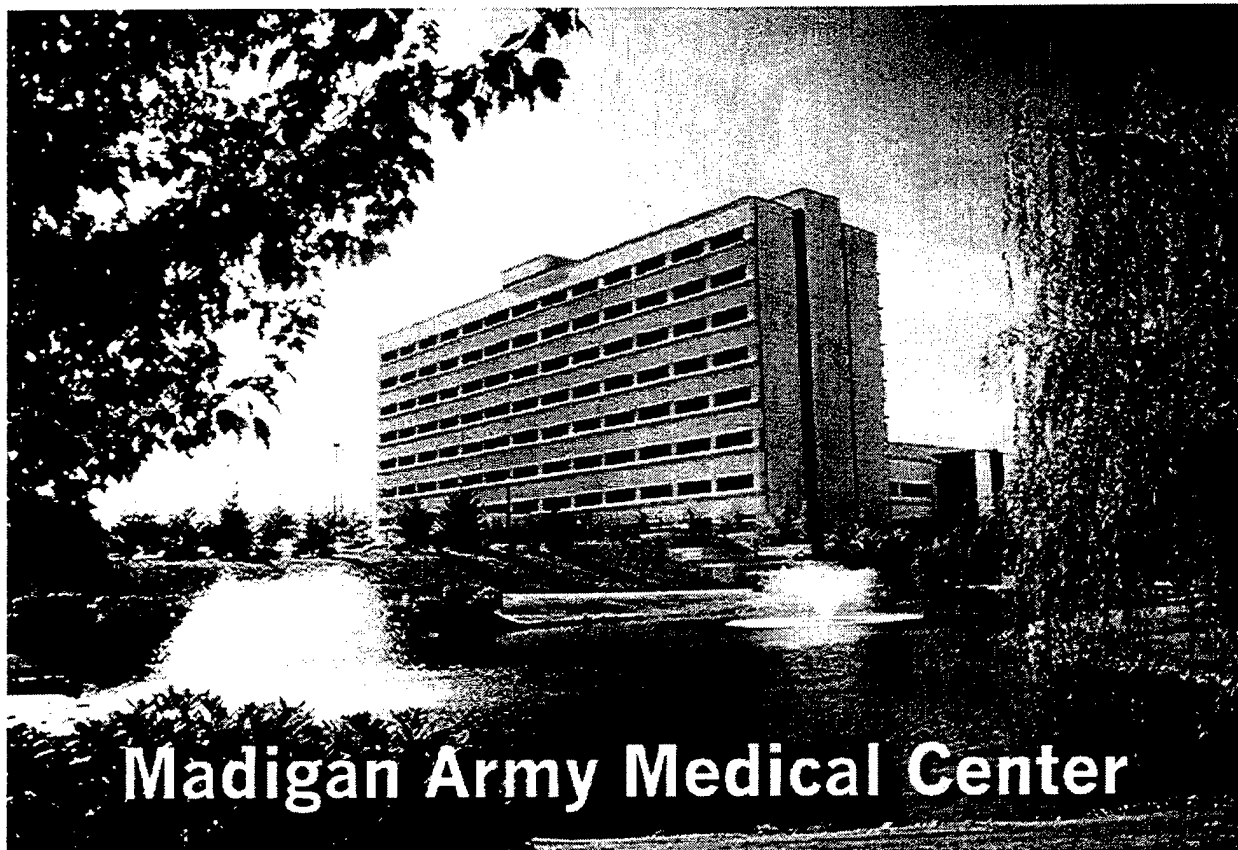
Chief or delegated representative of:

Department of Nursing
Department of Pediatrics
Department of Radiology
Department of Ministry and Pastoral Care
Department of Clinical Investigation
Pharmacy Service
Social Work Service
Center Judge Advocate
Non-institutional Member

Animal Use Committee
COL Roderick F. Hume, Jr.
Chairman

Chief or delegated representative of:

Department of Nursing
Northwest Veterinary Support Service Area
Non-institutional Member
Research Operations Service, DCI
Lab Animal & Surgery Service, DCI
NCOIC, Lab Animal & Resources Service, DCI



Research Day Proceedings

for

1 April 1999, Letterman Auditorium,
Madigan Army Medical Center
Fort Lewis, Washington

The goals for this program were threefold: Celebrate the Exceptional Scope of Scholarly Activities at MAMC, Incite Enthusiasm (for further studies, grant submissions, and publications at MAMC), and Attract Grant Support for MAMC.

Four presentations have been nominated for awards (Army Achievement Medal): Innovation, Interdisciplinary, Discovery, and Change In Practice.

INTRODUCTION

by
BG Mack Hill
Commanding

I truly believe that no forum offers better proof of what is RIGHT about MAMC than Madigan Research Day. MRD99 fulfills and exemplifies your clarification of our MISSION, PRIORITIES and CORE FUNCTIONS published 8 January 1999. How do we FOCUS on...OUR People? Patients, Soldiers, Leaders, Students, Residents, Fellows, Young Faculty are all the focus of the 23 oral and 10 poster presentations by teams of Clinical Investigators in MRD99. The novice presents the team's work with guidance from the mentors. We develop the future healthcare delivery readiness (MHS) while we perform our tasks today. The driving force behind the courage to be curious and open to peer review, manifests the ARMY motto: BE ALL YOU CAN BE, with the MAMC twist - prove that your process is the best it can be, now and into the future. The scientific approach to scholarship, improved clinical care, and better readiness remains critical to our continued growth as a center of excellence.

We celebrate the excellence of the scientific approach to today's problems and future solutions awarding best presentations in the following categories: Innovation, Discovery, Change of Practice, and Most Interdisciplinary. And we recognize the central role of the MENTOR in this process uniquely with the MENTOR'S CUBE. Thanks for joining us today.



FIRST ANNUAL MADIGAN RESEARCH DAY AWARDS

Each of the 66 submissions was eligible for the 4 awards. The awards were selected by judges scoring for the best in each of the following categories: Change of Practice, Discovery, Innovation, Interdisciplinary.

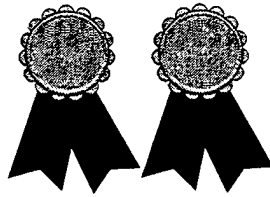
The First Annual MRD winners were:

Change of Practice - "The Effect of Loaded Foot Marching vs Running on Injury, Fitness, and Performance In US Army Light Infantry Soldiers" presented by CPT Dan C. Norvell, SP

Discovery - "Purple Toes" presented by CPT Brian P. Mulhall, MC

Innovation - "Tracheal Mucosal Healing in Response to Moderate Mucosal Injury Induced by Expandable Metallic Stents" presented by LCDR Keith Ulnick, MC USN

Interdisciplinary - "The Routine Pregnancy Process: Framework for Clinical Pathway Genesis" presented by 1LT Cristen Brandsma, AN



SECOND ANNUAL MADIGAN RESEARCH DAY AWARDS

Each of the 66 submissions was eligible for the 4 awards. The awards were selected by judges scoring for the best in each of the following categories: Change of Practice, Discovery, Innovation, Interdisciplinary.

Change of Practice - CPT Laura L. Feider, AN for “Risk Factors for Nosocomial Pneumonia in the Intensive Care Unit”

Mentor: Mary McCarthy, RN, MN, Critical Care Nursing

Discovery - CPT Samuel S. Jang, MC for “Targeting Hearing Loss Prevention at the High Risk Populations”

Mentor: LTC (P) Jeffrey D. Gunzenhauser, MC, Preventive Medicine

Innovation - CPT Eric Shry, MC for “Utility of Echocardiography in Asymptomatic Active Duty Service Members with Heart Murmur”

Mentor: MAJ Maureen Arendt, MC, Cardiology/Internal Medicine

Interdisciplinary - MAJ Brian Harrington, MC for “Evaluation of Clinical Standards Implementation at Madigan”

Mentor: COL Joseph Yetter, MC, Family Practice

MORNING SCHEDULE

| | |
|---|-------|
| Opening Remarks by BG Mack Hill | 08:00 |
| Military Unique Clinical Investigation Session [Moderated by LTC Carroll Ray Dotson, MS] | 08:15 |
| Sports Medicine in U.S. Army Rangers: A Look at Injuries, Physical Training, and Performance by CPT Daniel C. Norvell SP | 08:20 |
| External Fixation of Significantly Displaced Clavicle Fractures by MAJ Greer E. Noonburg MC | 08:35 |
| Assessing the Stages of Change for Contraceptive Use in the Prevention of Pregnancy and Sexually Transmitted Disease by CPT Jennifer H. Potter MC | 08:50 |
| Targeting Hearing Loss Prevention at the High Risk Populations by CPT Samuel S. Jang MC | 09:05 |
| Scientific Approach to Managed Care Session [Moderated by Nancy Newth Greenfield RN, MS] | 09:20 |
| Individual Cost Per Patient and Lengths of Stay as a Function of Patient Category and Clinic Service in a Military Medical Treatment Facility by MAJ William H. Millar MS | 09:25 |
| Minocycline Hyperpigmentation by CPT Eric J. Messner MC | 09:40 |
| Risk Factors for Nosocomial Pneumonia in the Intensive Care Unit by CPT Laura L. Feider AN | 09:55 |
| Utility of Echocardiography in Asymptomatic Active Duty Service Members with Heart Murmur by CPT Eric Shry MC | 10:10 |
| Keynote Lecture by COL Bonnie M. Jennings AN | 10:30 |
| Special Award Presentation by Nancy Whitten | 11:30 |
| BG George J. Brown Mentor's Cube Presentation | 11:40 |
| Lunch | 12:00 |

AFTERNOON SCHEDULE

| | |
|---|-------|
| Medical Education Research Session [Moderated by COL Pat Kelly MC] | 13:00 |
| Information for Optimal Decision-Making Course by Lori Loan | 13:05 |
| Determining Technical Competency for Family Practice Residents in Flexible Sigmoidoscopy by CDR John R. Holman MC USN | 13:20 |
| The Effects of Thermocouple Sensor Placement on Neonatal Skin Temperature Measurement by Susan E. Chambers BSN | 13:35 |
| Parental Assessment of Psychologic Adjustment in Children with Asthma: A Comparison of the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children (BASC) by CPT Veronica Baechler MC | 13:50 |
| Evaluation of Clinical Standards Implementation at Madigan by MAJ Brian Harrington MC | 14:05 |
| Experimental Design Session [Moderated by Katherine H. Moore, Ph.D.] | 14:20 |
| Changing Thyroid Hormone Status and Cognitive and Mood Alterations During Prolonged Antarctic Residence: Effect of Thyroxine Supplement-ation in the Polar T3 Syndrome by CPT Nhan Van Do MC | 14:25 |
| The Effect of Preoperative Administration of Ketorolac on Postoperative Bleeding in Anterior Cruciate Ligament Repair by CPT Angela Quintanilla AN | 14:40 |
| The Association Between Telomerase, p53 and Clinical Staging in Colorectal Cancer by CPT Tommy Brown MC | 14:55 |
| The Effects of Mitomycin-C on Airway Wound Healing After Laryngo-tracheoplasty and Stenting in a Pig Model by CPT George Coppit MC | 15:10 |
| The Expression of Adrenomedullin and its Receptor in the Human Placenta by MAJ Christina C. Apodaca MC | 15:25 |
| Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry by CPT Michael W. Quinn MC | 15:40 |
| Case Report Session [Moderated by COL Romeo Perez MC] | 16:00 |
| Adrenal Tumor Incidence in a Ferret Colony by SPC Sandra Fogelman | 16:05 |
| Unilateral Congenital Lymphedema Associated with Intestinal Lymph-angiectasia, Elevated Liver Transaminases, and Hypopigmentation by LtCol William M. Campbell MC USAF | 16:15 |
| Pseudo-dissection of the Main Pulmonary Artery on Computed Tomo-graphy by CPT Adam Benson MC | 16:25 |
| Pilomatrixoma of the Head and Neck by MAJ Richard W. Thomas MC | 16:40 |
| Findings of Fibular Hemimelia Syndrome with Radiographically Normal Fibulae by CPT Clark P. Searle MC | 16:50 |
| Closing Remarks by COL Roderick Hume MC | 17:00 |

MILITARY UNIQUE CLINICAL INVESTIGATION

Moderator: LTC C. Ray Dotson, MS

The care and welfare of our soldiers, airmen, and sailors is the central concern of our military research efforts. The essential process required to preserve and maintain the fighting strength (...salvage our manpower for the unique military missions...) is to anticipate the threat, solve the problems, and work through the medical challenges that the deployed soldier may encounter. At the Joint Services Graduate Medical Education Selection Board, Secretary Martin coined the term 'Military Unique Clinical Investigation'. Subsequently, the Surgeon General from each of the DOD services stated that more military unique curriculum development and more military unique research were needed. This message was clear and anticipated at Fort Lewis by both Madigan Army Medical Center (MAMC) and I Corps leadership. There is already an existing tradition of collaborative militarily relevant clinical investigation efforts between MAMC and I Corps and this remains a fundamental element of future plans at this installation.

Presentation Section: MUCI

Title: Sports Medicine in U.S. Army Rangers: A Look at Injuries, Physical Training, and Performance

Presenter: CPT Daniel C. Norvell, SP

Department: Physical Medicine and Rehabilitation

Mentor: COL Joseph R. Dettori, SP

Abstract:

The U.S. Army Rangers are a quick strike force capable of deploying within 18 hours to any location in the world. The Rangers most often deploy by parachuting near or onto a hostile airfield at night under intense physical and psychological demands. These demands rival, if not exceed, those of professional athletes. The purpose of this study is to analyze the rates, causes, and types of injuries that occur both in garrison and during deployments in Rangers. In addition, we describe an alternative method of handling these injuries by introducing a sports medicine program similar to a professional athlete setting. Injury data was collected prospectively over a 7-month period in the 2/75 Ranger Battalion, Fort Lewis, Washington. Deployment injury rates were found to be significantly higher than garrison injury rates (28.8/100 Rangers/month, RR = 4.36, 95% CI 2.87, 5.85 and 6.6/100 Rangers/month, respectively). The majority of deployment injuries were traumatic (73%) while garrison injuries were as a result of overuse (71%). The leading causes of injury during deployments were field training (22%), road marching (19%), and fast roping (17%). The leading causes of garrison injuries were related to physical training (PT); running (46%) followed by marching (29%). With the introduction of a sports medicine program, Ranger injuries are treated immediately both in garrison and during deployments and rehab takes place in their own fitness center during PT time or in the intermediate staging base during a deployment. In addition, a "Total Ranger" PT Program is being implemented consisting of 6 performance measures that closely resemble the physical demands of the battlefield. New PT exercises have been designed to reduce the amount of running and marching while improving skills like speed, agility, quickness and overall strength; attributes necessary to be successful in combat. This program, modeled very similarly to a professional or college sports medicine program, is being evaluated to determine if it produces more ready and better performing Rangers.

Presentation Section: MICU

Title: External Fixation of Significantly Displaced Clavicle Fractures

Presenter: MAJ Greer E. Noonburg, MC

Department: Surgery, Orthopedic Surgery

Mentor: LTC Patrick St. Pierre, MC

Abstract:

We propose the use of external fixation of mid-third clavicle fractures with significant displacement in order to reduce the likelihood of deformity that would interfere with the wearing of shoulder harnesses (rucksacks, parachutes, load bearing equipment, etc.) and decrease shoulder stiffness from prolonged immobilization. Currently, the standard treatment for significantly displaced clavicle fractures involves wearing a sling or figure-eight for 8 weeks. Mid-third clavicle fractures with over 100% displacement have been reported to have a 16% nonunion rate and over 32% unsatisfactory results in the general population. Many military personnel require shoulder harnesses in their occupations and cannot tolerate clavicular deformity, malunion or nonunion.

Thirteen individuals with acutely fractured clavicles that were displaced greater than 100% have been treated with external fixation. Within two days postoperatively, all were able to perform shoulder abduction to 90 degrees and engage in moderate shoulder activity without pain. There were no complications from surgery or post-op infections. The average time for external fixation was 56 days. Two individuals had to have the fixator adjusted to realign the clavicle but healed uneventfully. All were able to resume their normal activities after removal of the external fixator. Based on these results, external fixation of significantly displaced mid-third clavicle fractures is a viable option for individuals whose occupations require the use of shoulder straps and would be adversely affected by clavicular deformity.

Presentation Section: MICU

Title: Assessing the stages of change for contraceptive use in the prevention of pregnancy and sexually transmitted disease

Presenter: CPT Jennifer H. Potter, MC

Department: Family Practice

Mentor: LTC Diane M. Flynn, MC

Abstract:

Background and Methods: This study is a prospective controlled study to assess the stages of change of 300 AD soldiers regarding contraceptive use in the prevention of unintended pregnancy and sexually transmitted disease. The Stages of change is a construct of the Trans-theoretical model of health behavior change. The concept of Stages of change suggests that as individuals modify health behaviors, they progress through five stages: pre-contemplation, contemplation, preparation, action and maintenance phases. The Unintended Pregnancy Prevention Program (UPPP) is an ongoing program designed to determine if reproductive education and facilitated access to contraceptive services will decrease the rate of unintended pregnancy. Objectives of this study are to report: (1) participants' stage of change before the unintended pregnancy prevention program intervention (2) stages of change with respect to demographics of class (3) change in participants' stage of change before and after class as a function of class demographics.

This study is being performed via a questionnaire given to the study group before and after the UPPP intervention. The dependent variables for this study consist of the study group and the age/rank/gender of group participants. The method of analysis will be to use a chi-square to (1) compare the incidence of change within the study group before and after the intervention. The five different stages of change will also be converted to numerical rank to compare the mean ranks by group and by age/rank of participants using 2-factor Analysis of Variance.

Results: Currently are in data collecting stage of study. Results of the pre and post class surveys and the demographic data will be completed by 1 Feb 99.

Conclusions: The value of assessing the stage of change in UPPP participants is that it can provide a framework for forming interventions tailored to where individuals are in the process of change. It will also assess if the UPPP is making an effective difference in participant's stage of change. Awaiting results of data collection at this time.

Presentation Section: MICU

Title: Targeting Hearing Loss Prevention at the High Risk Populations

Presenter: CPT Samuel S. Jang, MC

Department: Preventive Medicine

Mentor: LTC (P) Jeffrey D. Gunzenhauser, MC

Abstract:

OBJECTIVE: To estimate rates of hearing loss among soldiers serving in various occupations.

METHOD: A retrospective cohort design involving soldiers on active duty in the US Army between 1986 to present. A priori, soldiers were assigned to "exposed" and "unexposed" groups based on their military occupational specialty. Audiograms were routinely performed and recorded in a central database during the study period. Rates of significant hearing loss were estimated in the various occupational groups. Crude and occupation-specific rates in the "exposed" group were compared with the "unexposed" using the rate ratio. Internal dose-response relationships of time in "high-risk" occupations with hearing loss were estimated. Dose (time in occupation) was related to response (hearing loss) to support a possible causal relationship.

RESULTS: Overall, there was a substantial reduction in the prevalence of significant hearing loss among soldiers assigned to combat occupational specialties. Other results are pending at this time.

CONCLUSION: This study will identify specific occupations at high risk for hearing loss. It will also determine if selected military occupations "cause" hearing loss, or whether observed trends could be due to other factors. Changes in hearing loss incidence rates over time will identify periods when hearing loss prevention may be most effective.



**MADIGAN RESEARCH DAY
AWARD WINNER
"Discovery" Category**

SCIENTIFIC APPROACH TO MANAGED CARE

Moderator: Nancy Newth Greenfield, RN, MS

Managed care is a concept and a framework for health care delivery. Maturation of managed care systems is occurring across the country and at Madigan. This framework, when actualized at Madigan, is a dynamic and evolving system. Our managed care system is incredibly complex, with overlapping and matrixed components. Some macro components of a managed care system are the benefits package and the "rules of engagement", such as how one enrolls, how care is accessed, and how an appointment is made. In addition, more cryptic components include customer service, satisfaction of the beneficiary and the providers, information availability and exchange, internal measurement of processes, priority setting for resource allocation and internal interfaces or handoffs. These cryptic components are governed and influenced by the "culture" of the organization. Organizational culture includes the openness of the system, communication style and expectation, self-exploration and self-analysis of the system itself, and the education and mentoring of the participants within the system. Why do some managed care systems thrive and others fail? That is where the "science" comes in.

Madigan has enjoyed an evolving culture carefully mentored to be inclusive of concepts of total quality management and continuous quality improvement, embraced by Madigan as we continue our journey into the development of our managed care system. The growth of managed care and science is intimately linked. How do we know what the "right thing, at the right time" is? How do cost factors influence the delivery of health care? Does decreased variability in health care delivery make a difference? How? Do clinical pathways improve outcomes?

The study of macro and micro components of our managed care system is a part of our culture, reflected in the proceedings of today. Mentoring of our staff to study our systems, resources to support that system, reward for the efforts and outcomes, information available to proceed, are all part of the Madigan culture, culminating in this session, the scientific approach to managed care.

Presentation Section: MC

Title: Individual Cost Per Patient and Lengths of Stay as a Function of Patient Category and Clinic Service in a Military Medical Treatment Facility: A Supporting Objective of a Graduate Management Project

Presenter: MAJ William H. Millar, MS

Department: Command Group

Mentor: COL Van R. Booth, MS

Abstract:

It is uncertain, under Medicare Subvention (Tricare Senior Prime Demonstration), and in the future enrollment based capitation, if military medical treatment facilities have a disincentive to treat Medicare-eligible patients, or if there is a methodology to adequately evaluate the financial effects of treating those same patients. While other studies have examined the impact of other variables on individual patient costs and lengths of stay, none have specifically focused on the impact of treating Medicare beneficiaries in military medical treatment facilities. The purpose of this retrospective study was to determine if any statistically significant relationship exists between the dependent variables of individual patient cost and lengths of stay and the independent variables of patient category and clinic service in one military medical treatment facility. Defense medical information for in-patient dispositions (n=1,743) from a surgery department of a military medical treatment facility was obtained for the first six months of fiscal year 1997. Trends for individual patient cost associated with independent variables revealed a moderate and statistically significant linear pattern across individual patient cost and lengths of stay with multiple R = .247 and .288, respectively. Hierarchical multiple linear regression analysis supports the linear individual patient cost and lengths of stay hypotheses, with $F(10, 1733) = 11.258$ and 15.663 , (with $p < .05$), respectively. Additional analysis revealed significant differences between individual cost per patient and lengths of stay to patient category by clinic service. Final results indicate that increased costs and lengths of stay are related to specific patient categories. This information may assist health care administrators and providers in understanding the significance of patient category on cost and lengths of stay, and thereby provide them a decision-making tool to manage the costs of providing health care to Medicare and military beneficiaries.

Presentation Section: MC

Title: Minocycline Hyperpigmentation

Presenter: CPT Eric J. Messner, MC

Department: Medicine, Internal Medicine

Mentor: MAJ David R. Finger, MC

Abstract:

OBJECTIVE: Minocycline (minocin) has been shown to be a safe and effective therapy for mild rheumatoid arthritis (RA) in several recent studies. Although cutaneous hyperpigmentation is a rarely (1%) reported adverse effect, the Rheumatology service at MAMC has observed this in 33% of RA patients taking this drug. This observation, made possible in part through adverse drug reaction reporting on CHCS, led us to investigate this further to identify possible predisposing risk factors or etiologies.

PATIENTS AND METHODS: All patients taking minocin for the treatment of RA at the MAMC Rheumatology clinic were examined for adverse cutaneous reactions. Patient characteristics were evaluated to include: age, gender, cumulative minocin dose, steroid use, cumulative steroid dose, daily steroid dose, and use of hydroxychloroquine (also known to cause hyperpigmentation). The various clinical subtypes of minocin hyperpigmentation are reviewed along with histopathology, clinical distinctions, and therapeutic options.

STATISTICAL ANALYSIS: ANOVA and chi-square

RESULTS: RA patients taking minocin with hyperpigmentation (WHP) (n=23) were compared to those RA patients taking minocin without hyperpigmentation (WOHP) (n=46):

| | |
|--------------------------|---|
| Gender: | 28% of females (13/44)WHP vs. 40% of males (10/25) (p=.366) |
| Age: | mean age 63.4 years WHP vs. 55.1 WOHP (p=.024)* |
| Cumulative minocin dose: | 64.7 grams WHP vs. 37.5 grams WOHP (p=.043)* |
| Daily steroid dose: | 6.04mg WHP vs. 4.46mg WOHP (p=.16) |
| Cumulative steroid use: | 3.7 years WHP vs. 2.0 years WOHP (p=.03)* |
| Hydroxychloroquine use: | 13% (3/23) WHP vs. 25% (24/46) WOHP (p=.002)* |
| Steroid use: | 87% (20/23) WHP vs. 63% (29/46) WOHP (p=.04)* |

*statistically significant (p < .05)

CONCLUSIONS: Advanced patient age, greater cumulative minocin dose, steroid use and duration of steroid use were statistically significant risk factors for the development of skin hyperpigmentation. Although unconfirmed at this point, the brand of minocin may also be a risk factor. Other Army MEDCENS contacted are using the Wyeth-Ayerst brand, and per telephonic conversations with their Rheumatology clinics, they have not observed this drug reaction. Our findings led to the removal of the current minocin brand (Teva), and the replacement product (Wyeth-Ayerst) will save MAMC over \$10,000 per year. The proper reporting of adverse drug reactions by physicians may lead to an increased recognition of toxicities and possibly to financial savings.

Presentation Section: MC

Title: Risk Factors for Nosocomial Pneumonia in the Intensive Care Unit

Presenter: CPT Laura L. Feider, AN

Department: PACU Tripler Army Medical Center

Mentor: Mary McCarthy, RN, MN

Abstract:

Background: Nosocomial pneumonia (NP) has the highest mortality rate (30-50%) of all nosocomial infections, but little is known about the risk factors and outcomes when nosocomial pneumonia occurs in the intensive care units.

Purpose: This retrospective chart review compared patients who did and did not develop nosocomial pneumonia in terms of risk factors, length of stay and mortality.

Methods: This case control study review of medical records was conducted at Madigan Army Medical Center in 3 intensive care units (SICU, MICU, and CCU). ICU subjects with nosocomial pneumonia (n = 60) were matched to ICU subjects without NP (n = 60) for age, admitting service, and length of stay for onset of NP diagnosis. Medical records were reviewed for physiologic and treatment risk factors. Data were analyzed with Chi square, McNemar and Paired t-Test tests.

Results: The two groups differed in comparing physiologic risk factors of aspiration (X² = 21.8, p < 0.003), bacteremia (X² = 4.4, p < 0.03; RR 2.6), and self-care inability (X² = 11.1, p < 0.01; RR 21.3). Treatment differences were seen in endotracheal intubation (X² = 20.7, p < 0.00001), performance of pulmonary exercises (X² = 21, p < 0.002), respiratory treatments (X² = 22.4, p < 0.0001), and number of consults (t = 6.3, p < 0.001). The outcomes differed. LOS (t = 3.7, p < 0.001) was 10.7 days longer and the mortality rate (X² = 6.5, p < 0.01) was twice that in the NP group.

Conclusion and Nursing Implications: ICU patients with NP have multiple risk factors associated with higher length of stay and mortality rates. The number of consults were higher, the length of hospital stay increased by 60%, and the mortality rate was doubled in the NP group. These risk factors can be monitored and modified by critical care nurses to reduce the incidence and consequences of nosocomial pneumonia in critically ill patients.



**MADIGAN RESEARCH DAY
AWARD WINNER
"Change in Practice" Category**

Presentation Section: MC

Title: Utility of Echocardiography in Asymptomatic Active Duty Service Members with Heart Murmur

Presenter: CPT Eric Shry, MC

Department: Medicine, Internal Medicine

Mentor: MAJ Maureen Arendt, MC

Abstract:

Background: Due to frequent screening, the military has a large number of healthy service members found to have heart murmurs. Frequently they are referred for cardiology consultation and echocardiography. The 1997 American College of Cardiology/American Heart Association (ACC/AHA) echocardiography guidelines have defined murmur characteristics that are thought to predict innocent murmurs and normal echocardiography.

Methods: Our hypothesis was that the ACC/AHA criteria for murmur screening would be validated, i.e. that innocent murmurs are predictive of normal echocardiography. 66 consecutive active duty service members referred to cardiology for evaluation of a heart murmur underwent a cardiovascular history, physical exam, electrocardiogram, and echocardiogram. Auscultation was performed by staff cardiologists or third-year cardiology fellows.

Results: 40 subjects had either a benign flow murmur or a fleeting murmur (was heard by referring provider but not appreciated at the time of cardiology consultation). All of these subjects had normal echocardiograms. 26 subjects had non-innocent murmur by examination. Of these, 7 had abnormalities requiring SBE prophylaxis on echocardiography. There was a strong association between a non-innocent murmur and an abnormal echocardiogram, $p < .002$ (Fisher's exact test). History, general physical exam (other than murmur auscultation), and electrocardiography did not predict abnormal findings on echocardiogram.

Conclusion: If a cardiology staff (or senior fellow) physician determines that a heart murmur in an asymptomatic service member represents a benign flow murmur, the incidence of echocardiographic abnormalities is very low. Confirmation of this data may make echocardiography unnecessary for the majority of the healthy, active-duty service members with heart murmurs.



**MADIGAN RESEARCH DAY
AWARD WINNER
"Innovation" Category**

KEYNOTE LECTURE

COL Bonnie M. Jennings, AN

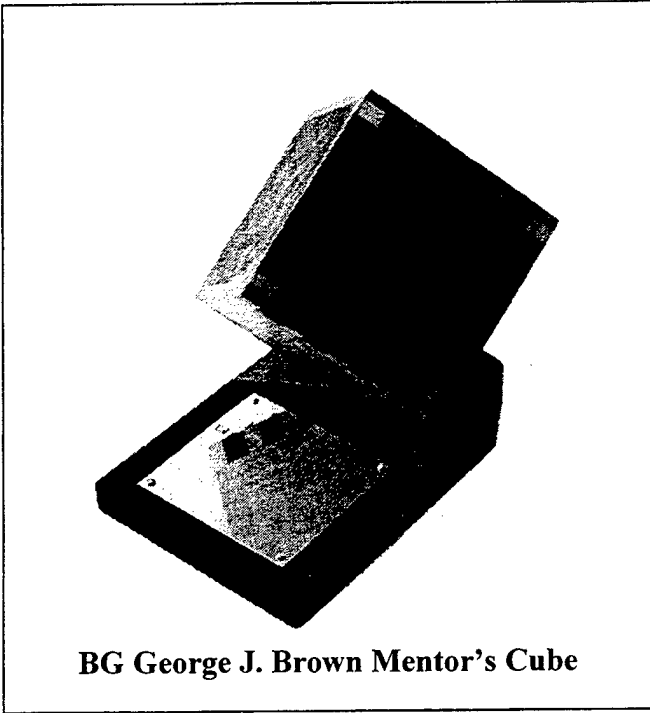
COL Jennings, PhD, now assigned to the Office of the Surgeon General, served at MAMC from 1994-1999, most recently as our Chief Nurse. COL Jennings was a Department of Defense representative to the National Advisory Council for Nursing Research (NINR/NIH) from 1991-1995. She is an extraordinary critical thinker, an exceptional research collaborator, and a wonderful teacher. She remains an active clinical investigator who continually finds the time to support the scholarly activity of others, and there are many of us at MAMC who have had the benefit of her famous purple pen. Dr. Jennings is a leading expert in the rapidly evolving field of Outcomes Research. We are most fortunate to have had her give the Keynote address for Madigan Research Day 1999.

SPECIAL AWARD PRESENTATION

Nancy Whitten

Nancy Whitten presented the first annual award for Outstanding Institutional Review Board Member. The first recipient was COL Ted Carter, MC. He was recently named the Chief, Department of Pediatrics.

BG GEORGE J. BROWN MENTOR'S CUBE PRESENTATION



BG George J. Brown Mentor's Cube

Madigan Center Research Day celebrates the breadth and depth of scholarly activity performed at MAMC. The basis for this event is the legacy of innovation, discovery, and interdisciplinary collaboration. We give high quality clinical care, while giving our students the capability to provide excellent care in future assignments. And we learn how to give better care and better teaching through our investigational efforts. We are willing to evaluate our performance and use this feedback to continually improve our process. At the core of this enterprise

is the mentor.

A mentor is the master communicator who holds your experience up for your inspection, in all of its facets, so that you can see from many angles. A mentor gives the protégé the cube of the shared experience. It is up to the student to build upon that foundation. The Madigan Mentor's Cube was made by COL Casey Jones, DCCS and named in honor of BG George J. Brown. The first recipient was COL Patrick Kelly.

BG George J. Brown

1999 BG GEORGE J. BROWN MENTOR'S CUBE FINALISTS

Nancy Greenfield
William Cahill
Lester Reed
Bonnie Jennings
Romeo Perez
Allen Almquist

1999 BG GEORGE J. BROWN MENTOR'S CUBE RECIPIENT

WILLIAM CAHILL, COL (RET), MS

MEDICAL EDUCATION RESEARCH SESSION

Moderator: COL Patrick Kelly, MC

Medical Education Research seeks to determine the best method to teach, to instruct, in order to optimize learning. How do we take the lead in learning? Curriculum development is only the beginning. How do you impart enthusiasm for life long learning in our students? What is the outcome by which we measure our success? MAMC teaches teachers, cultivates mentors, and empowers the investigator to question our educational process. Medical Education Research is truly force amplification by enhancing our future medical readiness.

Presentation Section: MER

Title: INFORM - Information for Optimal Data-Based Decision-Making

Presenter: Lori Loan

Department: Nursing Research Service

Abstract:

OVERVIEW - MAMC administrative and patient care managers are continually challenged to make decisions effecting productivity, cost and quality of care. As our Quality Management Program (QMP) decentralizes data acquisition and data-driven decision making, a broad array of MAMC managers are pressed to providing timely answers to complex business and clinical questions. New approaches for collecting, assessing and presenting data and useful information for decision-making are needed, as our managers are faced with minimal time to research options, an overabundance of data and the necessity to maximize the use of quality data. To address this need, the Research & Development Coordinating Activity recommends a course entitled, *INFORM - Information for Optimal Data-Based Decision-Making*.

PURPOSE - The *INFORM* course is designed to assist managers from many disciplines in developing core competencies pertaining to data quality and analytical techniques that will underpin solid decision-making to improve MAMC outcomes.

TARGET AUDIENCE - Managers (mid level and above) will be invited to participate. QMP Directors and other individuals who are expected to brief the EBOD will be highly encouraged to participate.

FORMAT - This course will consist of four, two-hour classes (Selecting the Right Metric, Planning and Performing the Information Quest, Reporting Useful Information, and Packaging the Presentation). Participants enrolling for the course will be required to attend all four classes. Class size will be limited to a maximum of 12 people. Participants will be given a class syllabus about two weeks before each class. Some outside of class work is required. For example, before the first class (*Selecting the Right Metric*), participants will be asked to read some course material and bring to class a management issue to be used to formulate their business question or metric and later their information presentation. Instructors will be available to provide a limited amount of one-on-one support to participants outside of class. Throughout the four classes participants will use data related to their service area to learn the course content. The classes will be at least two weeks apart to allow participants sufficient time to complete pre-class assignments. After the fourth class, participants will have prepared and presented an EBOD quality brief.

STAFFING - The Research & Development Coordinating Activity (RDCA) recommends, and the Madigan Consolidated Education (MCED) Director agrees that the INFORM course be administered through MCED in the same manner as other courses such as the current Health Care Managers Course. The MAMC Staff Development Coordinator will coordinate INFORM course registration, class resources and rooms. The RDCA will coordinate instructors and course content.

Presentation Section: MER

Title: Determining Technical Competency for Family Practice Residents in Flexible Sigmoidoscopy

Presenter: CDR John R. Holman, MC, USN

Department: Family Practice

Mentor: COL Joseph Yetter, MC

Abstract:

Question: Flexible sigmoidoscopy is a common procedure taught in family practice residencies. Programs document of the number of procedures performed, but this may not correlate with competency. Can easily determined measures of competency in the technical aspects of flexible sigmoidoscopy be identified? Are there patient characteristics that can predict an incomplete exam?

Methods: Over a 30 month period, 421 patients age 14 to 88 who presented for flexible sigmoidoscopy at the family practice clinic of a community hospital had data collected. These included demographics, depth of insertion (cm), time of procedure (min), indications, complications, reason for termination, performance of a biopsy and patient disposition. Diseases or procedures related to the abdomen or pelvis was recorded. Supervised family practice residents performed the procedures. Data analysis included simple descriptive, t-test, linear and logistic regression.

Results: The mean time for the procedure was 18 ± 9.3 minutes (17.2-19.6, 95% CI). The mean depth of insertion was 51.4 ± 12.6 cm (50.4-52.6 cm , 95% CI). Women who had pelvic surgery showed a decrease in depth of insertion (47 cm vs. 53 cm $p=0.002$, t-test). Multiple linear regression showed performance of a biopsy predicts time of procedure, controlling for other variables. Logistic regression for depth of insertion showed patients who had a biopsy had increased odds and patients with a history of pelvic surgery had decreased odds of the exam reaching 55 cm, controlling for other variables.

Conclusion: Family practice residents who, on average, achieve a depth of insertion of 50 cms in less than 20 minutes may be considered technically competent in flexible sigmoidoscopy. Residents who frequently perform biopsies or have patients with a history of pelvic surgery may have different averages. Exclusion of these types of patients from data analysis is necessary for an accurate assessment of competency.

Presentation Section: MER

Title: The Effects of Thermocouple Sensor Placement on Neonatal Skin Temperature Measurement

Presenter: Susan E. Chambers, BSN

Department: Nursing

Mentor: Lori A. Loan, RN, MS

Abstract:

Purpose: This study was directed toward investigation of the effects of thermocouple sensor placement on skin temperature readings in full term and preterm neonates. Skin temperature probes are commonly used in neonatal units. However, little is known about the influence of probe placement site on accuracy of temperature measurement. Many neonatal units limit probe placement to the torso and over non-bony prominences or two or more probes are used simultaneously to avoid having the infant lie on the probe when his/her position is changed. This descriptive study included 40 infants (20 from MAMC and 20 from Children's Hospital, Seattle) and was designed to objectively evaluate several common nursing practices and beliefs regarding the care of neonates and the placement of temperature probes. The study sought a physiologic basis to support and validate nursing practice.

Hypotheses: (1) There is no difference in the skin temperature readings between probes placed on the abdomen, back, axilla or heel of the infant. (2) There is no difference in infant skin temperature readings when the infant is lying-on vs. not lying on the temperature probe.

Methods: Four body sites were studied simultaneously through the use of a small thermocouple sensor and two-channel continuous readout device. Data were collected for 1 hour with the infant in each of two common positions: supine and prone. Environmental temperature and basic demographic data were also collected for each subject and study period. Descriptive statistics were used to examine differences in temperature readings. Further analysis examined changes in temperature between the four sites and between periods of lying-on vs. not lying-on the temperature sensor using ANOVA-RM.

Findings and Conclusions: Data are currently being analyzed and results and conclusions will be ready for presentation prior to MAMC Research Day.

Presentation Section: MER

Title: Parental Assessment of Psychologic Adjustment in Children with Asthma: A Comparison of the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children (BASC)

Presenter: CPT (P) Veronica R. Baechler, MC

Department: Developmental Pediatrics

Mentor: COL William O. Walker MC & COL Patrick C. Kelly MC

Abstract:

Hypothesis: Behavior rating scales have been utilized in the assessment of children with potential psychosocial and behavior problems particularly those affected with chronic medical illness. The BASC and CBCL rating scales have been endorsed as having high correlation in similar behavior scales in a normative population of children. However, there have been no studies evaluating correlation between the two in children with chronic illness. We hypothesis that the BASC and CBCL correlate well in an independent study of children with asthma. Furthermore, we suspect that children with asthma have higher levels of psychosocial maladjustment than healthy peers.

Methods: Subjects include 68 children with asthma, 8 to 16 years of age. Parents of the subjects completed BASC and CBCL questionnaires about the subject. T scores indicated level of clinical significance of behaviors endorsed in the questionnaires. Pearson Correlation Coefficient evaluated correlations between the BASC and CBCL in our population of asthmatic children. Chi square analysis assessed whether there was an increase in clinically significant psychosocial dysfunction in children with asthma. Fisher Exact Test analyzed the frequency of psychosocial difficulties in children with moderate to severe disease compared to those with mild asthma.

Results: Correlations between the BASC and CBCL in our population were similar to those obtained in the normative population. A significantly higher frequency of psychosocial maladjustment by questionnaire was observed in the school age group of children with asthma.

Conclusion: Since the BASC was shown to have good correlation with the CBCL in our population of children with asthma, then it presents an alternative in measurement of behavioral difficulties. As suggested by our findings, children with chronic illness are at greater risk for psychosocial dysfunction than a population of healthy children.

Presentation Section: MER

Title: Evaluation of Clinical Standards Implementation at Madigan

Presenter: MAJ Brian Harrington, MC

Department: Family Practice

Mentor: COL Joseph Yetter, MC

Abstract:

Introduction: Clinical standards are authorized and defined statements of minimum levels of acceptable performance or results. Their implementation has received greater emphasis than other practice guidelines. Attitudes, awareness, access and use are critical factors to address when implementing a program. This survey assesses these factors among primary care providers at Fort Lewis.

Methods: A 32 question confidential survey was distributed to all 201 primary care specialists at Fort Lewis, including family practice, pediatrics, the adult primary care clinic, the emergency department and all active duty clinics. Reminders were delivered via CHCS. Data were analyzed with SPSS using descriptive statistics, chi-square, linear and logistic regression.

Results: The response rate was 72 percent (144/201). Eighty-eight percent were aware of clinical standards. Eighty-nine percent felt clinical standards improved patient care. Sixty-three percent listed CHCS as an access point for clinical standards even though CHCS does not contain them. Ninety-three percent support further development. Over one-third access the standards at least weekly. Access barriers included the inability to access during clinic (66%) and not having a PC in their office (53%). Easier access to standards while seeing patients (81%) is a key to improved use. Regression analysis showed that older providers and female providers and were less likely to have viewed or used the standards. Increasing time at Ft. Lewis was associated with increased use and better regard for the standards.

Discussion: Primary care providers had an overall positive attitude towards clinical standards. However, they seemed to confuse them with other practice guidelines. Providers are incorporating clinical standards into their practice. Older providers may have established clinical scripts and be reluctant to change. Women reviewed and used the standards less than men. This survey provides information for implementing clinical standards programs. Since attitudes appear favorable, improvement efforts should focus on awareness and access.



**MADIGAN RESEARCH DAY
AWARD WINNER
"Interdisciplinary" Category**

Experimental Design Session

Moderator: Katherine H. Moore Ph.D.

The category of “Experimental Design” encompasses the basic science projects. This type of research typically will investigate a fundamental principle of cell biology or physiology, and is the easiest in which to appreciate the values of hypothesis, objective and experimental design. The importance of adherence to these values becomes clear in the ethical imperatives of clinical research. These ethical imperatives involve protection of research subjects, whether animal or human. Above all, rigorous experimental design, facilitates the search for truth, aiding investigators in avoiding fatal flaws. These flaws may remain unrecognized and could lead to false conclusions. We have seen in the papers already presented today that the importance of a hypothesis, objective and good experimental design is consistent throughout any research, including approach to managed care, military unique research and medical education.

The range of topics and experimental models that was presented last year was impressive. At least two of the studies have been published, one in Cancer, the other in Urologic Oncology. Many of the others have been presented at national and international meetings.

The papers being presented today are equally impressive. One was truly a collaborative effort, involving sample collection in the Antarctic, three were primarily performed in the DCI laboratories and animal care facility, and two were performed in the patient care arena. All project the creativity present within the Madigan staff.

Some may view basic science research projects as less important or necessary in a setting such as Madigan compared to other types of research. However, another view is that basic science projects and the disciplined approach necessary for their success are a critical step in the training of physicians and

nurses who then proceed to complete other projects and become the mentors for the next generation. The principles of study design, execution, and data analysis that are learned in a laboratory or carefully designed project utilizing human or animal subjects are relevant to the success of any research project. As in industry, in medicine the time lag between an idea being in the realm of basic science and practical application is becoming much shorter. I would not be surprised to find that some of the ideas presented in today's Experimental Design section will soon be applied to patient care. In many ways, researchers at Madigan are at the front of the wave that is leading the pathway of change in medicine.

Presentation Section: Exp

Title: Changing Thyroid Hormone Status and Cognitive and Mood Alterations During Prolonged Antarctic Residence: Effect of Thyroxine Supplementation in the Polar T3 Syndrome

Presenter: CPT Nhan Van Do, MC

Department: Medicine, Internal Medicine

Mentor: COL Lester H. Reed, MC

Abstract:

Introduction: Humans who live in Antarctica for greater than four months develop changes in their hypothalamic-pituitary-thyroid-tissue axis known as the Polar T3 Syndrome. To further test the functional relevance of the biochemical changes in thyroid hormone economy in this syndrome, we followed cognitive and mood alterations with serum measures of thyroid hormones before, monthly, and at the completion of 11 months Antarctic Residence (AR) of 12 euthyroid subjects using a double blind placebo control study design.

Methods: All subjects took placebo for the initial 5 months (period 1) then during remaining 6 months (period 2), subjects were randomized into a Levothyroxine (LT4) treated group (T4G) and a Placebo Group (PG). Computerized matching-to-sample (M-to-T) testing measured working memory and attention while Profile of Mood States (POMS) testing and Epidemiological Depressive-Scale measured mood.

Results: Serum FT4 declined from baseline by a mean of - 4.72% ($p < 0.017$) in the PG and increase by +7.6% ($p < 0.02$) in the T4G. FT3 declined in both group by -3.67% ($p < 0.02$). Serum TSH in the PG changed over the study in a sine distribution ($p < 0.01$) with peaks in November and July. There was a decline of -13% ($p < 0.026$) in M-to-T scores at the end of period 1, and with LT4 during period 2, the cognitive function of T4G returned to +3.16% of the baseline score while the PG remained -11.1% below baseline ($p < 0.01$). The T4G reported less fatigue ($p < 0.01$) and confusion ($p < 0.05$) compared with the PG. Increased serum TSH preceded high scores for depression, anxiety, anger, lack of vigor, and mood disturbance ($p < 0.001$) during the austral winter of Period-2. Decreased FT3 preceded high scores for fatigue and confusion ($p < 0.05$) during Period-2.

Conclusion: Prolonged Antarctic residence is associated with declines in cognitive performance and mood which are improved with supplemental thyroxine compared with placebo treatment.

Presentation Section: Exp

Title: The Effect of Preoperative Administration of Ketorolac on Postoperative Bleeding in Anterior Cruciate Ligament Repair

Presenter: CPT Angela Quintanilla AN & CPT Anne M. Silvasy AN

Department: Nursing

Mentor: LTC Howard Burtnett, AN

Abstract:

The use of ketorolac as a preemptive analgesic has been limited in the preoperative setting due to its potential effects on hemostasis. This study is designed to evaluate the effect of a single dose of preoperative ketorolac on platelet function and measured blood loss in subjects undergoing anterior cruciate ligament reconstruction. The sample will consist of 34 patients between the ages of 18 and 65 who have no contraindications for the administration of nonsteroidal anti-inflammatory agents. Subjects will be randomized to an experimental group that will receive 30 mg of ketorolac preoperatively or a control group that will receive an equal volume of 0.9% normal saline. Platelet aggregation tests will be drawn prior to the administration of the drug or placebo and then again 45 minutes later after the incision has been made. Total postoperative blood loss will be measured in milliliters by a hemovac drain. The results of this study could further the use of ketorolac in this population as a preemptive analgesic.

Presentation Section: Exp

Title: The Association Between Telomerase, p53 and Clinical Staging in Colorectal Cancer

Presenter: CPT Tommy Brown, MC

Department: General Surgery Service

Mentor: CPT Wade Aldous, MS

Abstract:

Background: p53 mutations are a proposed etiology of tumor activation while telomerase may serve as a key enzyme for maintenance of tumor cell proliferation.

Methods: Telomerase activity levels were measured in colorectal adenocarcinomas and corresponding normal tissue using a modified telomeric repeat amplification protocol, and identified p53 mutations using immunohistochemical staining. Results were compared with staging data using regression analysis.

Results: Telomerase activity was present in 23/23 (100%) of the tumors and only 2 (9%) of normal specimens ($p < 0.0001$). p53 mutations were present in 18/23 (78%) of the tumors. No significant correlation between p53 mutations, telomerase activity levels, and staging was found.

Conclusions: Telomerase activity in 100% of the tumors suggests telomerase activation is a universal event in colorectal tumor progression, however telomerase activity appears to be independent of p53 mutations and clinical staging.

Presentation Section: Exp

Title: The Effects of Mitomycin-C on Airway Wound Healing After Laryngotracheoplasty and Stenting in a Pig Model

Presenter: CPT George Coppit, MC

Department: Surgery, Orthopedics

Mentor: MAJ Jonathan Perkins, MC & MAJ Andrew B. Silva, MC

Abstract:

Objective: To assess the effects of mitomycin-C (MTC), a potent fibroblast inhibitor, on airway wound healing after augmentative reconstructive procedures and stenting.

Design: A prospective, blinded, randomized controlled animal study.

Subjects: 18 domestic pigs (*Sus scrofula*), divided into 6 groups of 3 animals each.

Interventions: Each animal underwent single-stage laryngotracheoplasty (SS-LTP) with auricular cartilage grafting and stenting. Group 1 and 2 animals were sacrificed on postoperative day 3 and 7, respectively. Group 3 and 4 animals underwent endoscopy on postoperative day 7 with stent removal and application of MTC or placebo (normal saline) at the grafted site. Group 3 animals were sacrificed on postoperative day 14, and group 4 animals on postoperative day 21. Segments of reconstructed airway were evaluated grossly and histologically for all animals.

Main Outcome Measures: Healing, reepithelization, graft incorporation, and airway diameter.

Results: Two-thirds of the animals demonstrated some degree of stent collapse on endoscopy. Graft site infection occurred in 50% of animals, with a trend towards resolution at 21 days postoperatively. Granulation tissue formation was seen in all animals, and resolved with stent removal. MTC did not affect the acute inflammatory response, nor reepithelization of the graft site. Airway diameter was smaller overall in the treated animals; however, they demonstrated better incorporation of the graft with fibrocartilage proliferation of the graft. Untreated animals demonstrated liquefactive necrosis of the graft.

Conclusions: MTC seems to prevent the liquefactive necrosis of SS-LTP grafts, allowing for improved graft incorporation. While the airway diameter was smaller in the treated animals, this may reflect improved structural integrity seen with better graft incorporation. MTC did not seem to affect the acute inflammatory response to SS-LTP or stenting, nor did it affect the reepithelization of the graft site. Further studies are needed to assess the effects of MTC on long term healing and stenosis following SS-LTP.

Presentation Section: Exp

Title: The Expression Of Adrenomedullin And Its Receptor In The Human Placenta

Presenter: MAJ Christina C. Apodaca, MC

Department: OB/GYN, Maternal-Fetal Medicine

Mentor: LTC Byron Calhoun, MC, USAF

Abstract:

OBJECTIVE: Our purpose was to identify the presence of adrenomedullin protein RNA and adrenomedullin receptor RNA in the various tissues of the human placenta and to assess semi-quantitatively the degree to which these components are expressed.

STUDY DESIGN: We obtained tissue samples from five placentas of women with uncomplicated pregnancies and two placentas of women with oligohydramnios. Five grams each of placental amnion, chorion, cotyledon, umbilical vein and umbilical artery were dissected, isolated, and frozen. Total RNA was extracted and the concentration and quality of RNA assessed using spectrophotometry.

A polymerase chain reaction was developed using a cell line known to be positive for adrenomedullin and its receptor. Total RNA was isolated from this cell line and used as a positive control in all experiments. b-2 microglobulin, a ubiquitously expressed mRNA served as control for the integrity of RNA isolated from the placental tissues.

Adrenomedullin was detected using primer sets with a predicted product of 291 base pairs. A nested probe was used to detect the specific adrenomedullin product. For adrenomedullin receptor amplification, a rat primer was used yielding a 471 base pair product. An antisense primer was used to make cDNA from the RNA template for both adrenomedullin and its receptor. Polymerase chain reaction products were analyzed using electrophoresis with 2 % agarose gels then transferred onto nylon filters. Southern blot analysis was then performed using ³²P-labeled oligonucleotide probes.

Immunocytochemistry using an antibody to human adrenomedullin was used to identify the presence of adrenomedullin in tissues where adrenomedullin was found by PCR. Tissue sections were stained with antibody against adrenomedullin, using an avidin-biotin-peroxidase complex technique.

RESULTS: With the use of PCR and Southern blot analysis, adrenomedullin RNA and adrenomedullin receptor RNA were identified in various placental tissues.

CONCLUSION: The demonstration of adrenomedullin and its receptor in the various tissue components of the placenta suggest that the placenta may function as an autoregulatory organ, producing adrenomedullin locally to affect local paracrine and autocrine vasoactive changes.

Presentation Section: Exp

Title: Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry

Presenter: CPT Michael W. Quinn, MC

Department: Medicine

Mentor: COL Thomas A. Dillard, MC

Abstract:

Introduction: Tricuspid valve regurgitation (TR) has been reported to decrease the accuracy of pulse oximetry in one study comparing patients with severe TR and patients without TR (Stewart and Rowbottom, Anesthesia 1991; 46: 668-670). TR may complicate cardiac failure and cor pulmonale in patients in whom monitoring with pulse oximeter oxygen saturation (SpO₂) is desirable. We sought to confirm the effect of severe TR on the accuracy of SpO₂ compared to the oxygen saturation as determined by co-oximetry (SaO₂) of arterial blood and to determine whether intermediate degrees of TR explain significant variability between SaO₂ and the SpO₂. Methods: Patients were grouped according to echocardiographic degree of TR: none; mild; moderate; moderate to severe; and severe. We obtained arterial blood by radial artery needle puncture while simultaneous measurement and graphing of the % SpO₂ by pulse oximetry was obtained (Marquette Transcope 12 system).

Results: Mean data:

| Degree of TR | %SaO ₂ | %SpO ₂ | %SaO ₂ - %SpO ₂ |
|-----------------|-------------------|-------------------|---------------------------------------|
| None | 96.9 | 97.0 | -0.1 |
| Mild | 96.8 | 97.1 | -0.3 |
| Moderate | 96.0 | 97.0 | -0.98 |
| Moderate-Severe | 96.9 | 98.9 | -2.0 |
| Severe | 96.5 | 98.3 | -1.83 |

The maximum difference between means is 1.9%.

Conclusion: These data confirm a small error in SpO₂ associated with TR. Our findings suggest that as TR becomes more severe, pulse oximetry over-estimates the oxygen saturation of arterial blood and refute the findings of Stewart and Rowbottom.

CASE REPORT SESSION

Moderator: COL Romeo Perez, MC

Science and medicine depend on communication, especially written communication from one scholar to another, to transmit observations, conclusions, interpretations, and speculations. The peer-review system has developed over the last 300 years as the principal form of this communication. The critical importance of the timely observation, thoughtfully researched, and carefully presented for review by ones peers remains the keystone for most of the advances in clinical investigation and clinical practice. It is through these little discoveries that a specific hypothesis can be formulated and tested in well-designed clinical studies. New diagnostic methods and therapies are validated through clinical trials. The series of presentations in this segment of the program will focus on brief descriptions of cases of a particular condition that are both unusual and provide new insight into diagnosis and or management. A brief review of pertinent literature and appropriate management implications are included.

Presentation Section: CR

Title: Incidence of Adrenal Tumors in the Ferret Colony

Presenter: SPC(P) Sandra Fogelman 91T

Department: Clinical Investigation

Mentor: CPT SF Felt VC: DVM 1st Special Forces Group

Abstract:

Pediatric advanced life support is an essential training program for Madigan Army Medical Center personnel. An in vivo pediatric model for intubation provides medical personnel hands on training to enhance their skills. Adult ferrets offer the ideal model for pediatric intubation. The airway of a neonate is very similar to that of the adult ferret, which provides realistic training. The ferret colony has now been maintained for 5 years, with some of the animals reaching older ages. Over the past year, a reoccurring problem and growing concern is adrenal disease in our geriatric ferrets. Ferrets with adrenal disease may have a suppressed immune system, making them more susceptible to microbial infections, as well as other health care problems.

The underlying cause of adrenal tumors in ferrets is unknown. Various etiological factors have been implicated including: premature neutering, diet, the lack of exposure to natural photoperiods, and genetics. Clinical signs vary for each ferret. One of the most significant findings in our colony was symmetrical alopecia.

Diagnosis of adrenal disease can be made based on physical examination findings. Routine blood work in ferrets with diseased adrenal glands are usually unremarkable, occasionally a complete blood count may reveal regenerative or nonregenerative anemia and an elevated ALT (Alanine Aminotransferase). Ultrasonography can be a highly reliable technique for diagnosing adrenal disease in ferrets. It can show the measurements and location of the adrenal gland. Width greater than 3mm is correlated with adrenal disease, although length does not seem to be a factor. The adrenocorticotropin (ACTH) hormone stimulation test and dexamethasone suppression test are useful in other mammals but not diagnosing adrenal disease in ferrets. Measurements of certain plasma steroids may be a reliable means of diagnosis. Exploratory laparotomy is an extremely useful tool for diagnosing adrenal disease, and provides curative solution with a diseased adrenal gland. Examination of the tissue by a pathologist is the only definitive diagnoses of adrenal disease in ferrets.

Samples from our colony showed that the plasma steroid tests may be specific but not sensitive for early diagnoses. Evaluation of the assays showed that they were valid for measurement of steroids in ferret plasma, but the steroid hormones in our animals (three affected animals vs. five young unaffected animals) were below the level of detection of the tests. Tissue samples were taken from the three affected animals and sent to Armed Forces Institute of Veterinary Pathology confirming adrenal disease.

The facilities at the Department of Clinical Investigation's Laboratory Animal Resources Service ensure the highest quality veterinary care for all laboratory animals. The veterinarian and animal technicians play a vital role of maintaining the health and well being of the ferret colony housed in the Department of Clinical Investigation.

Presentation Section: CR

Title: Unilateral Congenital Lymphedema Associated with Intestinal Lymphangiectasia, Elevated Liver Transaminases, and Hypopigmentation

Presenter: LTC William M. Campbell, MC

Department: Pediatrics

Mentor: Laura Martin, M.D., FAAP, FACMG

Abstract:

We report on a 16 year-old Filipino female with an unusual presentation of congenital lymphedema. The patient was noted at birth to have right facial puffiness that has persisted. She was later noted to have hypopigmented patches and increased circumference of her right extremities. Liver transaminases were persistently elevated at age 15 years. Serum bilirubin, alkaline phosphatase, copper, ceruloplasmin, and iron studies were normal. Evaluation for infectious causes of her hepatitis was negative. Past medical history was significant only for a single, brief generalized seizure at age 10 years. Growth parameters, development, and academic achievement were normal. Family history was significant for a maternal aunt with hypopigmented patches and several relatives with premature graying of the hair. There were no relatives with lymphedema, autoimmune disorders, or liver disease. Physical examination revealed right facial fullness but no dysmorphic features. There was pretibial pitting edema on the right, along with mild pitting and ridging of the nails. Right upper and lower extremity circumferences were increased compared to the left. There was no limb length discrepancy. Multiple ½ to 1-cm areas of hypopigmentation were noted on the extremities, right greater than left. She had scattered coarse, white hairs. Extremity radiographs showed increased reticulation in the subcutaneous fat on the right. Abdominal MRI showed right superficial femoral vein ectasia and focal dilatation of the distal right saphenous vein. MRI of the extremities showed asymmetry of subcutaneous fat laterally and anteriorly on the right. Liver needle biopsy showed mild, nonspecific portal and focal lobular chronic inflammatory changes. Duodenal biopsy showed marked lamina propria lymphangiectasia, consistent with congenital lymphedema. The constellation of findings in this patient, lymphedema, intestinal lymphangiectasia, elevated liver transaminases, patchy hypopigmentation, and coarse, white hairs, has not been described in the English literature and may represent a new syndrome.

Presentation Section: CR

Title: Pseudo-dissection of the Main Pulmonary Artery on Computed Tomography

Presenter: CPT Adam Benson, MC

Department: Radiology

Mentor: MAJ Sean P. Murray, MC

Abstract:

OBJECTIVE: To evaluate the main pulmonary artery on helical contrast enhanced chest CT for an artifact that could be readily mistaken for a pulmonary artery dissection.

MATERIALS AND METHODS: Following presentation of two index cases with findings suggestive of pulmonary artery dissection, 102 consecutive, contrast enhanced, helically acquired chest CT exams were evaluated retrospectively for similar artifacts. All studies were performed on a GE helical CT scanner. Indications for these studies were cancer staging or follow up, (n= 45); evaluation of mass or adenopathy, (n= 27); infection/inflammatory, (n=9), trauma, (n= 5); and miscellaneous (n= 16). The main pulmonary artery was evaluated and abnormalities within the main pulmonary artery were characterized.

RESULTS: Six of 102 (6%) helical chest CT studies exhibited artifacts with potential to represent a pulmonary artery dissection. These 6 cases were less worrisome than the two index cases, and were not prospectively identified. The most common location of this artifact was the left lateral main pulmonary outflow tract, and was noted on multiple (2 to 4) contiguous CT images. An additional 32 of 102 (32 %) demonstrated abnormalities within the pulmonary artery which were clearly artifactual. These artifacts are characterized.

CONCLUSION: Artifacts within the main pulmonary artery are more common than previously reported. Pseudo-dissection of the pulmonary artery is a previously unrecognized artifact, and is related to wall motion of the main pulmonary artery. Knowledge of this pseudo-dissection and other common artifacts may avert further invasive and noninvasive diagnostic studies.

Presentation Section: CR

Title: Pilomatrixoma of the Head and Neck

Presenter: MAJ Richard W. Thomas, MC

Department: Otolaryngology/Head and Neck Surgery

Mentor: Jonathan A. Perkins, MC

Abstract:

Background: Pilomatrixoma is a benign, usually asymptomatic neoplasm arising from the hair follicle matrix cells and often involves the head and neck area. The purpose of this paper is to describe our experience with patients treated for a pilomatrixoma during the past five years, and to compare these findings with previously reported results.

Methods: A five-year retrospective chart review was conducted to identify those patients treated for a histologically confirmed pilomatrixoma involving the head and neck region. Medical records were examined for presenting signs and symptoms, lesion characteristics, and outcome of treatment rendered to these patients.

Results: The medical record review identified fifty-six patients with a histologically confirmed pilomatrixoma. Of these, twenty-six patients (46%) with a mean age of 32.7 years were ultimately included in the study. All patients were treated for solitary tumors by simple surgical excision and closure. There were no reported adverse outcomes and no recurrences of neoplasm at the surgical sites.

Conclusions: Our results support simple surgical excision and primary closure as the treatment of choice for these tumors.

Presentation Section: CR

Title: Findings of Fibular Hemimelia Syndrome with Radiographically Normal Fibulae

Presenter: CPT Clark P. Searle, MC

Department: Surgery, Orthopaedic Surgery

Mentor: Dr. Paul Caskey and LTC Craig Ono, MC

Abstract:

Purpose of Study- Fibular hemimelia is the most common cause of limb deficiency in the lower extremity. The syndrome consists of variable degrees of fibular hypoplasia as well as other associated findings, including limb shortening, absent lateral rays of the foot, ball and socket ankle joint, tarsal coalition, hypoplasia of the lateral femoral condyle with knee valgus, tibial spine hypoplasia and cruciate ligament instability. We have noted a number of patients with features of the fibular hemimelia syndrome, but with radiographically normal fibulae. This study was undertaken to further define this group.

Methods and Materials- A retrospective and prospective review of the hospital records and radiographs of all limb deficiency patients at the Shriner's Hospital for Children, Spokane Unit over a 72 year period, 1925-1997, was conducted.

Results- We identified 16 limbs in 14 patients with findings of fibular hemimelia syndrome with radiographically normal fibulae, out of 149 limbs in 95 patients with features of fibular hemimelia. Thirteen of 16 had absent lateral rays with either ball and socket ankle joint, tarsal coalition or both. Of these 13, six had limb shortening of at least 4%. Five of the 13 were in patients with bilateral involvement, so shortening could not be assessed. The other two did not have adequate information to determine limb shortening. Five of the 13 had knee valgus (38%), 4 had hypoplastic tibial spines (31%), 3 had cruciate instability (23%), and 3 had clubfeet (23%). Three limbs in 3 patients did not have absent lateral rays, but had at least 2 other features of fibular hemimelia syndrome. All had ball and socket ankles and tarsal coalitions. Two had shortening of 4%, and the other had bilateral involvement. Two also had fusion of the 4th and 5th rays.

Conclusion- We feel that these patients represent a mild subset of fibular hemimelia syndrome, and propose that they be classified as Type 0 fibular hemimelia. These 16 limbs comprised 11% of our total fibular hemimelia population, and constitute a previously undescribed group of mild fibular hemimelia syndrome.

CONCURRENT POSTER SESSION

Posters were displayed in a separate room, and available for viewing all day.

Presentation Section: Poster

Title: Refractive Changes Due to Hypoxia Following LASIK Corneal Surgery

Presenter: MAJ Mark L. Nelson, MC

Department: Surgery, Ophthalmology

Mentor: COL Thomas Mader, MC

Abstract:

Purpose: To observe changes in corneal shape, thickness, and visual acuity that may take place in patients whose corneas are exposed to hypoxia following LASIK (laser in situ keratomileusis) corneal surgery. **Methods and materials:** Twenty LASIK patients and twenty myopic control patients were exposed to ocular surface hypoxia in one eye by filtering humidified, compressed 100% nitrogen (0% oxygen) through an air-tight goggle system at sea level for 2 hours. The other eye was exposed to humidified, compressed air (21% oxygen) simultaneously through the air-tight goggle system. Video keratography, cycloplegic refraction, and pachymetry were evaluated using repeated measures analysis of variance. **Results:** There was no significant change in corneal topography or cycloplegic refraction in either the myopic control group or the LASIK group after two hours exposure to hypoxia. There was a significant increase in central corneal thickness in both control and LASIK eyes exposed to hypoxia, and no change in eyes exposed to compressed air. **Conclusions:** These results suggest that corneal hypoxia does not cause significant refractive changes in LASIK patients, unlike patients who have had radial keratometry (RK) corneal surgery. This has important implications for refractive surgery patients who perform activities at high-altitudes.

Presentation Section: Poster

Title: Atypical Hyperplasia in the Era of Stereotactic Core Needle Biopsy

Presenter: CPT Tommy Brown, MC

Department: General Surgery Service

Mentor: LTC William Williard, MC

Abstract:

Objective: To characterize both atypical hyperplasia (AH) and the malignancies typically present at open surgical biopsy in women diagnosed with AH by stereotactic core needle biopsy (SCNB).

Methods: Patients with AH diagnosed by SCNB were advised to undergo surgical biopsy to rule out an associated malignancy. Mammography findings, pathology reports and follow-up data were analyzed.

Results: AH was identified by SCNB in 38 of 893 (4.3%) patients. Carcinoma was identified in 12 of 33 (36.4%) patients who went on to surgical biopsy. Ductal carcinoma in situ (DCIS) was present in 11 of the 12 patients with malignancy. There were no characteristic mammographic findings which would identify patients with carcinoma.

Conclusions: When SCNB returns a diagnosis of AH there is a substantial risk of an associated malignancy in the breast. There appear to be no definitive criteria to distinguish which patients harbor a malignancy, and surgical biopsy should always serve as an adjunct diagnostic procedure.

Presentation Section: Poster

Title: Prolonged Chest Discomfort Associated with Concomitant Use of Lisinopril and Fluvastatin

Presenter: CPT Ricardo Nannini, MS

Department: Pharmacy

Mentor: LTC(P) Dennis R. Beaudoin, MS

Abstract:

Adverse reactions associated with lisinopril include chest discomfort, myocardial infarction, angina, joint pain and shoulder pain. These reactions have been reported to occur in less than one percent of patients being treated with lisinopril. Patients taking fluvastatin have reported back and muscle pain. Documentation comparing the incidence of such adverse reactions attributed to the concomitant use of lisinopril and fluvastatin with either agent alone is not available. However, the authors have identified several cases in which patients being treated with both agents presented with the primary complaint of prolonged chest discomfort, shoulder pain, back pain and/or angina. In these cases, myocardial infarction was ruled out based on the lack of ECG changes consistent with ischemia or necrosis and the absence of elevated cardiac enzymes. The reported chest discomfort, pain or angina resolved upon discontinuation of lisinopril, fluvastatin or both agents. A retrospective evaluation is proposed to identify the relationship between the concomitant use of these agents and the occurrence of prolonged chest pain, shoulder pain and/or angina.

Presentation Section: Poster

Title: Diffuse Fungal Myositis: Diagnosis, Treatment, and the Clinical Utility of Tagged White Blood Cell Scans

Presenter: CPT Jennifer E. Jorgensen, MC

Department: Medicine, Internal Medicine Service

Mentor: LTC Joseph T. Morris III, MC

Abstract:

LEARNING OBJECTIVES. 1) Diagnose diffuse fungal myositis. 2) Assess treatment success using clinical and radiographic data. 3) Recognize the clinical utility and limitations of tagged white blood cell scans.

CASE. An otherwise healthy 36-year-old man was diagnosed with acute myelogenous leukemia and underwent induction chemotherapy. As anticipated he became neutropenic and subsequently developed fevers. He was initially treated with broad spectrum antibiotics and clinically improved. Vancomycin and later Amphotericin B were added when he became febrile again. Blood cultures revealed a yeast and *S. hemolyticus*. The patient developed a diffuse, papular, non-blanching rash and complained of muscle pain and weakness in his extremities. On exam he was areflexic and had diffusely decreased strength. A few days later the patient experienced respiratory failure and circulatory collapse requiring transfer to the ICU where he was intubated and treated with vasopressors. He continued to be febrile and demonstrate septic hemodynamic parameters, which prompted an aggressive search for an infectious foci. An abdominal CT was unrevealing. An indium labeled leukocyte study demonstrated diffuse uptake of both upper and lower extremities. This was consistent with either leukemic infiltration of skeletal muscle or a diffuse infectious myositis. Excisional biopsy of the posterior gastrocnemius demonstrated numerous budding yeasts and yeast in chains on special stains. No leukemic infiltrates were identified. Culture of fine needle aspirate of the muscle grew only *S. hemolyticus*. The patient was treated with vancomycin, amphotericin B, and fluconazole for an infectious myositis. A repeat indium labeled leukocyte scan was performed after 14 days of antimicrobial therapy and showed partial resolution. A third scan showed resolution of the fungal myositis.

DISCUSSION. Diffuse fungal myositis has been reported in the literature a few times. However, none of these patients survived and only one was diagnosed ante-mortum. The diagnosis of diffuse fungal myositis should be considered in neutropenic patients who present with the triad of diffuse myalgias, fever, and rash. Either positive blood cultures or characteristic muscle biopsies may confirm the diagnosis. The dilemma of how to determine if the infection has cleared so that chemotherapy may be resumed has not been addressed in the literature. We propose that a tagged white blood cell scan may be a helpful, less invasive method than repeat muscle biopsy of determining clearance of infectious myositis.

Presentation Section: Poster

Title: Cost Consequences of Implementation of an Early Obstetrical Discharge Program in a Military Teaching Hospital

Presenter: CPT Christine Kovac, MC

Department: OB/GYN

Mentor: LTC Byron C. Calhoun, MC, USAF

Abstract:

Objective: To evaluate the cost consequence of a voluntary early obstetrical discharge program in a military teaching hospital.

Methods: The study involved a control group of routine obstetrical discharge patients with uncomplicated vaginal delivery from 1 Mar-31 Aug 94 and the study group of early obstetrical discharge (24-48 hours) patients with uncomplicated vaginal delivery from 1 Mar-31 Aug 96.

Results: There were 1,042 total control patients with routine vaginal delivery from 1 March-31 August 1994 totaling 2668 hospital days with a mean number of hospital days of 2.56 per patient. The study group of early obstetrical discharge patients from 1 Mar-31 Aug 96 with uncomplicated vaginal delivery encompassed 1,050 patients with 1,965 hospital days with mean hospital days of 1.87 per patient. The total cost of admissions (cost calculation of \$1,221/hospital day) fell from \$3,257, 628 in the routine discharge group to \$2, 399, 625 in the early discharge cohort showing a total cost savings of \$858,003 over the six months study period. The average cost per obstetrical admission for routine vaginal delivery fell from \$3,126/ day to \$2, 285/ day without an increase in the postpartum pediatric or maternal adverse outcomes.

Conclusion: A early obstetrical discharge program at a military teaching hospital showed significant cost savings without concomitant increase in pediatric or maternal adverse outcomes.

Presentation Section: Poster

Title: Factors Associated with Hospitalization in Kidney Transplant Patients

Presenter: LTC Laura R. Brosch, AN

Department: Nursing, Nursing Research Service

Mentor: COL Bonnie Jennings, AN

Abstract:

Rehospitalization following kidney transplant (TX) surgery is a recurrent and costly event that detracts from the ultimate aims of the intervention. The purposes of this study were to: 1) estimate the rate of rehospitalization during the 90 days following surgery; 2) identify reasons for readmission; 3) identify patient factors associated with the likelihood of rehospitalization. Using a retrospective cohort design, data were abstracted from a consecutive series of 300 patients (mean age = 46.9 yrs \pm SD = 12.59) who received kidney TXs between March 1995 and February 1997. Twenty-two demographic and clinical factors were examined for their relationship to rehospitalization. The median length of initial hospital stay was 9 days (IQ range=7 - 15). Among the 300 patients, 161 patients (53.7%) were readmitted. The cohort experienced a total of 267 readmissions during the study period. Readmissions were primarily for infection (28.8%); acute rejection (27.3%); perinephric/ureteral problems (13%) and fluid and electrolyte imbalances (8%). The length of initial hospital stay (ILOS) was longer for recipients of kidneys, 60 years vs. kidneys < 60 years old: median = 14 vs.9 days, respectively, ($p < .001$). Patients with delayed graft function (DGF) also had significantly longer ILOS vs. those without: median = 17 vs. 8 days, respectively ($p < .0001$). Eleven of 22 patient-specific factors, significant in univariate logistic regression, were analyzed in a multivariate logistic regression model. Donor Age (O.R. 1.2, $p = .025$) and DGF (O.R. 2.53, $p = .008$) were significantly associated with the likelihood of rehospitalization. Charlson comorbidity score, donor/recipient CMV status, HLA-mismatch, donor source, immuno-suppression, technical complications, length of initial hospital stay, discharge disposition, and location of residence were not sufficiently associated with readmission to enter the model in the presence of donor age and DGF. Further research is needed to identify patient and treatment factors associated with readmission during the early posttransplant period, though findings suggest that the relation of donor age and DGF to readmission continue to be investigated.

Presentation Section: Poster

Title: Metastatic Crohn's Disease: Case Report and Literature Review

Presenter: LCDR Keith M. Ulnick, MC

Department: Surgery, Otolaryngology Service

Mentor:

Abstract:

Objective: Crohn's disease is a granulomatous inflammatory bowel disease with pathological findings of noncontiguous chronic inflammation along with noncaseating granulomas. Even though any segment of the gastrointestinal tract can be involved, it is uncommon to find it elsewhere. In this article we present a case of extraintestinal Crohn's disease with quiescent involvement of the lower gastrointestinal tract but flood involvement of the nasal cavity, supraglottic structures and skin.

Methods- A 45-year-old black male with known Crohn's disease, presented for evaluation of nasal obstruction. Physical examination revealed bilateral anterior nasal stenosis. Between 1985 and 1997, in conjunction with aggressive medical management the patient underwent laser procedures to correct this stenosis. None of these procedures were curative, but in combination with intensive medical therapy the frequency of surgical therapy was decreased. Follow-up visits demonstrated progressive hoarseness and physical examination revealed erythema and granulation tissue involving his supraglottic structures along with non-healing ulcerations of the scalp.

Results: A CO₂ laser was utilized to open the nasal passages by removing scar tissue. Direct laryngoscopy revealed edematous tissue with areas of granulation involving the false vocal folds and epiglottis. Histologically this was Crohn's disease, Post-operatively, his 6-mercaptopurine was increased two fold. The patient is still with disease but has noted improvement in his nasal airway over the past 11 months and only recently is experiencing nasal symptoms. The skin lesions are quiescent with pigmental changes remaining. Laryngeal examination reveals no change in the extent of supraglottic edema and erythema.

Conclusion: This case is unusual in that the disease process failed the standard medical management of systemic and topical steroids along with 6-mercaptopudne. With surgical intervention this process was slowed, but it remains a difficult management problem. This aggressive manifestation of Crohn's disease, which can be classified as metastatic Crohn's disease due to its intestinal and extraintestinal involvement, demonstrates the need to be aware of the existence of the disease and the requirement to be proactive in the management of these patients.

Presentation Section: Poster

Title: Prevention of Unintended Pregnancy in Female Soldiers

Presenter: LTC Diane M. Flynn MC

Department: Family Practice

Mentor: COL Roderick F Hume MC & COL Michael McCaffery MC

Abstract:

Objective: A comprehensive program to decrease unintended pregnancy was implemented at a large military installation.

Case: 55% of pregnancies in female soldiers presenting for prenatal care are unintended. To decrease unintended pregnancies, we instituted a program incorporating an educational intervention and enhanced access to reproductive health care. Participants are encouraged to explore their attitudes on contraception and to assume responsibility for their reproductive lives. The intervention will reach approximately 1000 women annually. Life table analysis will be used to measure program efficacy.

Discussion: There are no reports in the literature of interventions to decrease unintended pregnancy in military women. The program presented here addresses the five core goals of the Institute of Medicine Committee on Unintended Pregnancy: (1) reproductive health education; (2) increased access to contraception; (3) consideration of the role that feelings and attitudes play in contraception; (4) systematic program evaluation; and (5) stimulation of research.

Conclusion: This program represents the most comprehensive initiative to date with the objective of decreasing unintended pregnancy in female soldiers. If effective, it will have far-reaching implications for enhancing the quality of life of military families and for the prevention of unintended pregnancy in other populations.

Presentation Section: Poster

Title: Genetic Paradigm as Best Business Practice Model for Inherited Breast Cancer Susceptibility Testing: The Region 11 Demonstration Project Experience

Presenter: Jamilyn M. Daniels, MS CGC

Department: OB/GYN

Mentor: Charlene Holt, MD & COL Shelby R. Brammer, MC

Abstract:

Summary Description: The Region 11 Demonstration Project has provided the platform to experience and understand the complexities of implementing a genetic paradigm for testing individuals for inherited breast cancer susceptibility genes and offer the basis of our proposed best business practice model.

Purpose: Develop best business practice for offering pedigree analysis, genetic counseling, and genetic testing to a population of men and women at risk for inherited breast and ovarian cancer. Evaluate the molecular genetic laboratory services.

Setting: A Military Medical Center, with referrals from regional MTF's in Region 11.

Methodology: Due to the complexity of genetics testing many of our efforts have necessarily been under protocol (#97047). Clinical Pathway and the Counseling Program were presented last year. Since then we have adopted a process action committee (PAC) team under the leadership of the Northwest Lead Agent. The Director, Medical Genetics MAMC remains the Genetic Consultant, while the Chief, Department of Clinical Investigation provides additional oversight for this project. We have been successful in the completion of our program's objectives. We have organized our findings in a fashion to allow interpretive analysis of best business practice (benchmark) by providing the quantitative and qualitative data, graphical analysis of our experience, review of relevant recent advances, identification of challenges, and selective alternative solutions

Outcome Measures: Patient survey for level of risk and intensity of interest; compare laboratory turnaround times, final reports, responsiveness, and discrepant results.

Results: Survey: 311/526 patients completed survey: 56/311 had significant cancer pedigree, 40/56 wanted genetic counseling, 16 declined; of the 255 without significant cancer pedigree 55/255 wanted genetic counseling. Study IRB (#97047): 206 patients contacted. 106 declined to participate. 100 seen for genetic counseling, 30 eligible for genetic testing, 25 accepted, 20 completed results, 3 positive, 3 variants, 14 negative. 10/20 completed tests split samples; O 110 day average, > 90% final reports, <24 hr responsive; K 130 day average, 1/10 final reports, 5/10 discrepant findings, > 2 d response. Qualitative assessments of educational, outreach, recruitment and pathway completed.

Conclusion: Primacy of pedigree analysis, genetics counseling, and informed consent before laboratory testing allows for best business practice. Delay or discrepant results are the major source of frustration and anxiety for patients. Laboratory service with most turnaround time, 100% final reports, & most responsive staff should be Benchmark.

Recommendation: Genetic model should be used as the basis for best business practice for the integrated care approach to inherited breast cancer susceptibility testing.

Presentation Section: Poster

Title: Telomerase Activity in Cytologically Positive Bronchoscopy, Thoracentesis and Fine Needle Specimens

Presenter: Ravi Ramakrishna, MD

Department: Medicine, Pulmonary Service

Mentor: COL Thomas A. Dillard, MC

Abstract:

Purpose: The ribonucleoprotein enzyme telomerase occurs in immortal lines of mammalian cells including germ cells and most malignancies. The activity of telomerase has potential to emerge as a clinical tumor marker in prognosis or therapeutic options for lung cancer. Telomerase activity has been described in surgical and autopsy specimens of carcinomas but seldom in diagnostic specimens. We prospectively evaluated the feasibility of assessing telomerase activity in diagnostic specimens of thoracic neoplasma.

Methods: We assessed telomerase activity in twenty-five bronchoscopic, thoracentesis and fine needle specimens by gel electrophoresis and a PCR ELISA assay using a single blinded study design. The clinical specimens had cytologically confirmed malignancy consisting of 9 small cell carcinomas and 16 non-small cell lung carcinomas including 2 carcinomas metastatic to the thorax. In addition, we noted an absence of significant telomerase activity by the gel electrophoresis technique in four patients with pneumonia, trapped lung or eosinophilic pleuritis.

Results: We found telomerase activity by gel electrophoresis in 17 of 25 specimens (68%) including 10 of 13 bronchoscopy specimens (77%), 3 of 8 thoracentesis specimens (38%) and 4 of 4 fine needle aspirates (100%). When we examined the results by tissue type of carcinoma we found that 6 of 9 small cell (68%), and 11 of 16 non-small cell specimens (69%) had gel activity. Six specimens (24%) had relatively high telomerase activities (>0.312 A 450-690) by PCR ELISA assay. These consisted of 2 of 9 small cell (22%) and 4 of 16 non-small cell specimens (25%). Brushings, transbronchial needle aspirates and fine needle aspirates appeared to have greater combined sensitivity (92%) than pleural fluid and lavage specimens (42%).

Conclusions: Detection of telomerase activity in thoracic malignancies appears feasible from clinical diagnostic specimens such as bronchoscopy, thoracentesis and fine needle aspirates. The prevalence of telomerase activity by gel electrophoresis was similar in the small cell and non-small cell specimens in this study. Telomerase activity has moderate sensitivity as an indicator of cytologically confirmed malignancy.

Clinical Implications: Telomerase activity can be detected in clinical diagnostic specimens from patients with cytologically confirmed lung cancer. Should telomerase prove to be a valuable tumor marker, positivity in diagnostic specimens may obviate the need for more invasive procedures. Future studies using diagnostic specimens may aid in assessing the value of telomerase activity as a tumor marker.

Steger Award

This award is given to a resident, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1999:

Diphenhydramine for the Prevention of Akathisia Induced by Prochlorperazine: A Randomized Controlled Trial by CPT David R. Vinson, MC, Department of Emergency Medicine

Other nominees were:

The Association between Telomerase, p53, and Clinical Staging in Colorectal Cancer by CPT Tommy A. Brown, MC, General Surgery Service

The Effects of Mitomycin-C on Airway Wound Healing after Laryngotracheal Reconstruction and Stenting in a Pig Model by CPT George L. Coppit, III, MC, General Surgery Service

The Electronic Amplified Precordial Stethoscope versus the Traditional Precordial Stethoscope for Patient Monitoring During Deep Sedation for Oral and Maxillofacial Surgery Procedures by MAJ Henry W. Marcantoni, DE, Madigan Dental Clinic

Refractive Changes Due to Hypoxia Following LASIK Corneal Surgery by MAJ Mark L. Nelson, MC, Ophthalmology Service

The Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry by CPT Michael W. Quinn, MC, Internal Medicine Service

Validation of ACC/AHA Echocardiography Guidelines in Asymptomatic Active-Duty Service Members with Heart Murmur by CPT Eric A. Shry, MC, Internal Medicine Service

Pilomatrixoma of the Head and Neck by MAJ Richard W. Thomas, MC, Otolaryngology Service

Cranial Polyneuropathies in Multiple Sclerosis: Case Report and Literature Review by MAJ Richard W. Thomas, MC, Otolaryngology Service

Immediate Extubation Following Laryngotracheoplasty Using Expendable Metallic Stents by MAJ Richard W. Thomas, MC, Otolaryngology Service

Inflammatory Response Related to Bronchial Distention with Metallic Stents by MAJ Richard W. Thomas, MC, Otolaryngology Service

Postoperative Management of the Obstructive Sleep Apnea Patient by CPT Keith M. Ulnick, MC, Otolaryngology Service

Tracheal Mucosal Healing in Response to Moderate Mucosal Injury Induced by Expandable Metallic Stents by CPT Keith M. Ulnick, MC, Otolaryngology Service

Fellow's Research Award

This award is given to a fellow, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1999:

The Expression of Adrenomedullin and its Receptor in the Human Placenta by MAJ Christina Apodaca, MC, Department of Obstetrics/Gynecology.

Other nominees were:

Parental Assessment of Psychologic Adjustment in Children with Asthma: A Comparison of the Child Behavior Checklist and the Behavior Assessment System for Children by CPT Veronica R. Baechler, MC, Department of Pediatrics

Possible New Nonfamilial Syndrome of Unilateral Congenital Lymphedema and Intestinal Lymphangiectasia with Hypopigmentation, Scattered Coarse White Scalp Hairs, and Nail Pitting and Ridging by MAJ William Campbell, MC, Department of Pediatrics

The Effects of Lipopolysaccharide on Fetoplacental Vascular Tone and Production of Interleukin-6 in Isolated Placental Cotyledons by MAJ Richard K. Wagner, MC, Department of Obstetrics/Gynecology

Kenyon Joyce Award

This award is given to staff, submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1999:

Changing Thyroid Hormone Status and Cognitive and Physical Performance During Prolonged Antarctic Residence: Effect of Thyroxine Supplementation in the Polar T₃ Syndrome by COL H. Lester Reed, MC, Department of Medicine.

Other nominees were:

The Effects of Loaded Foot Marching versus Running on Injury, Fitness and Performance in U.S. Army Light Infantry Soldiers by CPT Daniel C. Norvell, SP, Physical Medicine & Rehabilitation Service

PUBLICATIONS

Department of Anesthesia & Operative Services

Francis LE, Landry RJ, Hanisch RK, Apodaca CC, Frietch SR. The Effectiveness of 5-hydroxytryptamine Type 3 (5-HT₃) Receptor Antagonists in the Treatment of Intrathecal Narcotic-induced Pruritus: Ondansetron Versus Naloxone. *AANA Journal* 1998.

Department of Clinical Investigation

Aldous WK, Marean AJ, DeHart MJ, Matej LA, Moore KH. Effects of tamoxifen on telomerase activity in breast cancer cell lines. *Cancer* 85(7): p 1523-1529, 1999.

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Department of Family Practice

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Holman JR, Stuessi KA. Adult circumcision. *American Family Physician* 59(6): p 1514-1518, 1999.

Rice MS, MacDonald DC. Appropriate Roles of Cardiac Troponins in Evaluating Patients with Chest Pain. *Journal of the American Board of Family Practice* 12(3): p 214-218, 1999.

Department of Medicine

Collins DM, Dillard TA, Grathwohl KW, Giacoppe GN, Arnold BF. Bronchial Mucormycosis with Progressive Air Trapping. *May Clinic Proceedings* 74(7): p 698-701, 1999.

Prinz PN, Scanlan JM, Vitaliano PP, Moe KE, Borson S, Toivola B, Merriam GR, Larsen LH. Thyroid Hormones: Positive Relationships with Cognition in Healthy, Euthyroid Older Men. *Journals of Gerontology, Series A, Biological Sciences & Medical Sciences* 54(3): p 111-116, 1999.

Quinn MW, Dillard TA. Delayed Traumatic Hemothorax on Ticlopidine and Aspirin for Coronary Stent. *Chest* 116(1): p 257-260, 1999.

Cardiology Service, Department of Medicine

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Endocrinology Service, Department of Medicine

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Reedy KR, Reed HL. Measuring metabolic change in humans residing in Antarctica: A thyroxine supplement placebo control trial. *Antarctic Journal*.

Seip R, Reed HL. The polar T₃ syndrome: metabolic and cognitive manifestations, their hormonal regulation and impact upon performance, mechanism of muscle adaptation to cold exposure. *Antarctic Journal*.

Infectious Disease Service, Department of Medicine

Baum SE, Morris JT, Gibbons RV, Cooper R. Reduction in Human Immunodeficiency Virus Patient Hospitalization and Nontraumatic Mortality after Adoption of Highly Active Antiretroviral Therapy. *Military Medicine* 164(9): p 609-612, 1999.

Internal Medicine Service, Department of Medicine

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Neurology Service, Department of Medicine

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Pulmonary Disease & Critical Care Service, Department of Medicine

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Department of Nursing

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Department of Obstetrics/Gynecology

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Hibbert ML, Palacio PE, Larsen FW, Davis GD, Perez RP. Enhancing advanced surgical laparoscopy; combined use of microlaparoscopes and macrolaparoscopes. *The Journal of Reproductive Medicine* 44(1): p 1-6, 1999.

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Department of Pathology

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Department of Pediatrics

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Department of Radiology

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Department of Surgery

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General Surgery Service, Department of Surgery

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Ophthalmology Service, Department of Surgery

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Orthopedics Service, Department of Surgery

Connolly B, Pitcher JD, Roth BJ, Youngberg RA, Devine J. Scrofuloderma of the Lower Extremity Treated with Wide Resection: A Case Report and Review of the Literature. *American Journal of Orthopedics (Chatham, NJ)* 28(7): p 417-420, 1999.

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Ruegamer JL, Perkins JA. Combined Rigid and Flexible Endoscopic Removal of a BB Foreign Body from a Peripheral Bronchus. *International Journal of Pediatric Otorhinolaryngology* 47(1): p 77-80, 1999.

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Thomas RW, Liening DA, Auber AE, Johnson RE. Cranial Polyneuropathies in Multiple Sclerosis: Case Report and Literature Review. *Ear, Nose, & Throat Journal* 78(2): p 118-121, 1999.

Thomas RW, Perkins JA, Ruegamer JL, Munaretto JA. Surgical Excision of Pilomatrixoma of the Head and Neck: A Retrospective Review of 26 Cases. *Ear, Nose, & Throat Journal* 78(8): p 544-546, 548, 1999.

Urology Service, Department of Surgery

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Lance RS, Aldous WK, Blaser J, Thrasher JB. Telomerase activity in solid transitional cell carcinoma, bladder washings, and voided urine . *Urologic Oncology* 4: p 43-49, 1999.

Johnson CA, Tollefson DFJ, Olsen SB. The Natural History of Early Recurrent Carotid Artery Stenosis. *The American Journal of Surgery* 177(5): p 433-436, 1999.

PRESENTATIONS

Department of Anesthesia & Operative Services

Quintanilla A, Silvasy AM, StPierre P. The Effect of Preoperative Administration of Ketorolac on Postoperative Bleeding in Anterior Cruciate Ligament Repair. Presented at American Association of Nurse Anesthetists Meeting, Boston, MA, USA, August 1999.

Department of Emergency Medicine

Vandenberg JT, McManus JG. A Physician Survey to Determine the Difficulties and Satisfaction of Standard Suctioning Equipment in the Emergency Department. Presented at Annual Meeting Society of Academic Emergency Medicine Meeting, Redondo Beach, CA, USA, March 1999.

Vinson DR, Drotts DL. Diphenhydramine Prevents Akathisia Induced by IV Prochlorperazine: A Randomized Controlled Trial. Presented at Joint Service Emergency Medicine Symposium Meeting, San Antonio, TX, USA, March 1999.

Wedmore IS, McManus JG, Migala A, Coonan K. Clonidine for Prophylaxis of Acute Mountain Sickness. Presented at World Congress on Wilderness Medicine Meeting, Whistler, BC, Canada, August 1999.

Department of Family Practice

Flynn DM. Prevention of Unintended Pregnancy in Military Women. Presented at Society of Teachers of Family Medicine (AAFP) Meeting, Orlando, FL, USA, November 1998.

Department of Medicine

Case S, Reed HL, Reedy K, Do NV, Finney N, Mino L, Seip R, Palinkas LA. The Effect of Energy Restriction on Weight, Metabolism, and Serum Thyroid Hormones Before and Following 11 Months of Antarctic Residence. Presented at The Endocrine Society Meeting, San Diego, CA, USA, June 1999.

Quinn MW, Dillard TA, LeClerc KM, Arendt MA, Gibbons RB, Gagnon-Bailey S. Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry. Presented at 1999 International Conference of the American Thoracic Society Meeting, San Diego, CA, USA, April 1999.

Reed HL, Reedy K, Case S, Do NV, Finney N, Seip R, Wright JR, Mino L, Palinkas LA. Circadian and Seasonal Structure to Serum TSH During Prolonged Antarctic Residence: Effect of Throxine Supplementation. Presented at The Endocrine Society Meeting, San Diego, CA, USA, June 1999.

Internal Medicine Service, Department of Medicine

Mulhall BP, Randall DC. Low Molecular Weight Heparins for Use as a Perioperative Anticoagulation Window. Presented at Society of General Internal Medicine Meeting, San Francisco, CA, USA, April 1999.

Pulmonary Disease & Critical Care Service, Department of Medicine

Ramakrishna RR, Aldous WK, Murray SP, Tracy DP, Caras WE, Dillard TA. Telomerase Activity in Cytologically Positive Bronchoscopy, Thoracentesis and Fine Needle Specimens. Presented at American College of Chest Physicians Meeting, Toronto, Ontario, Canada, November 1998.

Ramakrishna RR, Dillard TA, Aldous WK. Telomerase Activity in Bronchoscopic Samples from Patients with Sarcoidosis and Interstitial Lung Disease. Presented at American Lung Assoc/American Thoracic Society International Meeting Meeting, San Diego, CA, USA, April 1999.

Department of Obstetrics/Gynecology

Apodaca CC, Hume RF, Evans W, Martin LS, Evans MI, Calhoun BC. Comparison of Parental Perception of Risk and Decision-making Between Two Healthcare Systems: Choroid Plexus Cysts. Presented at American Institute of Ultrasound in Medicine, 43rd Annual Convention Meeting, San Antonio, TX, USA, March 1999.

Apodaca CC, Wagner RK, Calhoun BC, Hume RF. Evaluation of Abnormally Low Second Trimester Maternal Serum Unconjugated Estriol. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District American Annual Meeting, Kissimmee, FL, USA, October 1998.

Apodaca CC, Calhoun BC. The Expression of Adrenomedullin and Its Receptor in the Human Placenta. Presented at 2nd Annual Madigan Research Day Meeting, Tacoma, WA, USA, April 1999.

Asato AJ, Dainty LA. Laparoscopic Supracervical Hysterectomy: A Minimally Invasive Technique Employing Endocervical Resection and Poer Morcellation. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Asato AJ. Postpartum Pulmonary Edema Secondary to Ruptured Choradae. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Dainty LA, Hibbert ML, Calhoun BC, Wagner RK, Larsen FW. Small Bowel Obstruction in Pregnancy: An Uncommon Diagnosis in Patients Presenting with Common Abdominal Complaints. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District American Annual Meeting, Kissimmee, FL, USA, October 1998.

Dainty LA. Can Complete Tubal/Uterine Evaluation be Performed in the Office - Testing Feasibility in Operating Room. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Dequattro N. Local Anesthesia Microlaparoscopy Day: Providing Residents a Concentrated Educational Experience with Microlaparoscopy Performed under Local Anesthesia. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Dequattro N, Asato AJ. An Unusual Case of Mullerian Anomaly Misdiagnosed for Seventeen Years: The Use of Hydro-Vaginoscopy in its Diagnosis and Surgical Management. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Ellis J, Dainty LA, Buller JL, Larsen FW. Hysteroscopically-Assisted Laparoscopic Tubal Anastomosis: Facilitation Using Hysteroscopic Tubal Catheterization. Presented at 16th World Congress on Fertility and Sterility and the 54th Annual Meeting of the American Society for Reproductive Medicine Meeting, San Francisco, CA, USA, October 1998.

Ellis J, Dainty LA, Buller JL, Larsen FW. Hysteroscopically-Assisted Laparoscopic Tubal Anastomosis: Facilitation Using Hysteroscopic Tubal Catheterization. Presented at 1998 District VIII/IX Meeting of the ACOG Meeting, Portland, OR, USA, October 1998.

Ellis J, Dainty LA, Buller JL, Larsen FW. Hysteroscopically-Assisted Laparoscopic Tubal Anastomosis: Facilitation Using Hysteroscopic Tubal Catheterization. Presented at 1998 Armed Forces District Meeting of ACOG Meeting, Kissimmee, FL, USA, October 1998.

Ellis J, Dainty LA, Buller JL, Larsen FW. Hysteroscopically-Assisted Laparoscopic Tubal Anastomosis: Facilitation Using Hysteroscopic Tubal Catheterization. Presented at International Congress of Gynecologic Endoscopy & 27th Annual Meeting of the American Association of Gynecologic Laparoscopists Meeting, Atlanta, GA, USA, November 1998.

Frayer C. Innovative Applications of the Flexible Endoscope for the Gynecologic Surgeon. Presented at 37th American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Harkins GJ, Wagner RK, Apodaca CC, Calhoun BC. Chemotherapeutic Agents in Pregnancy: A Case Series. Presented at American College of Obstetricians and Gynecologists/Armed Forces District Meeting Meeting, Kissimmee, FL, USA, October 1998.

Kambiss SM. A Video Presentation of the Laparoscopic Management of Ovarian Torsion. Presented at 16th World Congress on Fertility and Sterility and the 54th Annual Meeting of the American Society for Reproductive Medicine Meeting, San Francisco, CA, USA, October 1998.

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Larsen FW, Buller JL, McClain R. Transvesical Needle Cystoscopy: A Minimally Invasive Method for Assessing Suture Placement and Ureteral Patency at the Time of Pelvic and Retropubic Surgery. Presented at 1998 District VIII/IX Meeting of ACOG Meeting, Kissimmee, FL, USA, December 1998.

Larsen FW, Buller JL, McClain R. Transvesical Needle Cystoscopy: A Minimally Invasive Method for Assessing Suture Placement and Ureteral Patency at the Time of Pelvic and Retropubic Surgery. Presented at International Congress of Gynecologic Laparoscopists Meeting, Atlanta, GA, USA, November 1998.

Pierce BT, Hume RF, Martin LS, Nielsen PE, Carter S, Calhoun BC, Salafia C. The Relationships Among Fetal Karyotype, Intrauterine Fetal Death, and Histologic Villous Mineralization. Presented at 46th Society of Gynecological Investigation Annual Meeting, Atlanta, GA, USA, March 1999.

Wagner RK, Hinson RM, Apodaca CC, Hoeldtke NJ, Moore KH, Nielsen PE, Hume RF, Calhoun BC. The Effects of Lipopolysaccharide, an Inflammatory Stimulus, on Fetoplacental, Vascular Tone and Production of Interleukin-6 in Isolated Placental Cotyledons. Presented at Society for Gynecologic Investigation Meeting, Atlanta, GA, USA, March 1999.

Department of Pathology

Vos JA, Simurdak JH, Davis BJ, Myers JB, Brissette MD. Vortex Disaggregation for Flow Cytometry: A Tissue Preserving Method. Presented at United States and Canadian Academy of Pathology Meeting, San Francisco, CA, USA, March 1999.

Department of Pediatrics

Baechler VR. Parental Assessment of Psychologic Adjustment in Children with Asthma: A Comparison of the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children (BASC). Presented at Northwest Society for Developmental Behavioral Pediatrics Meeting, USA.

Berkenbaugh JT, Larkin HR, O'Neill JT. Neuronal Nitric Oxide Synthase Inhibition Disrupts Autoregulation of Cerebral Blood Flow During Increased Cerebral Perfusion Pressure in Newborn Piglets. Presented at 1999 Pediatric Academic Societies' Annual Meeting Meeting, San Francisco, CA, USA, May 1999.

Campbell W. Unilateral Congenital Lymphedema Associated with Intestinal Lymphangiectasia, Elevated Liver Transaminases, and Hypopigmentation. Presented at Northwest Society for Developmental Behavioral Pediatrics Meeting, USA.

Davis BE. We Hold These Truths to be Self-Evident: Controversies in ADHD. Presented at Decision Making for Common Pediatric Problems Meeting, USA, January 1999.

Mahnke CB. Growth and Development of a Speciality: The History of Pediatrics. Presented at Decision Making for Common Pediatric Problems Meeting, USA, January 1999.

McGranahan M, Flores MS, Archer W, Kriebel G. Perplexing Pediatric Patients: A Pediatric Case Conference. Presented at Decision Making for Common Pediatric Problems Meeting, USA, January 1999.

Physical Therapy, Physical Medicine & Rehabilitation Service

Dettori JR, Patience TH, Hoyt RA, Nindl BC. Regional Adiposity Changes in Female Soldiers Following Pregnancy. Presented at American College of Sports Medicine, 46th Annual Meeting Meeting, Seattle, WA, USA, June 1999.

Preventive Medicine Service

Young SYN. Characteristics and Correlates of Asthma in the Military Population of the Northwestern United States. Presented at Prevention '99 Meeting, Washington, DC, USA, March 1999.

Department of Radiology

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DETAILED SUMMARY SHEETS

TABLE OF CONTENTS

Legend:

Column labelled "S" stands for Status of Protocol

C = Completed

O = Ongoing

T = Terminated

S = Suspended

| | | |
|---|--|------------|
| Hospital Dental Clinic | | 101 |
| Marcantoni HW #96/046 | C Evaluation of the Efficacy of Post-operative Antibiotics After Orthognathic Surgery | 102 |
| Marcantoni HW #99/010 | C The Electronic Amplified Precordial Stethoscope Versus the Traditional Precordial Stethoscope for Patient Monitoring During Deep Sedation for Oral and Maxillofacial Surgery Procedures | 103 |
| Department of Emergency Medicine | | 104 |
| Buck CP #99/070 | O A Survey to Determine the Incidence of Infection in Plantar Puncture Wounds | 105 |
| Coomes TR #99/104 | O A Randomized, Placebo-Controlled, Study of Intravenous Magnesium in Acute Benign Headaches | 106 |
| Pace SA #97/020 | O A Model for Prehospital 12-Lead Acquisition Without A Dedicated 12-Lead ECG Machine | 107 |
| Pace SA #98/002 | O Emergency Surgical Procedures Laboratory Training Using the Goat (<i>Capra hircus</i>) | 108 |
| Pace SA #98/021 | C Predicting Emergency Medicine Resident Success from Prospective Resident Application Materials | 109 |
| Pace SA #98/028 | O Pediatric Intubation Training Utilizing the Ferret (<i>Mustela putorius furo</i>) Model | 110 |
| Pace SA #98/109 | C A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice daily for Five Days in the Treatment of Influenza in Patients 12 Years or Over Diagnosed with Asthma or Chronic Obstructive Pulmonary Disease | 111 |
| Pace SA #99/105 | O A Double-blind, Randomized, Placebo-controlled Trial of a Tablet Formulation of Pleconaril in the Treatment of Viral Respiratory Infection | 112 |
| Vandenberg JT #99/011 | C Survey of Clinical Emergency Medicine Positions: Annals of Emergency Medicine, September 1998 | 113 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|--|------------|
| Vinson DR #98/110 | C | Randomized, Double-Blind, Comparative Trial of 15- minutes vs 2- minutes Infusion Rates on the Incidence of Prochlorperazine-Induced Akathisia | 114 |
| Wedmore IS #97/127 | C | Efficacy of Clonidine for Prophylaxis of Acute Mountain Sickness | 115 |
| Department of Family Practice | | | 116 |
| Chun YH #96/127 | C | Incidence of Exercise Induced Hematuria After the Army Physical Fitness Test (APFT) | 117 |
| Clark GW #99/098 | O | Can An Instructional Video Improve the Quality of Cervical Cytological Smears in A Family Practice Residency | 118 |
| Flynn DM #97/050 | O | Unintended Pregnancy Prevention Program | 120 |
| Harrington BC #99/047 | C | Association of Race, Gender, and Rank with the Use of Clinical Preventive Screening Tests | 121 |
| Holman JR #99/015 | C | Clinical Standards Implementation: A Survey of Primary Care Providers Attitudes and Use of Practice Guidelines | 122 |
| Holman JR #99/034 | C | Sensitivity and Specificity of Colposcopic Impression in a Family Practice Dysplasia Clinic | 123 |
| Krueger MV #99/067 | O | Effects of the Acetic Acid Wash on the Cytologic Interpretation of the PAP Smear | 124 |
| Potter JH #99/020 | O | Assessing the Stages of Change for Contraceptive Use in the Prevention of Pregnancy and Sexually Transmitted Disease | 125 |
| Runkle GP #96/090 | T | Treatment of Nocturnal Leg Muscle Cramps: A Double- Blind Placebo-Controlled Crossover Trial of Magnesium Oxide | 126 |
| Nichols CA #99/083 | C | A Comparison of the Values and Attitudes of Active Duty Soldiers and Civilians Under Age 35 to Those Over Age 35 at Madigan Army Medical Center | 128 |
| Cardiology Service, Department of Medicine | | | 129 |
| King JJ #99/042 | O | The Coreg Heart Failure Registry: COHERE | 130 |
| King JJ #99/053 | O | Multinational, Multicenter, Double-Blind, Randomized, Active Controlled, Parallel Group Study Compring the Efficacy and Safety of Long-Term Treatment with Valsartan, Captopril, and Their Combination in High-Risk Patients After Myocardial Infarction | 131 |
| LeClerc KM #98/079 | C | The Effect of Acute Norepinephrine Infusion on Exercise Oxygen Uptake Kinetics and Efficiency in Patients with Congestive Heart Failure and Normal Adults | 132 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------------|
| Miller SE #98/108 | T | A Comparison of Transradial versus Transfemoral Approach to Diagnostic Cardiac Catheterization: Patient Attitudes, Physician Attitudes, and Procedural Variables | 133 |
| Olson JP #96/069 | O | Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) | 134 |
| Schachter DT #99/013 | O | Magnesium in Coronaries (MAGIC): A Study of the Effect of Magnesium Administration in Patients with Acute Myocardial Infarction | 135 |
| Wink JS #99/055 | O | Low Dose Niacin Supplementation with Chronic Statin Therapy | 136 |
| Yandel ML #97/140 | O | A Double-Blind, Placebo-Controlled, Parallel Design Study to Determine the Effect of 100 mgs of Orally Administered Azimilide Dihydrochloride versus Placebo on Survival in Recent Post-Myocardial Infarction Patients at Risk of Sudden Death (ALIVE) | 137 |
| Yandel ML #99/036 | O | Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure | 138 |
| Endocrinology Service, Department of Medicine | | | 139 |
| Reed HL #97/124 | O | The Effect of Partial Energy Restriction on the Changes in Metabolic and Kinetic Measures of Thyroid Hormone Metabolism During Antarctic Residence | 140 |
| Gastroenterology Service, Department of Medicine | | | 141 |
| Hirota WK #98/005 | O | Intron A + Ribavirin for Treatment of Patients with Chronic Hepatitis C not Previously Treated with Interferon | 142 |
| Hirota WK #98/006 | O | Intron A + Ribavirin for Treatment of Patients with Interferon-Refractory or Interferon-Relapsed Chronic Hepatitis C | 143 |
| Tsuchida AM #96/164 | O | Epidemiology of Gallbladder Sludge and Stones in Pregnancy | 144 |
| Tsuchida AM #97/012 | O | A Pre-Clinical Research and Development Study to Evaluate Stool Specimens for Basement Membrane Fragments/Complexes and Cytoskeletal Proteins | 145 |
| Tsuchida AM #98/004 | O | Epidemiology of Barrett's Esophagus | 146 |
| Hematology/Oncology Service, Department of Medicine | | | 147 |
| Bertram KA #97/110 | C | Double Blind, Double Dummy, Randomized, Multicenter, 2-Arm, Phase III Trial Comparing Letrozole 2.5 mg versus Tamoxifen 20 mg as First Line Therapy in Postmenopausal Women with Advanced Breast Cancer | 148 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|--|------------|
| Jones MP #97/026 | C | A Phase II Trial of Thioplex Following Induction Chemotherapy to Decrease the Incidence of Brain Metastases in Limited Stage Small Cell Lung Cancer Patients | 149 |
| McCune DE #96/049 | C | An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other OTFC Studies | 150 |
| McCune DE #97/111 | C | Protocol AC 600/001: Multicenter, Double-Blind, Crossover Study of Oral Transmucosal Fentanyl Citrate (OTFC) Compared to Immediate Release Morphine Sulfate for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Opioids | 151 |
| McCune DE #97/112 | C | Protocol AC 600/002: An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in AC 600 Series Protocols | 152 |
| McCune DE #99/093 | O | Phase II Trial of Gemcitabine and Herceptin in HER2 Overexpressing Metastatic Breast Cancer | 153 |
| Infectious Disease Service, Department of Medicine | | | 154 |
| Morris JT #98/058 | C | Linezolid for the Treatment of Methicillin Resistant Staphylococcus aureus (MRSA) Infections: An Evaluator Blinded Trial Comparing Linezolid with Vancomycin Alone and Vancomycin Followed by Oral Linezolid | 155 |
| Internal Medicine Service, Department of Medicine | | | 156 |
| Duncan MB #99/032 | O | Cost Analysis of Prescreening for Hepatitis A Before Immunization in Patients with Chronic Liver Disease | 157 |
| Duncan MB #99/074 | C | The Prevalence of Hepatitis A in US Military Recruits | 158 |
| Gibbons RB #97/016 | T | A Controlled Clinical Trial to Improve Housestaff Identification of and Attitudes Toward Mental Disorders in Primary Care | 159 |
| Mulhall BP #98/015 | O | Use of Blood Cultures in the Evaluation of Febrile Episodes in Neutropenic Patients Receiving Broad Spectrum Antibiotics | 160 |
| Quinn MW #98/080 | C | Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry | 161 |
| Sullivan NR #99/066 | O | Spot Uric Acid/Creatinine Ratio vs. 24 Hour Collection for Evaluation of Uric Acid Excretion | 162 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------------|
| Neurology Service, Department of Medicine | | | 163 |
| Bolt JL #97/083 | C | Compassionate Use of Vigabatrin in Infantile Spasms | 164 |
| Pulmonary Disease & Critical Care Service, Department of Medicine | | | 165 |
| Caras WE #98/054 | T | The Use of Combined Ipratropium Bromide and Albuterol Given as Combivent MDI in COPD Exacerbation | 166 |
| Dillard TA #94/029 | O | A Prospective Study Using the Airway Occlusion Pressure (PO.1) To Predict the Outcome of Weaning From Mechanical Ventilation | 167 |
| Jorgensen JE #90/099 | O | Comparison of the Serum Effusion Albumin Gradient to Traditional Criteria for Transudates in Patients with Pleural Effusions Secondary to Congestive Heart Failure | 168 |
| McKinley BT #98/102 | O | The Effect of Saphenous Vein Versus Internal Mammary Artery Bypass on the Mortality and Morbidity of Severe Chronic Obstructive Pulmonary Disease Patients | 169 |
| Ramakrishna RR #96/138 | O | Active Inspiration/Expiration versus Tidal Volume Breathing During Transbronchial Biopsy | 170 |
| Ramakrishna RR #98/055 | O | Telomerase Activity in Bronchial Washings, Pleural Fluid, Sputum, and Cerebrospinal Fluid (CSF) | 171 |
| Ramakrishna RR #98/086 | O | Telomerase Activity in Non-surgical Specimens Obtained at Bronchoscopy and Fine Needle Aspiration | 172 |
| Roth BJ #92/024 | T | Resectable Bronchogenic Carcinoma: Value of Routine Contrast - Enhanced Cranial MRI in Preoperative Staging | 173 |
| Roth BJ #97/132 | O | Respiratory Care Team to Decrease the Misuse of Metered Dose Inhalers in Hospitalized Patients | 174 |
| Rheumatology Service, Department of Medicine | | | 175 |
| Irvin TL #99/078 | O | A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Prograf (Tacrolimus) in the Treatment of Rheumatoid Arthritis in Patients Who Have Failed One or More | 176 |
| Irvin TL #99/079 | O | An Open-Label, Long-Term Study to Evaluate the Safety of Prograf (tacrolimus) for the Treatment of Rheumatoid Arthritis | 177 |
| Department of Nursing | | | 178 |
| Brosch LR #98/044 | O | Physical Activity and Exercise in AD Female Soldiers | 179 |
| Brosch LR #98/107 | O | Nurses Influence on Patient Outcomes in US Army Hospitals | 180 |
| Brosch LR #99/028 | O | Factors Associated with Preventable Hospitalization in Older Military Retirees | 181 |

| Princ. Investigator Protocol Number | S Protocol Title | Page |
|--|---|------------|
| Brosch LR #99/110 | O The Effects of Using Four Different Missing Data Imputation Methods on the Psychometric Property of the SF36 | 182 |
| Hildreth PJ #96/132 | C Pressure Ulcer Prevention: Comparing Support Surfaces | 183 |
| Hildreth PJ #97/077 | C Linking Nursing Care to ANA Quality Indicators | 184 |
| Horne TA #99/022 | S Nurse Practitioner Manager Outpatient Heart Failure Program | 185 |
| Loan LA #95/190 | C The Effects of Thermocouple Sensor Placement on Neonatal Skin Temperature Measurement | 186 |
| Loan LA #96/125 | C A Survey of Access to Care in the TRICARE Environment | 187 |
| Loan LA #96/137 | C Single Woman's Breast Cancer Program | 188 |
| Loan LA #97/068 | O Effects of Stress Responses on Wound Healing | 189 |
| Loan LA #98/053 | O Improving Soldier Access to Urinary Incontinence Therapy | 190 |
| Loan LA #99/025 | O The Effects of Postoperative Supplemental Oxygen on Tissue and Wound Healing | 191 |
| Loan LA #99/029 | O Evaluation of the Clinical Status and Resource Utilization of Ventilated Patients with Acute Respiratory Failure in Intensive Care Units via a Longitudinal Observational Outcomes Database | 192 |
| McCarthy MS #95/076 | O Gastric/Jejunal Feeding: Nutritional Outcomes and Pneumonia | 193 |
| McCarthy MS #98/063 | O Improving ALI/ARDS Patient Outcomes with Metabolic Support | 194 |
| Moureau PM #97/106 | C Natural Killer Cell Activation and Apoptosis in Women with Early Stage Breast Cancer: Potential Measure for Nursing Research | 195 |
| Quintanilla A #99/009 | C The Effect of Preoperative Administration of Ketorolac on Postoperative Bleeding in Anterior Cruciate Ligament Reconstruction | 196 |
| Nutrition Care Division | | 197 |
| D'Amico M #99/082 | O Implementation and Evaluation of PEP (Personal Energy Plan) Health and Wellness Program Designed to Promote Healthy Eating and Physical Activity Among Adult Participants | 198 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|---|------------|
| Jordan SA #99/111 | O | An Evaluation of UPBEAT Weight Management Program | 200 |
| Department of Obstetrics/Gynecology | | | 201 |
| Burney RO #99/031 | O | Relationship of Cesarean Delivery for Arrest of Descent and Station at Onset of Maternal Pushing: A Case Control Study | 202 |
| Dainty LA #99/077 | O | Misoprostol for the Medical Management of Non-viable First Trimester Pregnancies | 203 |
| Nielsen PE #99/084 | O | Team Performance in Labor & Delivery: L&D MedTeams: Concept Phase | 205 |
| Maternal-Fetal Medicine, Department of Obstetrics/Gynecology | | | 206 |
| Apodaca CC #98/068 | O | The Expression of Adrenomedullin and Its Receptor in the Human Placenta | 207 |
| Apodaca CC #99/035 | O | Comparison of Elective Labor Induction and Spontaneous Labor: A Randomized, Controlled Clinical Trial | 208 |
| Apodaca CC #99/051 | O | The Use of Transvaginal Sonography in Predicting Preterm Delivery in Patients with Preterm Contractions | 209 |
| Calhoun BC #99/075 | O | Fetal Macrosomia in a Military Population | 210 |
| Calhoun BC #99/100 | O | Comparison of First and Second Trimester Screening for Prenatal Detection of Down Syndrome and Other Birth Defects | 211 |
| Nielsen PE #99/023 | O | Delayed Maternal Pushing with Labor Epidural Analgesia: Effects on Operative Vaginal Delivery | 212 |
| Nielsen PE #99/024 | O | Extending the Duration of Active Phase Arrest: Effects on Cesarean Delivery | 213 |
| Pierce BT #98/060 | T | Random Urine Protein/Creatinine Ratio for Quantification of Proteinuria in Pregnancy: An Outcomes Based, Cost Consequences Analysis | 214 |
| Pierce BT #99/018 | C | Fetal Outcome Following Single Umbilical Artery Diagnosis | 215 |
| Pierce BT #99/026 | O | The Relationship Among Fetal Karyotype, Intrauterine Fetal Death, and Histologic Villous Mineralization | 216 |
| Pierce BT #99/046 | O | Outcome of Infants Born at 22-28 Weeks Gestation: A Retrospective Review in Military Care Facilities | 217 |
| Pierce BT #99/064 | C | The Effects of Shear Stress on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon | 218 |
| Wagner RK #98/105 | C | The Effects of Magnesium Sulfate on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon | 219 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|---|------------|
| Urogynecology, Department of Obstetrics/Gynecology | | | 220 |
| Davis GD #97/107 | T | The Effectiveness of Mechanical Devices in the Prevention of Exercise Induced Urinary Incontinence in the Female Soldier | 221 |
| Davis GD #97/108 | O | A Pilot Study for Transanal Ultrasonography (TAUS) in the Repair of Episiotomy Anal Sphincteroplasty | 222 |
| Davis GD #99/102 | O | Comparison of Tolterodine and Oxybutinin for the Treatment of Urinary Incontinence among Female Soldiers | 223 |
| Potter ME #97/144 | O | Operative Endoscopy and Surgical Management of the Bowel and Urinary Tract Injuries in Gynecologic Surgery in the Pig (<i>Sus scrofa</i>) | 225 |
| Woodman PJ #99/103 | O | Prevalence of Anal Incontinence in New Mothers Trial (PAINT) | 226 |
| Department of Pathology | | | 227 |
| Russell AA #98/070 | C | The Stability of Reagents Used in A DEPMEDS Clinical Chemistry Analyzer | 228 |
| Department of Pediatrics | | | 229 |
| Carter ER #98/111 | T | Validation of the Symptom-Free Days Instrument in Children with Asthma | 230 |
| Davis BE #99/049 | T | National Standardization Study of the Brigance Infant-Toddler Screen | 231 |
| Fairchok MP #90/092 | O | Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses | 232 |
| Sweeney JK #97/056 | O | Physiological, Behavioral, and Feeding Effects of Neonatal Physical Therapy Procedures on Preterm Infants in a Neonatal Intensive Care Unit Setting | 233 |
| Pharmacy | | | 234 |
| Beaudoin DR #99/106 | O | Pilot Study to Determine the Effectiveness of Glutamine in the Treatment of Paclitaxel Induced Myalgia, Arthralgia and Neuropathy | 235 |
| Physical Therapy, Physical Medicine & Rehabilitation Service | | | 236 |
| Dougherty RW #98/094 | T | A Prospective Randomized Trial of Controlled Compression Cryotherapy versus Institutionalized Cryotherapy in Post-Operative Anterior or Posterior Cruciate Ligament Reconstruction Patients | 237 |
| Henderson NE #99/027 | O | Mandatory Physical Training and Physical Readiness in Postpartum Soldiers | 238 |
| Henderson NE #99/094 | C | Injury Rates and Interventions in the 75th Ranger Regiment | 239 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------------|
| Matekel RL #98/030 | O | Physical Therapy Treatment Effectiveness for Osteoarthritis of the Knee: A Prospective, Randomized, Controlled Comparison of Supervised Clinical Exercise and Manual Therapy Procedures versus A Home Exercise Program | 240 |
| Preventive Medicine Service | | | 241 |
| Bybee LB #99/061 | C | MAMC Stethoscopes and Methicillin Resistant Staphylococcus Aureus (MRSA) | 242 |
| Bybee LB #99/062 | C | Personal Cleanliness, Hygiene, Privacy, and Related Health Concerns of Female Soldiers in the Field Environment | 243 |
| Cook JE #99/076 | O | Immune Response to Community-Acquired Campylobacter jejuni Infection in United States Military Personnel on Deployment in Korat, Thailand (Cobra Gold 99) | 244 |
| Gunzenhauser JD #99/033 | O | Breast Cancer Risk Assessment Among Women Beneficiaries Eligible for Medical Care in the Pacific Northwest, Region 11 | 245 |
| Wempe JM #99/063 | C | Attrition Rates for Military Recruits Receiving A Medical Waiver for Skin Conditions Compared to Those Without a Waiver | 246 |
| Young SYN #99/030 | C | Characteristics and Correlates of Asthma in the Military Population of the Northwestern United States | 247 |
| Department of Psychiatry | | | 248 |
| Hicks RD #98/029 | C | Migraine Prevention with Magnatherm Pulsing Electromagnetic Fields | 249 |
| Department of Psychology | | | 250 |
| Brencick M #98/091 | T | Prevention of Tension Headaches with Microcurrent Electrical Stimulation: A Placebo Controlled Pilot Study | 251 |
| Lester KS #95/130 | C | MMPI-2 Profiles in Korean Military Dependents | 252 |
| Lester KS #99/016 | O | Prevalence of Anxiety Symptoms in General Pediatric and Specialty Pediatric Populations | 253 |
| Department of Radiology | | | 254 |
| Benson AJ #99/007 | C | Pseudo-dissection of the Main Pulmonary Artery by CT | 255 |
| Keadle DM #96/081 | T | Pulmonary Manifestations of Gastro-esophageal Reflux Disease: HRCT Findings | 256 |
| Keadle DM #99/088 | O | Comparison of Computed Tomography Angiography and Digital Subtraction Angiography for the Pre-Operative Evaluation of Carotid Artery Disease | 257 |
| Kim-Ahn GJ #99/085 | O | Radiographic and Clinical Correlation of the Outcome of Calcaneal Osteotomy for Talocalcaneal Valgus | 258 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|--|------------|
| Manzo AR #98/093 | O | Magnetic Resonance Imaging of the Sternum | 259 |
| Murray SP #98/047 | C | Clinical Evaluation and Diagnostic Tests for Suspected Pulmonary Embolic Disease: A Survey of Physician Attitudes and Correlation to Clinical Practice | 260 |
| Murray SP #98/106 | O | Peri-Hepatic Lymphadenopathy in Patients with Chronic Hepatitis | 261 |
| Murray SP #99/069 | O | Percutaneous Image-Guided Biopsy Service: Improved Diagnostic Yield with Case-Specific Use of Computed-Tomography, Ultrasound, and Fluoroscopy | 262 |
| Reinschmidt JP #98/034 | O | Computed Tomography Guided Percutaneous Placement of Injection Coils Ligated to Suture and Thoracoscopic Pulmonary Resection | 263 |
| Shaffer N #96/142 | C | Radiologic Guided Aspiration of Intra-articular Ganglia in the Knee | 264 |
| Shepherd PJ #99/099 | O | Comparison of MRI with Bone Scintigraphy in the Evaluation of Suspected Hip Stress Fractures | 265 |
| Youngberg RA #95/166 | O | Cost Effectiveness of Early MRI in Traumatic Wrist Injury | 266 |
| Ft. Lewis Rangers | | | 267 |
| Taylor C #97/117 | S | Special Operations Medical NCO Sustainment Training Using the Goat Model (<i>Capra hircus</i>) | 268 |
| General Surgery Service, Department of Surgery | | | 269 |
| Beekley AC #98/098 | O | Gastrin Releasing Peptide Receptor: A Potential Novel Marker of Clinical Aggression in Human Neuroblastoma Cells | 270 |
| Carter PL #97/047 | C | Genetic Testing for Inherited Cancer | 271 |
| Chung MH #96/045 | T | The Effect of Low-Dose Dopamine on Splanchnic Blood Flow with Intra-abdominal Hypertension in Domestic Yorkshire Swine, <i>Sus scrofa</i> | 272 |
| Eggebroten WE #99/005 | O | Emergency Surgical Procedures Laboratory Training Using the Goat (<i>Capra hircus</i>) | 273 |
| Haque MI #98/083 | O | Porcine Iliac Artery Injury Model for Testing of Absorbable Vascular Templates | 274 |
| Martin MJ #98/078 | O | Inflammatory Response Related to Tracheobronchial Distention in Pigs (<i>Sus scrofa</i>) Using Absorbable Tracheal Stents | 275 |
| McDonald JM #97/064 | T | Prognostic Significance of p53 Mutations in the Lymph Nodes of Dukes B Colon Cancer Patients | 276 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|---|------------|
| McDonald JM #99/021 | O | Development of an In-vivo Model of Free Radical Production Utilizing Dihydroethidine in the Mouse (mus musculus) | 277 |
| Ono CM #99/004 | O | Forward Surgical Team (FST) Sustainment Training Using the Goat Model (Capra hircus) | 278 |
| Porter CA #99/087 | O | Madigan Army Medical Center Advanced Laparoscopic Training Using the Pig (Sus scrofa) | 279 |
| Sanborn CK #95/022 | O | The Use of Autologous Fibrin Glue to Prevent Post-operative Seromas in Patients Undergoing modified Radical Mastectomy | 280 |
| Sanborn CK #99/006 | C | Effects of Differentiation on Telomerase Activity in Neuroblastoma Cell Lines | 281 |
| Sebesta JA #97/141 | C | A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in ERCP Brushings for Detection of Pancreatic and Biliary Cancer | 282 |
| Sebesta JA #97/143 | O | A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in Thyroid FNAs for the Detection of Thyroid Cancer | 283 |
| Sebesta JA #98/069 | T | Use of Alternative Medicine Therapies for Treatment of Cancer | 284 |
| Sebesta JA #98/096 | O | Gastrin Releasing Peptide: A Potential Growth Factor Expressed in Human Neuroblastoma Tumors | 285 |
| Sebesta JA #99/012 | O | Comparison of the Harmonic Scalpel and the Standard Technique for Right Hepatic Lobectomy in Pigs (Sus scrofa) | 286 |
| Sebesta JA #99/097 | O | Gastrin Releasing Peptide's Effect on Telomerase Activity in Human Neuroblastoma Cell Lines | 287 |
| Trombetta LJ #98/097 | C | Telomerase Level in Neuroblastoma Tumors: Can This Be Used to Guide Prognosis and Management? | 289 |
| Trombetta LJ #98/099 | O | Postoperative Cisapride Therapy After Abdominal Surgery in the Pediatric Patient | 290 |
| Trombetta LJ #98/100 | T | Intra-abdominal Pressure in Elective Aortic Surgery Patients: A Prospective Series | 291 |
| Trombetta LJ #99/086 | O | Telomerase Enzyme Activity in a Metastatic Neuroblastoma Nude Mouse Model | 292 |
| Ophthalmology Service, Department of Surgery | | | 294 |
| Ainbinder DJ #98/103 | C | Madigan Eye and Orbit Trauma Scale | 295 |
| Bushley DM #99/041 | O | Refractive Changes Due to Hypoxia Following Cataract Surgery | 296 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|---|------------|
| Chismire KJ #97/086 | C | A 6-Month, Randomized, Double-Masked Comparison of Fixed Combination of Latanoprost and Timolol with the Individual Components, Continuing into a 6-Month Open Label Safety Study of Fixed Combination in Patients with Glaucoma or Ocular Hypertension | 297 |
| Chun BB #97/060 | C | Radial Keratotomy and Phototherapeutic Keratectomy: Comparison of Corneoscleral Integrity After Controlled Blunt Trauma to Post Mortem Eyes That Had Refractive Surgery | 298 |
| Chun BB #99/017 | S | Activated Protein C Resistance in Ophthalmologic Ischemic Syndromes | 299 |
| Dahlhauser KF #98/050 | O | A Phase III Study of MDX-RA Compared with Placebo Administered in Patients Undergoing Phacoemulsification or Planned Extracapsular Extraction for Cataract | 300 |
| Mader TH #97/119 | O | The Use of Photorefractive Keratectomy on Active Duty U.S. Army Personnel for the Correction of Myopia | 301 |
| McMann MA #98/032 | C | Study of Differential Swelling Using an ORB Scan (ORBTEK, Inc.) in Corneas Which Have Undergone Radial Keratotomy and are Exposed to Hypoxia with Resultant Corneal Edema | 302 |
| Nelson ML #97/121 | T | Refractive Changes During Exposure to the Hyperbaric Environment Following Radial Keratotomy Surgery | 303 |
| Nelson ML #98/101 | C | Refractive Changes Due to Hypoxia Following LASIK Corneal Surgery | 304 |
| Parmley VC #99/052 | O | Correction of Low Myopia (-1.00 to -3.50 diopters) in Active Duty Personnel | 305 |
| Raymond WR #98/056 | C | Congenital Esotropia Observational Study (CEOS) | 306 |
| Orthopedics Service, Department of Surgery | | | 307 |
| Cannon CP #97/098 | C | Fixation of Salter Osteotomies with Bioabsorbable Pins | 308 |
| Cannon CP #98/085 | T | Healing of Tibial Stress Fractures Using Pulsed Electromagnetic Fields (PEMF) | 309 |
| Gerlinger TL #98/081 | O | A Prospective Randomized, Blinded Study, Comparing Treatment of Fifth Metacarpal Neck Fractures | 310 |
| Jones DEC #97/051 | T | Comparison of Small Bone Cannulated Screw Systems | 311 |
| Marchant BG #98/087 | S | Duplex Sonographic Analysis of the Common Femoral Vein in Non-Weight Bearing: Age Difference in Men | 312 |
| Marchant BG #98/088 | S | Blood Flow in the Common Femoral Vein in the Erect Patient with the Application of Compressive Devices | 313 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------------|
| Noonburg GE #97/125 | O | External Fixation of Displaced Clavicle Fractures | 314 |
| Pitcher JD #98/082 | C | A Dose-Ranging, Multicenter, Randomized, Subcutaneous, Low-Dose, Heparin-Controlled, Double-Blind Clinical Trial to Assess the Safety and Efficacy of Orally Administered Heparin With A Novel Carrier System (SNAC) in the Prevention of Major Venous Thromboembolic Events Following Elective Total Hip Arthroplasty | 315 |
| StPierre P #96/086 | O | A Prospectively Randomized Trial of Rotator Cuff Repair to Cortical Bone versus A Cancellous Trough | 316 |
| StPierre P #96/092 | O | A Prospectively Randomized Study on the Effectiveness of Post-Operative Knee Bracing for Anterior Cruciate Ligament Reconstruction | 317 |
| Williamson RV #97/095 | O | Delayed versus Immediate Open Repair of Achilles Tendon Rupture; A Randomized Prospective Trial | 318 |
| Williamson RV #97/099 | O | Tendon-Healing to Cortical Bone After Tendon Reattachment Using Suture Anchors. A Biomechanical and Histological Evaluation in Goats | 319 |
| Otolaryngology Service, Department of Surgery | | | 320 |
| Coppit GL #98/003 | C | Modification and Control of Wound Healing in Tracheobronchial Injuries Using Minimally Invasive Surgical Techniques and Biological Growth Regulators | 321 |
| Crawford JV #99/068 | O | Pharmacotherapy of Meniere's Disease. Project 1: Effects of General Anesthesia on the Vestibular System | 322 |
| Cupero TM #99/002 | C | The Effects of Functional Septoplasty on Facial Growth | 323 |
| Cupero TM #99/008 | C | The Effect of Pre-operative Local Injection of a Steroid/Anesthetic Mixture on Postoperative Tonsillectomy Pain | 324 |
| Downey TJ #99/065 | O | AlloDerm Tympanoplasty of Chronic Tympanic Membrane Perforations: An Animal Model | 325 |
| Mesaros GJ #94/177 | C | ENT Surgical Simulator Project | 327 |
| Silva AB #96/044 | T | Pediatric Bronchoesophagology Laboratory Using Swine (<i>Sus scrofa</i>) | 328 |
| Silva AB #99/050 | O | Pediatric Bronchoesophagology Laboratory Using Swine (<i>Sus scrofa</i>) | 329 |
| Urology Service, Department of Surgery | | | 330 |
| Ahuja SK #96/158 | O | Multi-center Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicor Inflatable Penile Prosthesis | 331 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Ahuja SK #98/023 | T | Quality of Life of Female Patients After Anti-incontinence Surgery | 332 |
| Ahuja SK #98/031 | C | Dose Escalation Study with Tolterodine in Patients with Overactive Bladder. A Single-Blind Study in Patients with Symptoms of Overactive Bladder Including Urinary Urgency and Frequency With or Without Urge Incontinence | 333 |
| Ahuja SK #99/044 | T | A Phase II, Double-Blind, Randomized, Placebo-Controlled, Crossover Study of the Safety and Efficacy of Dapoxetine HCl in the Treatment of Premature Ejaculation | 334 |
| Ahuja SK #99/048 | C | Screening Protocol for Identification of Patients with Erectile Dysfunction for Participation in Schering Study P00186 (Twelve-Week Double-Blind Treatment of Oral Phentolamine, Oral Sildenafil Citrate vs Placebo) | 336 |
| Ahuja SK #99/054 | C | A Double-Blind, Twelve-Week Comparative Efficacy and Safety Study of Oral Phentolamine Mesylate, Oral Sildenafil Citrate Vs. Placebo in Patients with Erectile Dysfunction | 337 |
| Costabile RA #99/080 | O | Phase III Randomized Study of a Single Adjunctive Instillation of Intravesical AD-32 (N-Trifluoroacetyladiamycin-14-Valerate) versus No Adjunctive Therapy Immediately Following Transurethral Resection in Patients with Multiple Superficial (Ta/T1) Bladder Tumors | 338 |
| Costabile RA #99/089 | O | Phase III Randomized, Double-Blind Study of DFMO vs. Placebo in Low Grade Superficial Bladder Cancer | 339 |
| Costabile RA #99/090 | O | A Randomized Double-Blind Placebo-Controlled Phase III Trial Evaluating Zoledronate Plus Standard Therapy versus Placebo Plus Standard Therapy in Patients with Recurrent Carcinoma of the Prostate Who Are Asymptomatic with Castrate Levels of Testosterone and Have Rising PSA Levels Without Radiologically-evident Metastatic Disease | 340 |
| Costabile RA #99/091 | O | A National Phase II Trial of Intron Interferon (Alpha 2b) Plus BCG for Treatment of Superficial Bladder Cancer | 341 |
| Costabile RA #99/095 | O | The Evaluation of Seminal Leucocytes and Cytokine Function of Infertile Males | 342 |
| Costabile RA #99/096 | O | Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens | 343 |
| Costabile RA #99/101 | O | A Six-Month, Two-Part, Sequential, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Endocrine Efficacy of Monthly Doses of LA-2500 in Patients with Advanced Prostate Cancer | 344 |
| Ellsworth JB #98/077 | C | Depo-Provera Therapy for Hot Flushes Associated with Hormonal Treatment of Advanced Carcinoma of the Prostate | 345 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------------|
| Lance RS #94/051 | O | Immunohistochemical Localization of Insulin-Like Growth Factor (IGF) Binding Proteins in Prostate Cancer | 346 |
| Lance RS #95/104 | O | Telomere Length and Telomerase Activity in Human Testicular Cancer | 347 |
| Lance RS #95/134 | C | Comparative Study of the Clinical Efficacy of Two Dosing Regimens of Eulexin: 250 mg Q8h vs 500 mg QD | 348 |
| Lance RS #97/097 | O | Telomerase Activity in Voided Urine and Bladder Washings As A Diagnostic and Surveillance Marker for Transitional Cell Carcinoma | 349 |
| Lance RS #97/120 | C | A Randomized, Double-Blind Study (With Open-Label Treatment Extension) to Evaluate the Efficacy and Safety of VIAGRA (Sildenafil) in Erectile Dysfunction | 350 |
| Lance RS #97/147 | O | Comparison of Quality of Life (QOL) Differences Between Radical Retropubic (RRP) and Radical Perineal Prostatectomy (RPP) for Clinically Localized Prostate Cancer | 351 |
| Lance RS #98/092 | O | Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcomes, and Prognostic Analysis | 352 |
| Lance RS #98/114 | O | A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemiological, Detection, Natural history, and New Management Strategies for Prostate Cancer | 353 |
| Lance RS #99/003 | O | A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEX) 150 mg Monotherapy Versus Placebo in Patients with a Rising PSA After Radical Prostatectomy for Prostate Cancer | 354 |
| Lance RS #99/109 | O | Limits of Serum Detection of Circulating Prostate and Bladder Cancer Cells using Telomerase Reverse Transcriptase (H-TERT) mRNA Detection by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) | 355 |
| O'Reilly KJ #97/129 | C | The Correlation Between Free and Total PSA, Prostate Specific Membrane Antigen and Sex Hormone Binding Globulin Across the Spectrum of Prostate Disease | 357 |
| Ruiz HE #99/043 | O | Liposomal Amikacin (MiKasome) in Complicated Urinary Tract Infections: Randomized, Double, Blind, Dose-Ranging Study | 358 |
| Vascular Surgery, Department of Surgery | | | 359 |
| Andersen CA #96/163 | O | Clinical Evaluation of the Handling and Performance of the HEMASHIELD Knitted Double Velour Fabric and Polytetrafluoroethylene (PTFE) Patched for Carotid Endarterectomy Patch Procedures in Patients | 360 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|--|------------|
| Johnson CA #95/097 | O | Abdominal Aortic Aneurysm (AAA) and Chronic Obstructive Pulmonary Disease (COPD); Is There a Relationship | 361 |
| Olsen SB #99/081 | O | A Double-Blind, Randomized, Parallel Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of NM-702 in Subjects with Intermittent Claudication | 362 |
| Weed Army Community Hospital | | | 363 |
| Price C #98/084 | O | Confirmation of Endotracheal Tube Placement by Special Operations Combat Corpsmen and Medics | 364 |
| Department of Clinical Investigation | | | 365 |
| Bullock JM #98/104 | O | Expression of Angiostatin and TSP1 in Human Microvascular Endothelial Cells and Breast Cancer Cells: In Vitro Study of a Potentially Superior Antiangiogenic Activity | 366 |
| Hume RF #97/128 | O | Enhancing the Effectiveness of Tamoxifen Therapy in Breast Cancer | 367 |
| Moore KH #95/025 | S | The Department of Clinical Investigation's Molecular Biology Short Course for Physicians | 368 |
| Moore KH #95/138 | T | The Effect of Tamoxifen and Ionizing Radiation on Expression of Bcl-2, Bcl-x, and p53 in Breast Cancer Cells In Vitro | 369 |
| Moore KH #97/033 | T | Is BRCA1 Loss of Expression Found in Tumors Others Than Breast and Ovarian Cancer? | 370 |
| Qabar AN #97/013 | C | The Role of Thrombospondin in Macrophage-Mediated Wound Healing. A Structural/Functional Dissection of Thrombospondin | 371 |
| Gynecology Oncology Group | | | 372 |
| Potter ME #81/035 | O | GOG 0041: Surgical Staging of Ovarian Carcinoma | 373 |
| Potter ME #81/105 | O | GOG 0052: A Phase III Randomized Study of Cyclophosphamide Plus Adriamycin Plus Platinol Versus Cyclophosphamide Plus Platinol in Patients with Optimal Stage II Ovarian Adenocarcinoma | 374 |
| Potter ME #84/033 | O | GOG 0072: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and a Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease | 375 |
| Potter ME #84/074 | O | GOG 0078: Evaluation of Adjuvant VP-16, Bleomycin, and Cisplatin (BEP) Therapy in Totally Resected Choriocarcinoma, Endodermal Sinus Tumor, Embryonal Carcinoma and Grade 3 Immature Teratoma of the Ovary, Pure and Mixed with Other Elements | 376 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|---|---|---|------------|
| Potter ME #86/089 | O | GOG 0085: A Randomized Comparison of Hydroxyurea versus 5-FU Infusion and Bolus Cisplatin as an Adjuvant to Radiation Therapy in Patients with Stages II-B, III, and IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes | 377 |
| Potter ME #87/104 | O | GOG 0092: Treatment of Selected Patients with Stage 1B Carcinoma of the Cervix After Radical Hysterectomy and Pelvic Lymphadenectomy: Pelvic Radiation Therapy versus No Further Therapy | 378 |
| Potter ME #87/028 | O | GOG 0095: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected IAi and IBi and IAii and IBii Ovarian Cancer, Phase III | 379 |
| Potter ME #87/091 | O | GOG 0099: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma | 380 |
| Potter ME #91/086 | O | GOG 0109 (SWOG 8797): 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 I-A2, I-B, and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection | 381 |
| Potter ME #91/074 | O | GOG 0115: Bleomycin (NSC #125066), Etoposide (NSC #141540) and Cisplatin (NSC #119875) (BEP) as First-Line Therapy of Malignant Tumors of the Ovarian Stroma (Granulosa Cell, Sertoli-Leydig Tumor, and Unclassified Sex Cord Stromal Tumor) | 382 |
| Potter ME #93/063 | O | GOG 0123: A Randomized Comparison of Radiation Therapy & Adjuvant Hysterectomy vs Radiation Therapy & Weekly Cisplatin & Adjuvant Hysterectomy in Patients with Bulky Stage IB Carcinoma of the Cervix | 383 |
| National Surgical Adjuvant Breast and Bowel Project (NSABBP) | | | 384 |
| Bertram KA #99/001 | O | NSABBP C-06: A Clinical Trial Comparing Oral Uracil/Ftorafur (UFT) Plus Leucovorin (LV) with 5-Fluorouracil (5-FU) Plus LV in the Treatment of Patients with Stages II and III Carcinoma of the Colon | 385 |
| Bertram KA #93/147 | O | NSABBP R-03: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5-FU-LV and RTX) in Patients with Operable Carcinoma of the Rectum | 386 |
| Pediatric Oncology Group | | | 387 |
| Palmer SR #98/072 | C | POG 7837: Evaluation of Systemic Therapy for Children with Lymphoblastic Lymphoma Including T-Cell Disease | 388 |
| Palmer SR #98/073 | O | POG 8602: Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC #14) | 389 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Palmer SR #98/076 | O | POG 8615: A Phase III Study of Large Cell Lymphomas in Children and Adolescents: A Comparison of Two Treatment Regimens - ACOP+ versus APO | 390 |
| Palmer SR #93/141 | O | POG 8650: Intergroup National Wilms' Tumor Study - 4 | 391 |
| Palmer SR #98/074 | O | POG 8823/34: Recombinant Alpha-Interferon in Childhood Chronic Myelogenous Leukemia | 392 |
| Palmer SR #95/052 | C | POG 8930: A Comprehensive Genetic Analysis of Brain Tumors | 393 |
| Palmer SR #98/075 | O | POG 9005: ALinC #15 - Dose Intensification of Methotrexate and 6-Mercaptopurine for ALL in Childhood - A Randomized Phase III Study | 394 |
| Palmer SR #95/018 | O | POG 9031: Treatment of Children with High Stage Medulloblastoma: Cisplatin/VP-16 Pre vs Post-Irradiation | 395 |
| Palmer SR #93/164 | O | POG 9047: Neuroblastoma Biology Protocol | 396 |
| Palmer SR #95/008 | C | POG 9153: Intergroup Rhabdomyosarcoma Study/Laboratory Evaluation of Tumor Tissue | 397 |
| Palmer SR #95/084 | O | POG 9182: HIV/Malignancy Biology Protocol | 398 |
| Palmer SR #95/056 | O | POG 9201: ALINC #16 Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia, A Pediatric Oncology Group Phase III Study | 399 |
| Palmer SR #94/033 | O | POG 9219: Treatment of Localized Non-Hodgkin's Lymphoma, A POG Phase IV Study | 400 |
| Palmer SR #93/148 | C | POG 9233/34: A Phase III Randomized Trial of standard vs Dose-Intensified Chemotherapy for Children Less Than 3 Years of Age With A CNS Malignancy Treated With or Without Radiation Therapy | 401 |
| Palmer SR #96/096 | O | POG 9315: A Phase III Study of Large Cell Lymphomas in Children and Adolescents; Comparison of APO vs. APO + IDMTX/HDARA-C | 402 |
| Palmer SR #94/072 | C | POG 9317: Chemotherapy for Children with Advanced Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B Cell ALL | 403 |
| Palmer SR #95/168 | O | POG 9323: Interferon-Alpha 2b Plus Hydroxyurea and Ara-C for Chronic Phase ACML in Children, A POG Pilot Study | 404 |
| Palmer SR #94/092 | O | POG 9351/CCG 7921: Trial of Doxorubicin, Cisplatin, and Methotrexate With and Without Ifosfamide, With and Without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma | 406 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Palmer SR #95/087 | O | POG 9362: A Phase II Study of Alpha Interferon in HIV-Related Malignancies | 407 |
| Palmer SR #95/058 | O | POG 9400: ALinC 16 Classification (C) Protocol | 408 |
| Palmer SR #96/144 | O | POG 9404: T-Cell #4 Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma | 409 |
| Palmer SR #95/059 | O | POG 9405: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL) | 410 |
| Palmer SR #95/060 | O | POG 9406: ALinC #16 - Protocol for Patients With Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL) | 412 |
| Palmer SR #95/089 | O | POG 9421: Phase III Evaluation of Standard vs. High Dose ARA-C Induction Followed by the Randomized Use of Cyclosporine A As An MDR Reversal Agent, Compared to Allogeneic BMT, in Childhood AML | 414 |
| Palmer SR #97/071 | O | POG 9425: Advanced Stage Hodgkin's Disease, A POG Phase III Study | 415 |
| Palmer SR #97/054 | O | POG 9426: Response Dependent Treatment of Stages IA, IIA, and IIIA(1-micro) Hodgkin's Disease with DBVE and Low Dose Involved Field Irradiation with or without Zinecard | 416 |
| Palmer SR #96/097 | O | POG 9440: National Wilms Tumor Study - 5: Therapeutic Trial and Biology Study | 417 |
| Palmer SR #98/090 | O | POG 9442: National Wilms Tumor Late Effects Study | 418 |
| Palmer SR #96/039 | O | POG 9457: Intensive Therapy with Growth Factor Support for Patients with Ewing's Tumor Metastatic at Diagnosis | 419 |
| Palmer SR #98/048 | C | POG 9464: Cyclophosphamide Plus Topotecan in Children with Recurrent or Refractory Solid Tumors | 420 |
| Palmer SR #96/035 | O | POG 9490: Topotecan Followed by Multimodal, Multiagent Therapy for Children and Adolescents with Newly Diagnosed Stage IV/Clinical Group IV Rhabdomyosarcoma, an IRS-V Pilot Study | 421 |
| Palmer SR #97/089 | O | POG 9553: A Phase II of Neoadjuvant Vincristine, Ifosfamide, Doxorubicin, and G-CSF in Children with Advanced Stage Non-rhabdomyosarcoma Soft Tissue Sarcomas | 422 |
| Palmer SR #96/120 | O | POG 9605: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL) | 423 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------|
| Palmer SR #99/045 | O | POG 9631: A Phase II Feasibility Study of Oral Etoposide Given Concurrently with Radiotherapy Followed with Dose Intensive Adjuvant Chemotherapy for Children with Newly-Diagnosed High Stage Medulloblastoma | 424 |
| Palmer SR #98/065 | O | POG 9641: Primary Surgical Therapy for Biologically Defined Low-Risk Neuroblastoma; A Pediatric Oncology Group Children's Cancer Group, Phase III, Intergroup Study | 425 |
| Palmer SR #98/064 | O | POG 9701 (A09701): A Phase II Study of Temodal (SCH 52365; Temozolomide, IND #52797) in Children and Adolescents with Recurrent Central Nervous System (CNS) Tumors | 426 |
| Palmer SR #98/066 | O | POG 9720: Idarubicin and Cladribine in Recurrent and Refractory Acute Myeloid Leukemia: A Pediatric Oncology Group Phase II Study | 427 |
| Palmer SR #97/088 | O | POG A9961: A Phase III Prospective Randomized Study of Craniospinal Radiotherapy Followed by one of Two Adjuvant Chemotherapy Regimens (CCNU, CDDP, VCR, or CPM, CDDP, VCR) in Children with Newly-Diagnosed Average Risk Medulloblastoma | 428 |
| Palmer SR #97/090 | O | POG D9501: Topotecan and Cyclophosphamide, Followed by Multimodel, Multiagent Therapy for Children & Adolescents with Newly Diagnosed Stage IV/Clinical Group IV Rhabdomyosarcoma, an IRS-V Pilot Study | 429 |
| Palmer SR #97/145 | O | POG D9602: Actinomycin D and Vincristine with or without Radiation Therapy for Newly Diagnosed Patients with Low-Risk Rhabdomyosarcoma or Undifferentiated Sarcoma: An IRS-V Protocol | 430 |
| Radiological Diagnostic Oncology Group | | | 431 |
| Smith DV #95/136 | C | RDOG(5) 6881: Stereotactic Fine Needle Aspiration Biopsy and Core Needle Biopsy in the Work-up of Lesions Detected by Mammography | 432 |
| Southwest Oncology Group | | | 433 |
| Bertram KA #77/054 | T | SWOG 7406: Advanced Hodgkin's Disease: Remission Induction (MOPP #5). Phase III | 434 |
| Bertram KA #77/053 | T | SWOG 7433: Non-Hodgkin's Lymphomas (Stages I, IE, II, and IIE). A Phase III Study. | 435 |
| Bertram KA #77/024 | C | SWOG 7436: Combined Modality Therapy of Breast Cancer | 436 |
| Bertram KA #77/018 | T | SWOG 7510: Intensive Adjuvant Chemotherapy with or without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel | 437 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------|
| Bertram KA #78/002 | T | SWOG 7713/14: Chemoimmunotherapy in Non-Hodgkin's Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy: Levamisole vs No Maintenance After Remission Induction | 438 |
| Bertram KA #78/047 | T | SWOG 7808: Combination Modality Treatment for Stage III and Stage IV Hodgkin's Disease, MOPP #6 | 439 |
| Bertram KA #79/096 | T | SWOG 7827: Combined Modality Therapy for Breast Carcinoma, Phase III | 440 |
| Bertram KA #84/018 | T | SWOG 8216/38: Comparison of BCG Immunotherapy and Adriamycin for Superficial Bladder Cancer | 441 |
| Bertram KA #85/076 | T | SWOG 8269: Concurrent Chemo-Radiotherapy for Limited Small Cell Carcinoma of the Lung, Phase II | 442 |
| Bertram KA #83/056 | O | SWOG 8294: Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study | 443 |
| Bertram KA #84/059 | T | SWOG 8313: Multiple Drug Adjuvant Chemotherapy for Patients with ER Negative Stage II Carcinoma of Breast, Phase III | 444 |
| Bertram KA #85/009 | T | SWOG 8410: Combination Chemotherapy of Intermediate and High-Grade Non-Hodgkin's Lymphoma with m-BACOD, Phase II | 445 |
| Bertram KA #86/007 | T | SWOG 8417/19: Evaluation of Two Consolidation Regimens in the Treatment of Adult Acute Lymphoblastic Leukemia, Phase III | 446 |
| Bertram KA #87/107 | T | SWOG 8507: Maintenance versus No Maintenance BCG Immunotherapy of Superficial Bladder Cancer, Phase III | 447 |
| Bertram KA #86/080 | T | SWOG 8516: A Phase III Comparison of CHOP versus m-BACOD versus ProMACE-CytaBOM versus MACOP-B in Patients with Intermediate or High-Grade Non-Hodgkin's Lymphoma | 448 |
| Bertram KA #85/073 | O | SWOG 8590: Phase III Study to Determine the Effect of Combining Chemotherapy with Surgery and Radiotherapy for Resectable Squamous Cell Carcinoma of the Head and Neck, Phase III Intergroup | 449 |
| Bertram KA #87/045 | T | SWOG 8600: A Randomized Investigation of High-Dose Versus Standard Dose Cytosine Arabinoside with Daunorubicin in Patients with Acute Non-lymphocytic Leukemia | 450 |
| Bertram KA #88/065 | T | SWOG 8736: Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy | 451 |
| McCune DE #94/119 | O | SWOG 8794: Treatment of Pathologic Stage C Carcinoma of the Prostate With Adjuvant Radiotherapy | 452 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Bertram KA #88/066 | O | SWOG 8796: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III Intergroup (INT 0074) | 453 |
| Bertram KA #90/064 | T | SWOG 8809: A Phase III Study of Alpha-Interferon Consolidation Following Intensive Chemotherapy with ProMACE-MOPP (Day 1-8) in Patients with Low Grade Malignant Lymphomas | 454 |
| Bertram KA #89/080 | O | SWOG 8814 (ECOG 4188, NCCTG 883051): Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Breast Cancer Having Involved Axillary Nodes and Positive Hormone Receptors | 455 |
| Bertram KA #91/087 | O | SWOG 8819: Central Lymphoma Repository Tissue Procurement Protocol; Companion Protocol to SWOG Studies: 8516, 8736, 8809, 8907, and 8954 | 456 |
| Bertram KA #90/027 | O | SWOG 8851 (EST 5811, INT-0101): Phase III Comparison of Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + Zoladex or CAF + Zoladex + Tamoxifen) in Premenopausal Women with Axillary Node-Positive, Receptor- Positive Breast Cancer | 457 |
| Bertram KA #90/047 | T | SWOG 8854: prognostic Value of Cytometry Measurements of Breast Cancer DNA from Postmenopausal Patients with Involved Nodes and Receptor Positive Tumors: A Companion Protocol to SWOG 8814 | 458 |
| Bertram KA #91/067 | O | SWOG 8855: Prognostic Value of Cytometry Measurements of Cellular DNA Parameters in Locally Advanced, Previously Untreated Head and Neck Cancer Patients | 459 |
| Bertram KA #90/055 | T | SWOG 8892 (EST 2388, RTOG 8817, INT 0099): A Study of Radiotherapy with or without Concurrent Cisplatin in Patients with Nasopharyngeal Cancer, Phase III | 460 |
| Bertram KA #90/029 | O | SWOG 8897 (EST-2188, CALGB-8897, INT-0101): Phase III Comparison of Adjuvant Chemotherapy With or Without Endocrine Therapy in High-Risk, Node Negative Breast Cancer Patients, and a Natural History Follow-up Study in Low-Risk, Node Negative Patients | 461 |
| Bertram KA #89/021 | O | SWOG 8899: A Prospectively Randomized Trial of Low-Dose Leucovorin = 5-FU, High-Dose Leucovorin + 5-FU, Levamisole + 5-FU, or Low-Dose Leucovorin + 5-FU + Levamisole Following Curative Resection in Selected Patients with Durke's B or C Colon Cancer | 462 |
| Bertram KA #91/089 | O | SWOG 8947: Central Lymphoma Serum Repository Protocol; Companion Protocol to SWOG Studies 8516, 8736, 8809, and 8816 | 463 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Bertram KA #91/007 | T | SWOG 8957: Feasibility Trial of Post-Operative Radiotherapy Plus Cisplatin Followed by Three Courses of 5-FU Plus Cisplatin in Patients with Resected Head and Neck Cancer, Phase II Pilot | 464 |
| Bertram KA #90/056 | O | SWOG 8997 (ECOG 3887): Phase III Chemotherapy of Disseminated Advanced Stage Testicular Cancer with Cisplatin Plus Etoposide with Either Bleomycin or Ifosfamide | 465 |
| Bertram KA #93/056 | O | SWOG 9003: Fludarabine for Waldenstrom's Macroglobulinemia (WM): A Phase II Study for Untreated and Previously Treated Patients | 466 |
| Bertram KA #91/094 | O | SWOG 9007: Cytogenetic Studies in Leukemia Patients, Ancillary | 467 |
| Bertram KA #92/051 | T | SWOG 9008: Trial of Adjuvant Chemoradiation After Gastric Resection for Adenocarcinoma, Phase II | 468 |
| Bertram KA #91/033 | O | SWOG 9013 (RTOG 89-11, INT-0113): A Prospective Randomized Comparison of Combined Modality Therapy for Squamous Carcinoma of the Esophagus: Chemotherapy Plus Surgery Versus Surgery Alone for Patients with Local REgional Disease | 469 |
| Bertram KA #93/143 | T | SWOG 9019: A Phase III, Randomized, Prospective Comparison Between Chemotherapy Plus Radiotherapy, and the Same Chemotherapy Plus Radiotherapy Together With Surgery for Selected Stage IIIA (Positive Mediastinal Nodes) and Selected Stage IIIB (No Malignant Effusion) Non-Small Cell Lung Cancer | 470 |
| Bertram KA #92/052 | T | SWOG 9031: A Double Blind Placebo Controlled Tiral of Daunomycin and Cytosine Arabinoside With or Without rhG-CSF in Elderly Patients With Acute Myeloid Luekemia, Phase III | 471 |
| Bertram KA #95/062 | O | SWOG 9035: Randomized Trial of Adjuvant Immunotherapy with an Allogeneic Melanoma Vaccine for Patients with Intermediate Thickness, Node Negative Malignant Melanoma, Phase III | 472 |
| Bertram KA #91/069 | O | SWOG 9040 (CALGB-9081, INT-0014): Intergroup Sectal Adjuvant Protocol, A Phase III Study | 473 |
| Bertram KA #94/104 | O | SWOG 9041: Chemoprevention of Recurrent Adenomas and Second Primary Colorectal Carcinoma. A Phase III Pilot Study. | 474 |

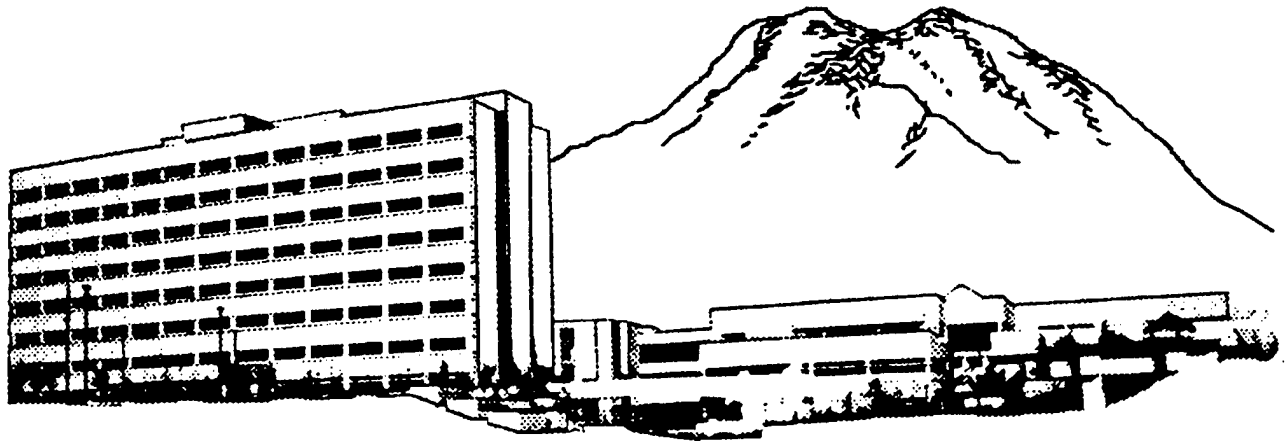
| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------|
| Bertram KA #97/096 | O | SWOG 9059 (E1392, INT-0126): Phase III Comparison of Standard Radiotherapy versus Radiotherapy plus Simultaneous Cisplatin, versus, split-Course Radiotherapy plus Simultaneous Cisplatin and 5-Fluorouracil, in Patients with Unresectable Squamous Cell Carcinoma of the Head and Neck | 475 |
| Bertram KA #93/032 | O | SWOG 9061 (EST-2190, INT 0121): A Phase III Study of Conventional Adjuvant Chemotherapy vs High Dose Chemotherapy and Autologous Bone Marrow Transplantation or Stem Cell Transplantation as Adjuvant Intensification Therapy Following Conventional Adjuvant Chemotherapy in Patients with Stage II and III Breast Cancer at High Risk of Recurrence | 476 |
| Bertram KA #92/017 | T | SWOG 9125: A Phase II Trial of CVAD/Verapamil/Quinine for Treatment of Non-Hodgkin's Lymphoma | 478 |
| Bertram KA #94/097 | O | SWOG 9133: Randomized Trial of Subtotal Nodal Irradiation versus Doxorubicin Plus Vinblastine and Subtotal Nodal Irradiation for Stage I-IIA Hodgkin's Disease, Phase III | 479 |
| Bertram KA #97/042 | O | SWOG 9201 (RTOG 91-11): Phase III Trial to Preserve the Larynx: Induction Chemotherapy and Radiation Therapy versus Concomitant Chemotherapy and Radiation Therapy Versus Radiation | 480 |
| Bertram KA #93/097 | O | SWOG 9205: Central Prostate Cancer Serum Repository Protocol | 481 |
| Bertram KA #94/115 | O | SWOG 9208: Health Status and Quality of Life in Patients With Early Stage Hodgkin's Disease: A Companion Study to SWOG 9133 | 482 |
| Costabile RA #94/010 | O | SWOG 9217: Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III, Intergroup | 483 |
| Bertram KA #95/023 | C | SWOG 9219: A Phase II Evaluation of Interleukin-4 (IL-4) in Patients With Non-Hodgkin's Lymphoma or Hodgkin's Disease | 484 |
| Bertram KA #93/136 | O | SWOG 9221, MDACC ID 91-025, INT-191-001: Phase III Double-Blind Randomized Trial of 13-Cis Retinoic Acid (13-cRA) to Prevent Second Primary Tumors (SPTs) in Stage I Non-Small Cell Lung Cancer | 485 |
| Bertram KA #93/108 | O | SWOG 9237: Evaluation of Topotecan in Refractory and Relapsing Multiple Myeloma | 486 |
| Bertram KA #93/092 | O | SWOG 9245: Central Lymphoma Repository Tissue Procurement Protocol for Relapse or Recurrent Disease | 487 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| Bertram KA #94/161 | O | SWOG 9250 (INT-0136): Phase III Intergroup Prospectively Randomized Trial of Perioperative 5-FU After Curative Resection, Followed by 5-FU/Levamisole for Patients With Colon Cancer | 488 |
| Bertram KA #94/073 | O | SWOG 9300: A Randomized Phase II Evaluation of All Trans-Retinoic Acid with Interferon-Alfa 2a or All Trans-Retinoic Acid with Hydroxyurea in Patients with Newly Diagnosed Chronic Myelogenous Leukemia in Chronic Phase | 489 |
| Bertram KA #93/166 | O | SWOG 9303: Phase III Study of Radiation Therapy, Levamisole, and 5-Fluorouracil versus 5-Fluorouracil and Levamisole in Selected Patients With Completely Resected Colon Cancer | 490 |
| Bertram KA #94/111 | O | SWOG 9304: Postoperative Evaluation of 5-FU by Bolus Injection vs 5-FU by Prolonged Venous Infusion Prior to and Following Combined Prolonged Venous + Pelvic XRT vs Bolus 5-FU +Leucovorin + Levamisole Prior to and Following Combined Pelvic XRT + Bolus 5-FU + Leucovorin in Patients with Rectal Cancer, Phase III Intergroup | 491 |
| Bertram KA #94/170 | O | SWOG 9313: Phase III Comparison of Adjuvant Chemotherapy With High-Dose Cyclophosphamide + Doxorubicin vs Sequential Doxorubicin Followed by Cyclophosphamide in High-Risk Breast Cancer Patients with 0-3 Positive Nodes | 492 |
| Bertram KA #94/107 | O | SWOG 9321: Standard Dose Versus Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma, Phse III | 493 |
| Bertram KA #94/058 | O | SWOG 9331 (E2192): Outcome Prediction by Histologic Grading in EST 1180 (SWOG 8294), Ancillary | 494 |
| Bertram KA #95/147 | C | SWOG 9333: A Randomized Controlled Trial of Mitoxantrone & Etoposide vs Daunomycin & Cytosine Arabinoside as Induction Therapy in Patients Over Age 55 with Previously Untreated Acute Myeloid Leukemia | 495 |
| Bertram KA #94/121 | O | SWOG 9336: A Phase III Comparison Between Concurrent Chemotherapy Plus Radiotherapy, and Concurrent Chemotherapy Plus Radiotherapy Followed by Surgical Resection for Stage IIIA (N2) Non-Small Cell Lung Cancer | 496 |
| Bertram KA #95/024 | T | SWOG 9349: A Randomized Phase II Trial of CHOP with G-CSF Support or ProMACE-CytaBOM With G-CSF Support for Treatment of Non-Hodgkin's Lymphoma | 497 |
| Bertram KA #95/003 | O | SWOG 9401: A Controlled Phase III Evaluation of 5-FU Combined with Levamisole and Leucovorin as Surgical Adjuvant Treatment Following Total Gross Resection of Metastatic Colorectal Cancer | 498 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|---|------|
| Bertram KA #95/093 | O | SWOG 9402: Phase III Intergroup Randomized Comparison of Radiation Alone vs Pre-Radiation Chemotherapy for Pure and Mixed Anaplastic Oligodendrogliomas | 499 |
| Bertram KA #94/163 | O | SWOG 9410 (INT 0148): Doxorubicin Dose Escalation, With or Without Taxol, As Part of the CA Adjuvant Chemotherapy Regimen for Node Positive Breast Cancer: A Phase III Intergroup Study | 500 |
| Bertram KA #95/094 | O | SWOG 9415: Phase III Randomized Trial of 5-FU/Leucovorin/Levamisole versus 5-FU Continuous Infusion Levamisole as Adjuvant Therapy for High -Risk Resectable Colon Cancer, Intergroup | 501 |
| Bertram KA #95/151 | C | SWOG 9416: A Phase II Intergroup Trial of Induction Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer Involving the Superior Sulcus (Pancoast Tumors) | 502 |
| Bertram KA #97/134 | O | SWOG 9419: Tumor Tissue Biopsy for Thymidylate Synthase Expression in Patients with Colorectal Cancer, Ancillary | 503 |
| Bertram KA #97/006 | C | SWOG 9420: A Phase III Trial of Continuous Low-Dose Infusion Versus Intermittent High-Dose Infusion of 5-Fluorouracil in Patients with Disseminated Colorectal Cancer | 504 |
| Bertram KA #98/039 | O | SWOG 9431: Cytogenetic, Molecular, and Cellular Biology Studies in Metastatic Melanoma Patients, Ancillary | 505 |
| McCune DE #98/113 | O | SWOG 9444: Gastrointestinal Tumor Repository Protocol, Ancillary | 506 |
| Bertram KA #96/102 | T | SWOG 9445: Prognostic Factor Panel to Predict Preferred Therapy for Node Positive Postmenopausal Breast Cancer Patients (CAF vs Tamoxifen) (A Companion Protocol to SWOG 8814) | 507 |
| Bertram KA #96/094 | C | SWOG 9446: Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-Cis Retinoic Acid in Head and Neck Cancer | 508 |
| Bertram KA #97/009 | O | SWOG 9457: Paclitaxel (Taxol) and Carboplatin for Advanced Transitional Cell Carcinoma of the Urothelium | 509 |
| Bertram KA #97/059 | C | SWOG 9503 (NCCTG 93-72-52): Phase III Trial of BCNU and Cisplatin Versus BCNU Alone and Standard Radiation Therapy Versus Accelerated Radiation Therapy in Patients with Grade 4 Glioma | 510 |
| Bertram KA #97/041 | O | SWOG 9510: Evaluation of Topotecan in Hormone Refractory Prostate Cancer, Phase II | 511 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| McCune DE #99/057 | C | SWOG 9512: A Phase III Study of Adjuvant Ganglioside Vaccination GM2-KLH/QS-21 Therapy vs. High-Dose Inteferon Alfa-2b (Intron A) for High-Risk Melanoma (T4>4mm Primary or Regional Lymph Node Metastis) | 512 |
| Bertram KA #96/095 | O | SWOG 9514: Phase III Double-Blind, Placebo-Controlled, Prospective Randomized Comparison of Adjuvant Therapy with Tamoxifen vs. Tamoxifen & Fenretinide in Postmenopausal Women with Involved Axillary Lymph Nodes and Positive Receptors, Intergroup | 513 |
| Bertram KA #96/118 | O | SWOG 9515: Phase III Intergroup Trial of Surgery Followed by (1) Radiotherapy vs. (2) Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck | 514 |
| McCune DE #99/019 | O | SWOG 9808: Long-Term Follow-Up Protocol: An Administrative Tool | 515 |
| McCune DE #98/112 | O | SWOG C9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-1A Versus No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma | 516 |
| McCune DE #99/014 | O | SWOG C9741: A Randomized Phase III Trail of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide, or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer | 517 |
| McCune DE #99/107 | O | SWOG E1395: A Randomized Phase III Evaluation of Paclitaxel + Cisplatin Versus Cisplatin + 5-FU in Advanced Head and Neck Cancer | 518 |
| McCune DE #99/071 | O | SWOG E2197: Phase III Study of Adriamycin/Taxotere vs. Adriamycin/Cytoxan for the Adjuvant Treatment of Node Positive or High Risk Node Negative Breast Cancer | 519 |
| McCune DE #99/056 | O | SWOG E3695: A Randomized Phase III Trial of Concurrent Biochemotherapy with Cisplatin Vinblastine, Dacarbazine, IL-2, and Interferon A-2b versus Cisplatin, Vinblastine, Dacarbazine (CVD) Alone in Patients with Metastatic Malignant Melanoma | 520 |
| Bertram KA #97/070 | O | SWOG JBR.10 (NCIC CTG BR.10): A Phase III Prospective Randomized Study of Adjuvant Chemotherapy with Vinorelbine and Cisplatin in Completely Resected Non-small Cell Lung Cancer with Companion Tumour. | 521 |
| McCune DE #99/040 | O | SWOG JMA.17: A Phase III Randomized Double-Blinded Study of Letrozole Versus Placebo in Women with Primary Breast Cancer Completing Five or More Years of Adjuvant Tamoxifen (SWOG) | 522 |

| Princ. Investigator Protocol Number | S | Protocol Title | Page |
|--|---|--|------|
| McCune DE #99/072 | O | SWOG S9626: A Phase III Trial of Placebo Versus Megestrol Acetate 20 mg/Day Versus Megestrol Acetate 40 mg/Day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer | 523 |
| McCune DE #99/073 | O | SWOG S9700: A Phase II Trial of Infusional 5-Fluorouracil (5-FU), Calcium Leucovorin (LV), Mitomycin-C (Mito-C), and Dipyradamole (D) in Patients with Locally Advanced Unresected Pancreatic Adenocarcinoma | 524 |
| McCune DE #99/037 | C | SWOG S9713: A Phase II Trail of Cisplatin/Etoposide and Concurrent Radiotherapy Followed by Paclitaxel/Carboplatin Consolidation for Limited Stage Small Cell Lung Cancer | 525 |
| McCune DE #99/092 | O | SWOG S9714: Phase II Trial of Paclitaxel by 96-Hour Infusion in Stage IIIB and IV Bronchioloalveolar Carcinoma (BAC) | 526 |
| McCune DE #99/058 | C | SWOG S9718: A Phase II Trial of Gemcitabine Plus Cisplatin in Patients with Extensive Small Cell Lung Cancer | 527 |
| McCune DE #99/039 | C | SWOG S9801: Evaluation of Gemcitabine - Cisplatin Combination Chemotherapy in Esophageal Carcinoma | 528 |
| McCune DE #99/059 | O | SWOG S9803: The Evaluation of Gemcitabine (Gemzar) in Resistant and Relapsing Multiple Myeloma, Phase II | 529 |
| McCune DE #99/060 | O | SWOG S9806: Randomized Phase II Trial of Carboplatin/Gemcitabine Followed by Paclitaxel or Cisplatin/Vinorelbine Followed by Docetaxel in Advanced Non-Small Cell Lung Cancer | 530 |
| McCune DE #99/038 | O | SWOG S9832: Enhancing Well-Being During Breast Cancer Recurrence | 531 |
| McCune DE #99/108 | O | SWOG S9911: A Phase II Pilot Trial of CHOP Followed by Iodine-131-Labeled Monoclonal Anti-B1 Antibody for Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphomas | 532 |



Detail Summary Sheets

Hospital Dental Clinic

Detail Summary Sheet

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|-----------------|----------------|-------------------|
| Date: 30 Sep 99 | Number: 96/046 | Status: Completed |
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Title: Evaluation of the Efficacy of Post-operative Antibiotics After Orthognathic Surgery

Principal Investigator: MAJ Henry W. Marcantoni, DE

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| Department: Dentistry | Facility: MAMC |
|-----------------------|----------------|

Associate Investigator(s): LTC Charles R. Weber, DC; COL Andrew A. Vorono, DE; MAJ Timothy Bandrowsky, DE; MAJ Thomas J. Borris, DE

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|---------------------------|---------------------------------|--------------------------------|
| Start Date: 01/19/1996 | Est. Completion Date: Nov 96 | Periodic Review: 01/26/1999 |
|---------------------------|---------------------------------|--------------------------------|

Study Objective: To compare the efficacy of a standard perioperative antibiotic regiment with and without a one week postoperative antibiotic regimen for patients undergoing orthognathic surgery in a prospective, randomized, double-blind study.

Technical Approach: Either isolated mandibular bilateral sagittal split ramus osteotomies, isolated maxillary Lefort I osteotomies, or a combination of the two procedures will be performed on all patients enrolled in the study. Patients in each operative group will be further subdivided randomly into one of two groups. The experimental group will receive prophylactic antibiotics as follows: one preoperative dose and intraoperative doses at two hour intervals for the duration of the surgery. The control group will receive the same preoperative and perioperative regimen along with a seven day oral postoperative regimen. The patients will be monitored for objective signs of infection, and WBC counts will be drawn preoperatively and post-operatively at one week.

Progress: Fifty additional patients were entered in FY 99 for a total of 100 subjects entered in the study.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/010

Status: Completed

Title: The Electronic Amplified Precordial Stethoscope Versus the Traditional Precordial Stethoscope for Patient Monitoring During Deep Sedation for Oral and Maxillofacial Surgery Procedures

Principal Investigator: MAJ Henry W. Marcantoni, DE

Department: Dentistry

Facility: MAMC

Associate Investigator(s): LTC Charles R. Weber, DC

Start Date:
11/17/1998

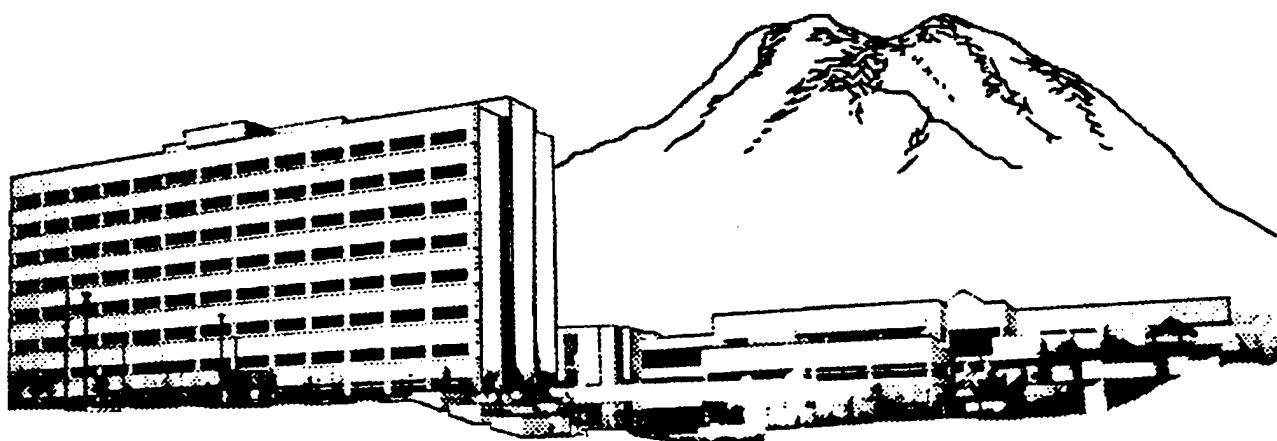
Est. Completion Date:
Feb 99

Periodic Review:
N/A

Study Objective: To illustrate that an amplified precordial stethoscope enhances monitoring of the patient's respiratory status during deep sedation for extraction of third molars.

Technical Approach: The principal investigator will function as the anesthesia provider for all subjects in this study. Desaturation events during the perioperative period will be evaluated. When oxygen saturation drops at or below 95% per pulse oximetry an event marker will be activated by the principal investigator to time how long it takes for the surgeon to verbalize that the patient's airway needs to be opened. The event marker will be disengaged when this occurs. These timed values will then be recorded. Both types of stethoscopes will be used on each subject. Subjects will be assigned by random number list to determine which stethoscope will be used while extracting teeth on the right and left side. Data will be recorded and then evaluated using parametric unpaired t-test. Following completion of the surgical procedure, the surgeon and surgical technician will answer a questionnaire that compares the conventional versus the amplified stethoscope. This data will be analyzed using a Mann-Whitney non-parametric test.

Progress: 8 subjects have been entered in FY 99 for a total of 8 subjects enrolled. This study concluded that amplified precordial stethoscope improved monitoring of the patient by amplification of heart and breath sounds, and by including the surgical team.



Detail Summary Sheets

Department of Emergency Medicine

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/070 | Status: Ongoing |
| Title: A Survey to Determine the Incidence of Infection in Plantar Puncture Wounds | | |
| Principal Investigator: CPT Charles P. Buck, MC | | |
| Department: Emergency Medicine | | Facility: MAMC |
| Associate Investigator(s): CPT Austin W. Burgess, MC; MAJ David A. Della-Giustina, MC | | |
| Start Date: 06/22/1999 | Est. Completion Date: Jul 99 | Periodic Review: N/A |

Study Objective: To determine the incidence of infection in plantar puncture wounds, and to determine if infection rates are different for healthy vs. immune compromised and aggressive vs. conservative initial management groups.

Technical Approach: The hypothesis of this study is that the incidence of plantar puncture wound infections has been overestimated. The objectives are to determine not only the incidence of infection, but also to attempt correlation with initial wound management and host factors (affecting immune system). This investigation will be an improvement over the previous survey (1), by increasing sample size to 400 ambulatory patients seen in the Emergency Room. New information requested will concern initial wound treatment and immuno-suppressive host factors. The medical application of this study is to help to determine the most appropriate approach of treating plantar puncture wounds.

All adult ambulatory patients identified by the triage nurse as having a prior plantar puncture wound will be asked to complete an anonymous survey. These surveys will be available on a designated table in the ED/AIC lobby. After completion the parents will then place them in a designated box on the same table. Investigators will periodically collect the forms and transfer the data to spreadsheets for further analysis.

Method of data analysis: There are one primary and two secondary research questions in this study. The primary is the overall incidence of infection of plantar puncture wounds. Data will be analyzed at 95% confidence intervals. The secondary research questions is the infection rate for two groups. These will consist of subjects that had aggressive initial treatment vs. conservative treatment, and those who were healthy at the time of injury vs. those with vascular or immuno-compromising diseases. These groups will be analyzed by Chi-Square to determine statistical significance at $p < 0.05$. For the purpose of analysis, subjects indicating foil "a" to question 6 in the survey will be considered conservative; foil "b" aggressive. Any response to foils "a-d" to question 9 will place subjects in the vascular or immuno-compromise group; foil "e" the healthy group.

Progress: 50 subjects have been entered in FY 99 for a total of 50 subjects enrolled. To date this survey has been hampered by a low number of patients actually completing the survey. PI is looking into ways to heighten awareness of the survey in the waiting area of AIC in hopes of increasing response rate. It is anticipated that the survey will take another 3-4 months before enough data has been collected.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/104 **Status:** Ongoing

Title: A Randomized, Placebo-Controlled, Study of Intravenous Magnesium in Acute Benign Headaches

Principal Investigator: CPT Thomas R. Coomes, MC

Department: Emergency Medicine **Facility:** MAMC

Associate Investigator(s): Marvin K. Valrey, MD; Leonard Frank, MD; Laura Fife, MD

Start Date:
9/28/1999

Est. Completion Date:
Oct 00

Periodic Review:
N/A

Study Objective: Our purpose is to evaluate the efficacy of IV magnesium in acute headache pain, in a prospective randomized, double blind, placebo-controlled trial. Because of the difficulty of classification, as well as the desire to make this study more applicable to the typical clinical practice of emergency medicine, we will evaluate all patients who present with benign headache pain.

Technical Approach: The Pharmacy will pre-prepare bags of drug and placebo in lots of ten by standard randomization procedures. Each bag will be labeled with a study number, the name of the study, and the date of preparation/expiration. Emergency Department personnel and patients will be blinded to the study treatment. The Pharmacy will hold the randomization code which will only be broken in the event of an emergency. Staff and resident physicians in the Emergency Room will obtain patient consent. Enrolled patients will be assigned the next available treatment number and corresponding treatment. The physician via infusion pump will administer the study treatment. Data collection before, during, and after treatment, may be done by physician or nursing staff. Study data forms will be placed in opaque envelopes labeled "Mg/HA study" and placed in the secure drug cabinet. Study investigators (Coomes and Valrey) will periodically collect the data sheets and compile the data.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 97/020 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: A Model for Prehospital 12-Lead Acquisition Without A Dedicated 12-Lead ECG Machine

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine

Facility: MAMC

Associate Investigator(s): Fritz P. Fuller, N.R.E.M.T.-P; COL Alice M. Mascette, MC

Start Date:
02/21/1997

Est. Completion Date:
May 96

Periodic Review:
02/23/1999

Study Objective: To verify that a 12-lead ECG obtained with a cardiac monitor/defibrillation unit is comparable in accuracy to that of a dedicated 12-lead ECG machine.

Technical Approach: The management of ischemic chest pain and acute myocardial infarction hinges on early diagnosis and treatment with thrombolytic agents if indicated. It has been shown that prehospital recognition of acute MI using 12-lead electrocardiography and interpreted by nurses/paramedics trained in ECG evaluation can result in significantly faster times to thrombolytics compared to patients who did not receive a prehospital ECG. Today there are several portable 12-lead machines with computer assisted diagnosis available, but they have only recently become available and are very expensive. By utilizing a portable 12-lead machine (Lifepak 10) and demonstrating that it can produce diagnostic quality ECG's, we hope to make available to a large group of prehospital providers 12-lead capability without an increased monetary investment.

Progress: No subjects have been entered in FY 99 for a total of 50 subjects enrolled. 50 ECG readings & data analysis is still being done.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/002 **Status:** Ongoing

Title: Emergency Surgical Procedures Laboratory Training Using the Goat (*Capra hircus*)

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine **Facility:** MAMC

Associate Investigator(s): MAJ Nathan T. Rudman, MC; MAJ James T. Vandenberg, MC; CPT Garrett R. Baer, SP

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 10/17/1997 | Oct 00 | 10/20/1998 |

Study Objective: The objectives of this training exercise are to teach physicians one safe method of performing six life-saving procedures for trauma patients.

Technical Approach: The procedures listed below will be performed under the supervision of a staff member and the veterinarian assigned to Clinical Investigation. All animals will be anesthetized and then will be sacrificed immediately after the procedures. The procedures consist of 1) Chest tube insertion, 2) Thoracotomy, 3) Pericardiocentesis, 4) Diagnostic peritoneal lavage, 5) Venous cutdown, 6) Cricothyroidotomy

Progress: No sessions were held during FY 99.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/021 | Status: Completed |
|------------------------|-----------------------|--------------------------|

Title: Predicting Emergency Medicine Resident Success from Prospective Resident Application Materials

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine

Facility: MAMC

Associate Investigator(s): MAJ Nathan T. Rudman, MC; Stacie J. Patterson ; Terri L. Blake, Ph.D.

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| Start Date: 12/18/1997 | Est. Completion Date: May 98 | Periodic Review: N/A |
|----------------------------------|--|--------------------------------|

Study Objective: To identify items in the application materials that correlate with successful completion of the residency by a retrospective review of emergency medicine resident files at MAMC.

Technical Approach: Resident files for DEM residents who commenced training between 1978 and 1993 (sample size approximately 100) will be examined. Resident files will be scored for positive and negative predictor variables dealing with residency candidate academic ability, work ethic, and interpersonal skills. The predictor variables will be statistically analyzed to determine the degree to which they correlate with successful completion of residency training.

Progress: No subjects have been entered in FY 99 for a total of 120 subjects enrolled. All data gathering is complete. Retrospective nature of this study and lack of GME records we previously thought were available, in addition to variety of data gathered over the years, has limited the quality of this project overall. We are reviewing what we have and may attempt publication.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/028 **Status:** Ongoing

Title: Pediatric Intubation Training Utilizing the Ferret (*Mustela putorius furo*) Model

Principal Investigator: Steven A. Pace, MD

Department: Emergency Medicine

Facility: MAMC

Associate Investigator(s): CPT Daniel Mcilmail, MC; MAJ Nathan T. Rudman, MC;
MAJ James T. Vandenberg, MC

Start Date:
12/18/1997

Est. Completion Date:
Dec 00

Periodic Review:
12/15/1998

Study Objective: To improve the skill of physicians and other health care providers in pediatric endotracheal intubation, thereby improving the outcome of pediatric patients they treat.

Technical Approach: Ferrets will be anesthetized and course participants will be given the opportunity to intubate a ferret employing a laryngoscope and endotracheal tube. 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.

Progress: No training sessions were held in FY 99.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/109 | Status: Completed |
| Title: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice daily for Five Days in the Treatment of Influenza in Patients 12 Years or Over Diagnosed with Asthma or Chronic Obstructive Pulmonary Disease | | |
| Principal Investigator: Steven A. Pace, MD | | |
| Department: Emergency Medicine | | Facility: MAMC |
| Associate Investigator(s): MAJ Peter J. Benson, MC; Roger Wang | | |
| Start Date: 09/15/1998 | Est. Completion Date: Apr 99 | Periodic Review: N/A |

Study Objective: To evaluate the efficacy of inhaled zanamivir administered twice daily over 5 days in the treatment of influenza A and B in patients, 12 years and over, diagnosed with asthma or COPD and to assess the impact of treatment of influenza with zanamivir on patient productivity and health care resource use.

Technical Approach: All subjects will receive study medication twice daily for five days. The first dose will be administered at the First Treatment Visit (Day 1); subjects will attend a Post-Treatment Visit (Day 6) on completion of study treatment and a Follow-up Visit on Day 28. Telephone contact will be made on Day 56 to complete the resource utilization data. Additional unscheduled visits may occur as required (due to exacerbations of underlying disease). Subjects will maintain a diary with symptom assessment, adverse event, pulmonary function results and concomitant medications. Safety evaluations will include lab analyses of blood and clinical adverse event inquiries.

Prior to initiating the treatment trial, Madigan will participate in a surveillance study to identify the presence of the influenza virus in the community. Patients will be consented with a short surveillance study form and a throat swab will be performed.

Progress: This protocol closed to patient entry. One patient was enrolled at MAMC and completed the study with no adverse events.

Detail Summary Sheet

| | | |
|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 99/105 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: A Double-blind, Randomized, Placebo-controlled Trial of a Tablet Formulation of Pleconaril in the Treatment of Viral Respiratory Infection

Principal Investigator: Steven A. Pace, MD

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|---------------------------------------|-----------------------|
| Department: Emergency Medicine | Facility: MAMC |
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Associate Investigator(s): MAJ James Terrio, MC; CPT Leah P. McMann, MC; Shirley Newcomb, BSN, MPH

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|---------------------------------|--|--------------------------------|
| Start Date: 9/28/1999 | Est. Completion Date: May 00 | Periodic Review: N/A |
|---------------------------------|--|--------------------------------|

Study Objective: To determine the therapeutic effect of pleconaril on the time to complete resolution of all symptoms of VRI. Complete resolution is defined as a total score of 0 for 24 hours with no subsequent relapse of symptoms.

Technical Approach: This double-blind, placebo-controlled, randomized study will evaluate and compare a Placinoral tablet dosage regimen to matching placebo therapy on the reduction of the duration and severity of viral respiratory tract symptoms in adults presenting to ambulatory care or emergency medical clinics for treatment. The study will be conducted at approximately 100 centers throughout the US and Canada. Approximately 810 patients with suspected picornaviral respiratory infection will be randomized to receive Placinoral 400 mg t.i.d. or placebo t.i.d. for 7 days. Randomization will be stratified by smoking status. A nasal mucus sample will be collected at baseline for the determination of picornavirus by RT-PCR (patients discharge nasal mucus into a plastic sheet and the mucus is transferred to sample collecting tube).

Patients meeting the entrance criteria will receive their first dose of study drug immediately following signing the informed consent statement. The time of the first dose must be no more than 36 hours after onset of the first symptom of scoring system. Patients will continue the dosing regimen for the next 7 days after enrollment. A total of 21 doses will be administered to each study participant and the first 3 doses must be administered during the first 24 hours after randomization. Patients will be assigned blister packs of the study medication upon enrollment and will be carefully instructed on proper dosing. Subjects will record their symptoms, activity and concomitant medication use twice daily (midday and evening) in the diary. Patients will be contacted every other day preferably by the same person, until they are discharged from the study or have complete resolution of all symptoms. Patients will be discharged from the study on Day 21 and advised to return to the clinic for further evaluation if symptoms occur beyond this point. Symptomatic patients will remain under observation for as long as is judged necessary by the investigator for purposes of the study. The Biostatistics department of ViroPharma Incorporated will analyze the data of this study.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/011

Status: Completed

Title: Survey of Clinical Emergency Medicine Positions: Annals of Emergency Medicine, September 1998

Principal Investigator: MAJ James T. Vandenberg, MC

Department: Emergency Medicine

Facility: MAMC

Associate Investigator(s): CPT Mark Buettner, MC; CPT Carl Decker, MC; CPT Kurtis R. Hold, MC; Marvin K. Valrey, MD

Start Date:
11/17/1998

Est. Completion Date:
Oct 98

Periodic Review:
N/A

Study Objective: To survey Emergency Medicine clinical positions offered in the Annals of Emergency Medicine job bank September 1998. A description of the type of employment structure and survey of specific contract issues will be included.

Technical Approach: Physicians from the Department of Emergency Medicine will make telephone contacts to the representatives listed in the ads of the September 1998 issue of Annals of EM. Questions asked will include: What is the employment status of the position offered? (Hospital Employee, Contract Management Group, Private Group Partnership); What is the method for termination between the employer or group and the practicing physician?; Is there a Restrictive Covenant or Non Compete Clause written in the contract?; and Will the employee have full access to information regarding revenue generated on the physician's billings? As well as complete access to all financial records of the employer? A description of the findings will be prepared and obvious trends reported.

Progress: Data collection on this study was completed 7 Jun 99, with analysis continuing. The PI stated an abstract would be forwarded to DCI after final analysis of data is completed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/110 **Status:** Completed

Title: Randomized, Double-Blind, Comparative Trial of 15-minutes vs 2- minutes
Infusion Rates on the Incidence of Prochlorperazine-Induced Akathisia

Principal Investigator: CPT David R. Vinson, MC

Department: Emergency Medicine **Facility:** MAMC

Associate Investigator(s): CPT Alexandre F. Migala, MC; Chad M. Bentsen; CPT
Walter A. Fink, Jr., MC; Marcus A. Trione; MAJ James T. Vandenberg, MC

Start Date:
09/15/1998

Est. Completion Date:
Jun 99

Periodic Review:
9/28/1999

Study Objective: To assess the impact of a slow-infusion on the incidence of prochlorperazine-induced akathisia.

Technical Approach: Subjects will receive in a randomized, double-blind fashion both a 2-minute infusion and a 15-minute infusion of saline, one syringe of which will also contain 10-mg prochlorperazine. The presence of akathisia will be assessed in the customary fashion and the incidences will be compared. Data will be gathered to assess the influence of a slow infusion of prochlorperazine on the incidence of prochlorperazine-induced akathisia.

Progress: 160 subjects were entered in FY 99 for a total of 160 subjects enrolled. **Conclusion:** Adjuvant diphenhydramine decreased the incidence of single-dose prochlorperazine-induced akathisia by about 60%. There was a small but significant increase in sedation with co-administration.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/127

Status: Completed

Title: Efficacy of Clonidine for Prophylaxis of Acute Mountain Sickness

Principal Investigator: MAJ Ian S. Wedmore, MC

Department: Emergency Medicine

Facility: MAMC

Associate Investigator(s): CPT Alexandre F. Migala, MC; MAJ John G. McManus, Jr., MC

Start Date:
07/18/1997

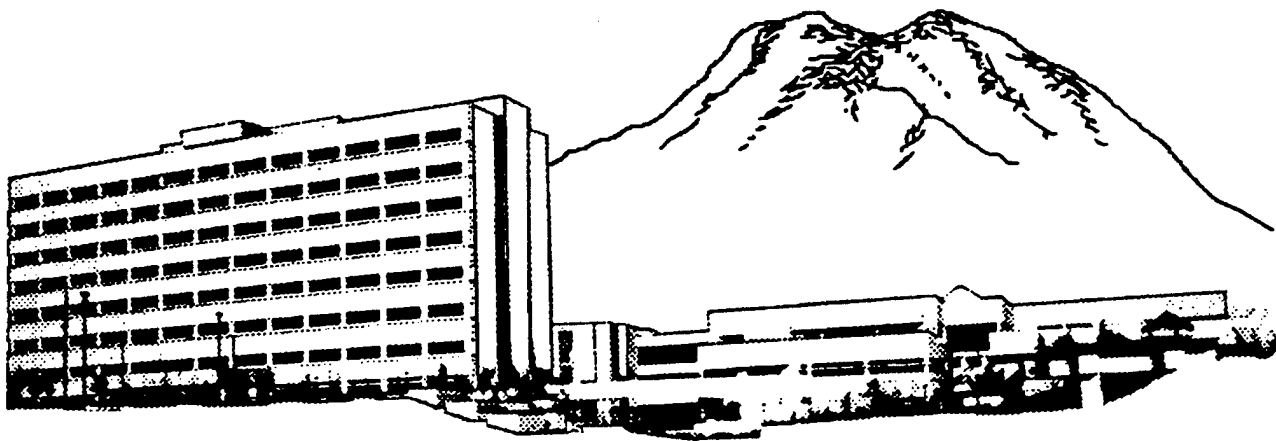
Est. Completion Date:
Oct 98

Periodic Review:
07/27/1999

Study Objective: A double blind placebo controlled study to determine if clonidine is effective in preventing or reducing the incidence of acute mountain sickness (AMS).

Technical Approach: Climbers will take a study drug dose the night prior to climbing and BID thereafter until returning to sea level. ESQs will be completed at sea level, 6000 ft, 10000 ft, and 14400 ft elevations. These will be completed 15 minutes after arrival at each altitude. Should the climb be terminated due to weather or any other objective condition preventing arrival at the summit, an ESQ will be conducted at the high point obtained. Four doses of study drug will be utilized, this will allow drug to be started 12 hours prior to beginning the climb and continued on a q12 hour basis until the completion of the climb. Results of the ESQs will be analyzed to determine if subjects meet criteria for AMS.

Progress: 3 subjects have been entered in FY 99 for a total of 40 subjects enrolled. No subject had AMS symptoms at 0, 6000, and 10000 feet above sea level. At high point 17 of 19 (89%) placebo subjects had AMS and 9 of 18 (50%) clonidine subjects had AMS. This difference was significant ($p=0.023$) as determined by a continuity corrected chi-square test. No significant side effects were noted by any subject.



Detail Summary Sheets

Department of Family Practice

Detail Summary Sheet

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|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 96/127 | Status: Completed |
| Title: Incidence of Exercise Induced Hematuria After the Army Physical Fitness Test (APFT) | | |
| Principal Investigator: CPT Yong H. Chun, MC | | |
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| Department: Family Practice | Facility: MAMC | |
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| Associate Investigator(s): MAJ Charles Payne, MC | | |
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| Start Date: 06/21/1996 | Est. Completion Date: Aug 96 | Periodic Review: 07/27/1999 |

Study Objective: 1) To determine the incidence of hematuria in a young healthy population. 2) To determine the effect of routine exercise, such as the APFT, on urinalysis for blood and protein. 3) To modify a guideline for assessment of painless hematuria after routine exercise.

Technical Approach: The purpose of this study will be to identify the incidence of exercise-induced hematuria secondary to routine physical training and develop guidelines for proper urine collection and triage of patients found to have hematuria after exercise. 500 male and female ROTC Cadets will be recruited during routine physical examinations which includes a urinalysis. A questionnaire will be completed and urine will be collected following a standard APFT. Urinalysis will check for blood and protein. If positive for blood, the specimen will be forwarded for microscopic study to determine if >3 RBC/HPF are present. If so, the participant will be asked to provide specimens at 24 hrs, 48 hrs, 72 hrs, and 1 week after the APFT. The data will be collected and analyzed as part of a descriptive study.

Progress: 10 subjects have been entered in FY 99 for a total of 139 subjects enrolled. In the process of writing up the results.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/098

Status: Ongoing

Title: Can An Instructional Video Improve the Quality of Cervical Cytological Smears in A Family Practice Residency

Principal Investigator: CPT Gary W. Clark, MC

Department: Family Practice

Facility: MAMC

Associate Investigator(s): COL Joseph F. Yetter III, MC

Start Date:
9/28/1999

Est. Completion Date:
Aug 00

Periodic Review:
N/A

Study Objective: 1) To determine if the rate of limited cervical smears can be reduced through the use of an instructional video. 2) To determine if the instructional video would be an acceptable tool to be used by family practice and OB/GYN provides either for resident education or continuing quality improvement.

Technical Approach: Phase 1: Quantitative analysis of the TAMC TQI Project

The Papanicolaou smear has proven to be a successful screening test for the prevention of cervical cancer. Yet, the ability of the smear to detect cervical abnormalities is dependent, in part, upon the provider's ability to produce a slide that is as free from artifact and distortion as possible. The specific aim of this study is to determine if the viewing of an instructional video that demonstrates one proper method of obtaining a cervical smear will lead to providers producing fewer smears limited by artifact and distortion.

Since the advent of widespread routine cervical screening in the 1950's, the incidence of cervical cancer has plummeted. Despite this success, the Papanicolaou smear is not perfect. False negative rates range from 8-48%. The quality of the sample submitted for evaluation significantly effects the cytologist's ability to detect smear abnormalities. Despite an interest in the quality of cervical smear samples, there is very little written about the proper method of using the Ayre spatula and the Cytobrush, the present standard collection method for patients with a cervix, to collect the sample.

The Bethesda System utilizes three categories when describing adequacy (quality) of the smear: satisfactory, satisfactory but limited and unsatisfactory. One possible way of decreasing the number of limited and unsatisfactory smears is to train practitioners to utilize a standard method to obtain and prepare a cervical smear. Because the literature did not support any one sampling or plating technique, a technique was chosen based on the 1994 NCCLS Papanicolaou Technique approved guidelines. A video explaining and demonstrating this technique was prepared to facilitate uniform instruction.

The rate of limited smears for all providers in a family practice clinic over a one-year period was determined. One half of the providers in the clinic were then randomly selected to observe a video that reviewed the purpose of the cervical smear, discussed the limiting factors outlined by the Bethesda System, and demonstrated a proper method of obtaining and preparing a smear. This group of providers was asked to use this method in obtaining their cervical smears from that time forward. The rest of the physicians in the clinic were not shown the video. The percentage of limited smears obtained by each provider was compared with his/her percentage of limited smears prior to beginning of the study. Laboratory personnel were not aware that the study was being conducted.

The study population consists of providers assigned to a family practice clinic from 1 October 1995 to 30 September 1996 for the baseline collection phase and from 1 February 1997 to 31 January 1998 for the intervention phase. The investigator and those providers who were not

present to participate in both phases of the study were excluded from analysis. This resulted in a total of 25 providers, 12 of who were in the study group and 13 in the control group.

The data will be extracted from an existing clinic database and entered into an Excel spreadsheet and analyzed using SPSS software.

The difference between the rate of limited smears before and after the intervention will be determined for each provider. The intervention and control groups will then be compared using the Mann-Whitney test to see if the providers who viewed the video produce a statistically significant greater improvement in cervical smear quality.

Phase II: MAMC qualitative analysis

Phase I of the study serves as the backdrop for phase II. For an educational tool to be effective, it must, when used, be able to do what it was designed to do: improve smear quality. In addition, those who will be using the educational tool must deem it acceptable. Without the approval of the actual user of the product, an excellent educational resource will go unused. This phase of the study examines the acceptability of the instructional video to the family practice and OBGYN providers of MAMC. In addition providers will be asked to suggest how to best use the video. Providers from both clinics will be shown the video and asked to fill out a brief survey. The results of the survey will be reported using simple descriptive statistics.

Progress: No samples have been collected, awaiting kits from Dr. Sawin.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/050

Status: Ongoing

Title: Unintended Pregnancy Prevention Program

Principal Investigator: MAJ Diane M. Flynn, MC

Department: Family Practice

Facility: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC; COL Roderick F. Hume Jr., MC; Ann K. Lancaster, CHN; LTC Jeffrey B. Clark, MC

Start Date:

02/21/1997

Est. Completion Date:

Mar 97

Periodic Review:

02/23/1999

Study Objective: The purpose of this study is to evaluate the effect of an intervention consisting of education and facilitated access to contraception on the unintended pregnancy rate of active duty US Army soldiers serving at Ft Lewis, WA.

Technical Approach: This research project is a randomized clinical trial designed to determine the effect of education and facilitated access to contraception on unintended pregnancy rates among female soldiers at Ft Lewis. Effectiveness of the intervention will be determined by: 1) Calculating annualized pregnancy rates using SIDPERS data and positive beta-HCG results from the MAMC clinical laboratory; unintended pregnancy rates will be determined from a survey completed at prenatal care orientation. 2) A questionnaire mailed to women in the Intervention Group and the Control Group one year after the intervention designed to assess contraception use, whether the intervention affected contraception use, and the rate of unintended pregnancy.

Progress: 25 participants were educated in FY 99 for a total of 509 participants trained.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/047 | Status: Completed |
| Title: Association of Race, Gender, and Rank with the Use of Clinical Preventive Screening Tests | | |
| Principal Investigator: CPT Brian C. Harrington, MC | | |
| Department: Family Practice | | Facility: MAMC |
| Associate Investigator(s): COL Joseph F. Yetter III, MC; TM Wickizer; C Spigner | | |
| Start Date: 03/23/1999 | Est. Completion Date: Jun 98 | Periodic Review: N/A |

Study Objective: To determine if universal access to care as practiced in the Military Health System (MHS) is associated with variations in screening test utilization based on race, sex, and rank.

Technical Approach: Universal access to health care, such as that available to military beneficiaries, may eliminate differences in health services utilization rates as witnessed in the civilian sector. In particular the Military Health System may minimize the impact that race, gender and socioeconomic status have on services utilization. This retrospective cohort study examines patients having at least one primary care visit at Fort Lewis during 1995. The presence or absence of clinical preventive screening tests for each cohort patient during a 2-year follow-up study frame will be determined. The clinical preventive screening tests of interest include mammograms, pap smears, hemoccult screens, cholesterol screens, and prostate specific antigen screens. Data will be obtained from the MHS, which contains descriptive data on the independent patient variables of race, sex, military sponsor's rank and age. It also contains dependent variable information about tests and procedures performed. The cohort's use of specific screening tests during the study period will be surveyed to determine if it varies by race, sex and rank. Patient age as an extraneous variable will be recorded for rate adjustment.

Progress: Approximately 40,000 patient CHCS records were examined. Data analysis revealed little variation of clinical services test utilization based on race. Men were more likely to utilize cholesterol screens. Officers were more likely than enlisted or warrant officers to utilize prostate specific antigen (PSA), cholesterol checks, mammography, pap smears and fecal occult blood tests (FOBT).

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 99/015 | Status: Completed |
|------------------------|-----------------------|--------------------------|

Title: Clinical Standards Implementation: A Survey of Primary Care Providers Attitudes and Use of Practice Guidelines

Principal Investigator: CDR John R. Holman, MC

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| Department: Family Practice | Facility: MAMC |
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Associate Investigator(s): Heflin ; CPT Brian C. Harrington, MC

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| Start Date: 12/15/1998 | Est. Completion Date: Mar 99 | Periodic Review: N/A |
|----------------------------------|--|--------------------------------|

Study Objective: To survey the attitudes and use patterns of clinical practice guidelines by primary care providers and identify potential aids and barriers to use.

Technical Approach: A brief survey will be sent to over 200 primary care providers in the Madigan system asking about how they use the guidelines, how they access the guidelines, what their general attitudes regarding guidelines are and what barriers or aids exist for using the guidelines. The results will be used to plan future implementation of clinical practice guidelines at Madigan.

Progress: A 32 question confidential survey was distributed to all 201 primary care specialists at Fort Lewis, including family practice, pediatrics, the adult primary care clinic, the emergency department and all active duty clinics. The response rate was 72% (144/201). 88% were aware of clinical standards. 89% felt clinical standards improved patient care. 66% listed CHCS as an access point for clinical standards even though CHCS does not contain them. 93% support further development. Over 1/3 access the standards at least weekly. Access barriers included the inability to access during clinic (66%) and not having a PC in their office (53%). Easier access to standards while seeing patients (81%) is a key to improved use. Regression analysis showed that older providers and female providers were less likely to have viewed or used the standards. Increasing time at Ft. Lewis was associated with increased use and better regard for the standards.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/034 | Status: Completed |
| Title: Sensitivity and Specificity of Colposcopic Impression in a Family Practice Dysplasia Clinic | | |
| Principal Investigator: CDR John R. Holman, MC | | |
| Department: Family Practice | Facility: MAMC | |
| Associate Investigator(s): CPT Michael Bryant, MC; COL Joseph F. Yetter III, MC | | |
| Start Date: 02/23/1999 | Est. Completion Date: Apr 99 | Periodic Review: N/A |

Study Objective: To determine the sensitivity and specificity of colposcopic visual impression when compared to histologic diagnosis in a family practice dysplasia clinic and to determine the positive and negative predictive value of colposcopic visual impression in a family practice dysplasia clinic.

Technical Approach: A database containing over 1000 patient visits to a family practice dysplasia clinic will be analyzed for the sensitivity, specificity, positive and negative predictive value of the provider's colposcopic visual impression compared with histology. The data will also be analyzed by resident year group and experience to evaluate for effects of increasing experience on colposcopic impression.

Progress: During a 6 year period, the results of 2613 patient visits to a family medicine residency program dysplasia clinic were used to determine the sensitivity and specificity of colposcopic visual impression. Crosstab queries were conducted to determine sensitivity and specificity of the provider's impression. The predictive values of a positive and negative test and likelihood ratios were then calculated. The sensitivity of a normal visual impression was 65% and the specificity 85% and for visual impression of inflammation/atypia 67% and 73%. Sensitivity and specificity of visual impression of low-grade were 43% and 88% with high-grade 19% and 92% respectively. Positive and negative predictive values for normal impression were 74% and 78% respectively and for inflammation/atypia 62% and 76%. Low-grade impression positive predictive value was 71% and negative predictive value 70% with high-grade having a positive predictive value of 64% and negative predictive value of 63%. Likelihood ratios were also low.

Conclusions: In this population of patients and providers, colposcopic visual impression had poor sensitivity and inadequate specificity to be an adequate diagnostic test for cervical dysplasia. Correct colposcopic diagnosis depends on a combination of cytology and histology results together with the colposcopic visual impression.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/067

Status: Ongoing

Title: Effects of the Acetic Acid Wash on the Cytologic Interpretation of the PAP Smear

Principal Investigator: CPT Mary V. Krueger, MC

Department: Family Practice

Facility: MAMC

Associate Investigator(s): CPT Brian C. Harrington, MC; CPT Robert H. G. Holland, MC; COL Mark E. Potter, MC; CPT Veronica Santee, MC

Start Date:

04/27/1999

Est. Completion Date:

Sep 99

Periodic Review:

N/A

Study Objective: To determine if interpretation of cervical intraepithelial neoplasia is altered by applying acetic acid prior to taking the Pap smear during colposcopic examination.

Technical Approach: Premenopausal, nonpregnant females with abnormal Pap smears (ASCUS or higher grade) presenting for first time colposcopy within 6 months in Family Practice and OB/GYN clinics at Madigan who agree to participate in the study will be stratified based on presenting Pap diagnosis (ASCUS, LGSIL, HGSIL), then randomized to the saline (Group 1) or acetic acid (Group2) groups. Each group will have a Pap smear done: after saline washing in Group 1, and after acetic acid washing in Group 2. The cytologist will be blinded to the use of saline vs acetic acid for the wash. Cytologic diagnoses will be based on the Bethesda criteria. We will compare the results between the saline and acetic wash groups to assess whether acetic acid changes the diagnosis, specificity, and/or increases the number and/or grade of abnormal slides.

Progress: Data on 7 subjects have been collected during FY 99. PI will change to Dr. Mary Krueger.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/020 | Status: Ongoing |
| Title: Assessing the Stages of Change for Contraceptive Use in the Prevention of Pregnancy and Sexually Transmitted Disease | | |
| Principal Investigator: CPT Jennifer H. Potter, MC | | |
| Department: Family Practice | | Facility: MAMC |
| Associate Investigator(s): MAJ Diane M. Flynn, MC; COL Roderick F. Hume Jr., MC; LTC Jeffrey D. Gunzenhauser, MC; CPT Gary W. Clark, MC | | |
| Start Date: 12/15/1998 | Est. Completion Date: May 99 | Periodic Review: N/A |

Study Objective: To determine the effect of the unintended pregnancy prevention program on the stage of change of AD women with regard to contraceptive behavior.

Technical Approach: This is a prospective controlled study to assess the stages of change of 600 AD soldiers regarding contraceptive use in the prevention of unintended pregnancy and sexually transmitted disease. Questionnaires will be given to the study group before and after the UPPP intervention. It will also be given to a group who has not received the class at the same time interval to act as a comparison group. Dependent variable consist of the study group, the control group and the age/rank/gender of group participants. Analysis will be chi-square to (1) compare the study group's incidence of change to the control group's incidence of change regarding contraceptive behavior, (2) compare the incidence of change within the study group before before and after the intervention. The five different stages of change will also be converted to numerical rank to compare the mean ranks by group and by age/rank of participants using 2-factor analysis of variance.

Progress: 165 subjects have been entered in FY 99 for a total of 165 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/090 **Status:** Terminated

Title: Treatment of Nocturnal Leg Muscle Cramps: A Double-Blind Placebo-Controlled Crossover Trial of Magnesium Oxide

Principal Investigator: LTC Guy P. Runkle, MC

Department: Family Practice **Facility:** MAMC

Associate Investigator(s): MAJ Alan J. Barker, MC; CPT John P. Barrett, MC; LTC Bruce A. Woolman, MC

Start Date:
04/19/1996

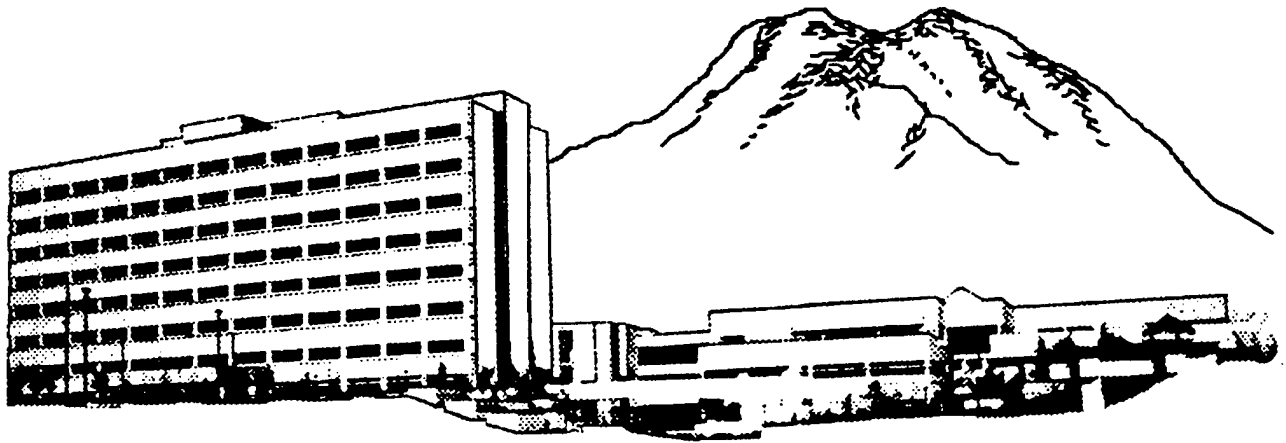
Est. Completion Date:
Jul 96

Periodic Review:
06/22/1999

Study Objective: To determine the effectiveness of magnesium oxide in reducing or eliminating nocturnal leg muscle cramps when compared to placebo.

Technical Approach: No current pharmacologic agent is approved for use in the treatment or prevention of nocturnal leg muscle cramps. Quinine appears to be an effective remedy but sufficient evidence for its efficacy and safety are lacking. Magnesium supplementation has been given trial in Europe for the treatment of night leg cramps. No studies have been done in this country to assess the efficacy of magnesium. Patients with a history of nocturnal leg muscle cramps and who are experiencing 2 or more cramps per week will be considered for enrollment in this study. Patients will be primarily identified from Family Practice Clinic physician panels with open invitation to other interested patients who are eligible DOD beneficiaries not followed in MAMC FP Clinic. Subjects will be observed via a 2 week symptom diary prior to treatment for 2-weeks with either magnesium oxide or placebo. During the full four weeks of the study, patients will keep a daily symptom diary that will be given to one of the investigators at each clinic visit. These symptom diaries will record the number, severity and duration of muscle cramps experience. The data obtained will be analyzed for statistical significance.

Progress: Work on the study has been stalled since the departure of the original PI, Dr. Woolman. The new PI, Dr. Runkle, decided to terminated this study due to its previous low enrollment rate and the high amount of time required to pursue this project to completion.



Detail Summary Sheets

Madigan Consolidated Education Division

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/083 **Status:** Completed

Title: A Comparison of the Values and Attitudes of Active Duty Soldiers and Civilians Under Age 35 to Those Over Age 35 at Madigan Army Medical Center

Principal Investigator: Carol A. Nichols

Department: MCED **Facility:** MAMC

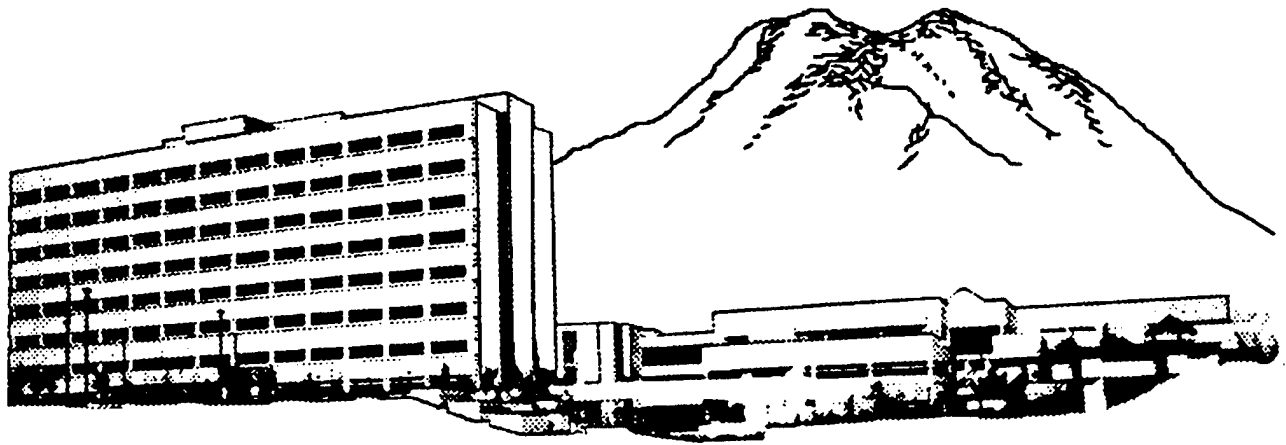
Associate Investigator(s): Leona Dalrymple-Kaufman, Ph.D.; COL Melissa A. Forsythe, AN

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 08/24/1999 | Oct 00 | N/A |

Study Objective: Does the work values and attitudes of young workers at Madigan Army Medical Center differ from those of older workers?

Technical Approach: This study will survey 250 civilian and active duty staff members at Madigan Army Medical Center to determine if a difference exists in work values, traits and attitudes between workers under age 35, and those 35 and over. Work values will be identified using a Survey of Work Values. Attitudes, values and preferences will be analyzed by chi-square.

Progress: 160 subjects have been entered in FY 99 for a total of 160 subjects enrolled. Descriptive data and instructor interviews indicated that younger workers in a military setting had even high work values than younger workers depicted in the literature. Interview revealed young students performed very competently when traditional instructional methods were employed, especially hands-on and lecture format, as long as lectures were interactive and less than 30 minutes per topic area.



Detail Summary Sheets

Cardiology Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/042 **Status:** Ongoing

Title: The Coreg Heart Failure Registry: COHERE

Principal Investigator: LTC James J. King, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): MAJ James P. Olson, MC; MAJ Rosemary P. Peterson, MC; MAJ Michael L. Yandel, MC

Start Date:
02/23/1999

Est. Completion Date:
Jun 99

Periodic Review:
N/A

Study Objective: (1) To collect clinically pertinent outcome data (e.g., mortality, need for hospitalization, use of concomitant medications, patient global assessment, NYHA class in patients with heart failure) receiving Coreg under the care of a broad population of community physicians. (2) To compare the clinical characteristics of the patients treated in the US Phase III and early extended physician use programs with those treated in the community and to assess outcome differences in major subpopulations. (3) To characterize the experience with initiation of Coreg in the community. (4) To compare patient characteristics and management approaches between cardiologists and internists.

Technical Approach: The Coreg Heart Failure Registry will document the relationship of selected patient characteristics to outcomes, such as morbidity, mortality, need for hospitalizations, quality of life and change in clinical status as well as tolerability. By the year 2000, COHERE will contain the most up-to-date information on the natural history of, and effect of B-Blockade in CHF. COHERE will involve approximately 600 participating physicians, and will enroll 6,000 patients with heart failure receiving Coreg. The live portion of the registry will take place over 30 months, and patients will be assessed over a period of 24 months.

Progress: 2 subjects have been entered in FY 99 for a total of 2 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/053

Status: Ongoing

Title: Multinational, Multicenter, Double-Blind, Randomized, Active Controlled, Parallel Group Study Compring the Efficacy and Safety of Long-Term Treatment with Valsartan, Captopril, and Their Combination in High-Risk Patients After Myocardial Infarction

Principal Investigator: LTC James J. King, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): COL Alice M. Mascette, MC; MAJ James P. Olson, MC; LTC David T. Schachter, MC; CPT Kenneth M. LeClerc, MC; MAJ Steven E. Miller, MC; LTC Michael J. Wilson, MC

Start Date:
03/23/1999

Est. Completion Date:
Apr 03

Periodic Review:
N/A

Study Objective: 1) To demonstrate that long-term administration of valsartan is more effective than captopril in reducing total mortality after acute myocardial infarction.

2) To demonstrate that long-term administration of the combination of valsartan with captopril is more effective than captopril alone in reducing total mortality after acute myocardial infarction.

3) If valsartan as monotherapy cannot be shown to be superior to captopril as in objective 1, to demonstrate that long-term administration of valsartan given as monotherapy is at least as effective as captopril given as monotherapy in reducing total mortality after acute myocardial infarction.

Technical Approach: VALIANT is a prospective multinational, multicenter, double-blind, randomized, active-controlled phase III study with three parallel treatment groups. The three treatment groups are 1) Captopril monotherapy (active control drug). The target dose is 50 mg three times daily; 2) Valsartan monotherapy (investigational drug). The target dose is 160 mg twice daily; 3) The combination of captopril and valsartan (investigational regimen). The target doses are 50 mg three times daily and 80 mg twice daily, respectively. The study consists of two phases: 1) a study medication initiation and titration phase and 2) maintenance phase. The duration of these two phases depends upon the patient's status and response to study medication. Randomization and initiation of study medication will occur at Visit 1 on Day 1. For most patients, this will occur in hospital. Dose titration and maintenance will occur at Visits 2-16. Visit 2 will occur on Day 15 or at hospital discharge, whichever is first. For patients not in hospital at the time of randomization, Visit 2 will occur on Day 15. Visits 3-16 are planned as outpatient visits, but depending on the patient's status, may occur in hospital. They are to be performed at specified time points but some flexibility is allowed. During the first year, visit may take place up to 15 days before or after the protocol-scheduled visit. Telephone follow-up is permitted if the patient cannot come for follow-up visits. The study will end when the required number of primary endpoints has been reached. This may occur prior to or after Month 48. If the study ends prior to Month 48, the procedures listed for Visit 16 will be completed for all patients. If the study is extended beyond Month 48, the procedures listed for Visit 15 will be completed every 4 months until study end, at which point the procedures listed for Visit 16 will be completed.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/079 **Status:** Completed

Title: The Effect of Acute Norepinephrine Infusion on Exercise Oxygen Uptake Kinetics and Efficiency in Patients with Congestive Heart Failure and Normal Adults

Principal Investigator: CPT Kenneth M. LeClerc, MC

Department: Medicine/Cardiology **Facility:** MAMC

Associate Investigator(s): Wayne C. Levy, M.D.

Start Date:
05/22/1998

Est. Completion Date:
Aug 98

Periodic Review:
05/27/1999

Study Objective: To evaluate the effect of acute norepinephrine infusion on the exercise oxygen kinetics in patients with stable congestive heart failure as well as normal adults; and to evaluate slow oxygen uptake kinetics during a submaximal workload, oxygen debt and deficit, perceived exertion, blood pressure and heart rate responses, and serum lactate responses.

Technical Approach: Norepinephrine or IV placebo will be infused into both normal adults and patients with heart failure, while they do light to moderate exercise for six to ten minutes. Calorimetry will be used to measure oxygen use before, during, and after this exercise.

Progress: Exercise testing and data analysis have been conducted on 19 healthy adult subjects and on two heart failure subjects. The procedure has been well tolerated. Conclusions showed acute low dose norepinephrine infusion raises oxygen consumption during steady state exercise in heart failure patients but not normal adults. Similarly, exercise efficiency was adversely affected in heart failure subjects.

Detail Summary Sheet

| | | |
|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 98/108 | Status: Terminated |
|------------------------|-----------------------|---------------------------|

Title: A Comparison of Transradial versus Transfemoral Approach to Diagnostic Cardiac Catheterization: Patient Attitudes, Physician Attitudes, and Procedural Variables

Principal Investigator: MAJ Steven E. Miller, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): LTC David T. Schachter, MC; LTC James J. King, MC

Start Date:
09/15/1998

Est. Completion Date:
Apr 99

Periodic Review:
N/A

Study Objective: (1) Comparisons of physician preferences and dislikes for two different arterial access approaches (radial artery verses femoral artery) to cardiac catheterization, (2) comparison of patient preferences and dislikes for two different arterial access approaches (radial artery verses femoral artery) to cardiac catheterization, and (3) to compare arterial access times, total case times, fluoroscopy times, volume of contrast used, number of catheters used and complication rates for both transradial and transfemoral approaches.

Technical Approach: 100 subjects will be randomized to either radial artery or femoral artery cardiac catheterization. Measures will be taken on arterial access times, contrast volumes, coronary angiography times, left ventriculography times, total fluoroscopy times and number of catheters used. Surveys on physician and patient satisfaction will be obtained.

Progress: This protocol was terminated due to the PCS of the PI. Data had been collected on 18 patients. The PI plans to apply for IRB approval of this study at his new station.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/069

Status: Ongoing

Title: Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

Principal Investigator: MAJ James P. Olson, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): MAJ Patrick A. Cambier, MC; COL Roger F. Chamusco, MC; COL Alice M. Mascette, MC; MAJ Herman E. Collier III, MC; LTC Karl C. Stajduhar, MC; MAJ Michael D. Eisenhauer, MC; CPT John A. McHenry, MC; MAJ Maureen A. Arendt, MC; CPT Thomas M. Roe, MC

Start Date:
02/16/1996

Est. Completion Date:
Mar 01

Periodic Review:
02/23/1999

Study Objective: 1) To compare whether optimized antiarrhythmic drug therapy administered to attempt to maintain sinus rhythm has an impact on total mortality when compared to optimized therapy which controls the heart rate. 2) Since stroke is such an important endpoint in trials of patients with atrial fibrillation, composite endpoints will include the following: total mortality, disabling stroke or anoxic encephalopathy, major bleeding and cardiac arrest; cost; quality of life.

Technical Approach: This is a multi center trial sponsored by the National Heart, Lung, and Blood Institute. The purpose is to compare the effect on survival of two different treatment plans in patients with atrial fibrillation. One treatment is aimed at rate control and the other at maintaining a normal sinus rhythm. The primary physician will choose which drug or drugs are used to obtain each treatment objective. The physician will initially determine the treatment to convert patients to normal sinus rhythm after which the patient will be randomized to one of the treatments described above. Patients will be followed at month 2 and 4 and then at least every 4 months until the year 2001. Patients will complete a quality of life questionnaire and have an assessment of their functional status completed at various time points. Patients who fail their assigned treatment or are intolerant will continue to be followed regardless of crossover to another therapy. We anticipate enrolling 15 patients at Madigan Army Medical Center.

Progress: 9 subjects have been entered in FY 99 for a total of 29 subjects enrolled.

Detail Summary Sheet

| | | |
|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 99/013 | Status: Ongoing |
| Title: Magnesium in Coronaries (MAGIC): A Study of the Effect of Magnesium Administration in Patients with Acute Myocardial Infarction | | |
| Principal Investigator: LTC David T. Schachter, MC | | |
| Department: Medicine/Cardiology | Facility: MAMC | |
| Associate Investigator(s): LTC James J. King, MC | | |
| Start Date: 12/15/1998 | Est. Completion Date: Mar 01 | Periodic Review: 12/15/1999 |

Study Objective: To determine if administration of intravenous magnesium within 6 hours of symptom onset in high-risk patients with suspected acute MI reduces all cause and 30-day mortality.

Technical Approach: Subjects will be randomly assigned study drug or placebo in a double-blinded fashion. Subjects will be stratified by site, and by whether the subject is eligible for reperfusion therapy or not. Stratum I will include subjects who are 65 years or older and are eligible for reperfusion therapy. Stratum II will include patients of any age who are not eligible for reperfusion therapy. Subjects will receive either magnesium sulfate or placebo by bolus followed by 24 hour continuous infusion. Follow-up evaluation by telephone or clinic visit will be performed by the PI. The primary endpoint is 30-day all cause mortality. Secondary endpoints include (1) use of intravenous inotropic therapy and/or vasopressors and/or mechanical support for a failing circulation (IABP, LVAD), (2) electrical reversion of ventricular fibrillation or sustained ventricular tachycardia, and (3) placement of an external or transvenous pacemaker.

Progress: 3 subjects have been entered in FY 99 for a total of 3 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/055 **Status:** Ongoing

Title: Low Dose Niacin Supplementation with Chronic Statin Therapy

Principal Investigator: CPT Jennifer S. Wink, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): LTC James J. King, MC

Start Date:
03/23/1999

Est. Completion Date:
Dec 99

Periodic Review:
N/A

Study Objective: This study tests the hypothesis that very low dose niacin will positively affect the lipid profile, by significantly raising high-density lipoprotein cholesterol levels.

Technical Approach: This study will be a randomized, double-blinded, placebo controlled study. 40-50 subjects will be recruited with 30 completing the study. They will receive either 50 mg BID niacin or placebo for 90 days. Other anti-lipid therapies will be stable. Neither the principal nor the associate investigators will be aware of randomization until analysis occurs at the end of the study. HDL, Lipids, glucose, LFT, TSH and electrolytes will be recorded at day 0 and day 90. A paired T-test will be used to compare HDL, Lipids, glucose, LFT, TSH and electrolytes levels.

Progress: This protocol has not received final IRB approval; therefore, no patients have been recruited for this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/140

Status: Ongoing

Title: A Double-Blind, Placebo-Controlled, Parallel Design Study to Determine the Effect of 100 mgs of Orally Administered Azimilide Dihydrochloride versus Placebo on Survival in Recent Post-Myocardial Infarction Patients at Risk of Sudden Death (ALIVE)

Principal Investigator: MAJ Michael L. Yandel, MC

Department: Medicine/Cardiology

Facility: MAMC

Associate Investigator(s): MAJ Maureen A. Arendt, MC; MAJ Karen A. Hicks, MC; MAJ James P. Olson, MC; LTC James J. King, MC; LTC David T. Schachter, MC; CPT Kenneth M. LeClerc, MC; CPT Allan B. Wicks, MC; MAJ Steven E. Miller, MC; MAJ Theresa A. Horne, AN; COL Alice M. Mascette, MC; LTC Michael J. Wilson, MC

Start Date:
09/19/1997

Est. Completion Date:
May 99

Periodic Review:
9/28/1999

Study Objective: To evaluate the effects of 75 mg of azimilide dihydrochloride versus placebo or 100 mg of azimilide dihydrochloride versus placebo on all-cause mortality, based on longitudinal intent-to-treat observations in patients with a recent (within 6 to 21 days) acute MI, low left ventricular ejection fraction (15 to 35%), and low heart rate variability (≤ 20 U). These patients are defined as "at high risk" of sudden death.

Technical Approach: This is a randomized, double-blind, placebo-controlled, multi-national study at approximately 500 study centers. A treatment regimen consisting of daily oral doses of 75 or 100 mg of azimilide dihydrochloride will be compared to a placebo group in a parallel design. Patients will be equally randomized across all 3 treatment groups. Patients who have recently experienced an acute MI and meet other study entrance and screening criteria will receive their first dose of study medication within 6-21 days of that MI. Once-daily treatment will be administered for approximately one year. No specific hospitalization is required for treatment. Screening procedures (to include a 24 hour Holter monitor) will be done to determine the group "at high risk" of sudden arrhythmic death. Evaluations during the treatment period will take place at Week 2, and at Months 1, 4, 8, and 12. Monthly serum pregnancy tests will be performed on females of childbearing potential who are not surgically sterile. Patients who complete 365 days of dosing will be followed for one month after completion of their participation in the study. Patients who withdraw from the trial early will return within 4 weeks for study exit procedures and furthermore, will be followed to assess survival status until the time at which they would have completed 365 day of dosing had they remained in the trial. Safety monitoring will include but is not limited to, clinical laboratory test results, 12-lead ECG measurements and frequency and severity of adverse events.

Progress: One subject was enrolled in FY 99 for a total of two subjects at MAMC. Since 1 Oct 98 only one patient has been randomized. Patient recruitment is expected to continue through Feb 2000. Currently there have been no serious adverse events at MAMC.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/036 **Status:** Ongoing

Title: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure

Principal Investigator: MAJ Michael L. Yandel, MC

Department: Medicine/Cardiology **Facility:** MAMC

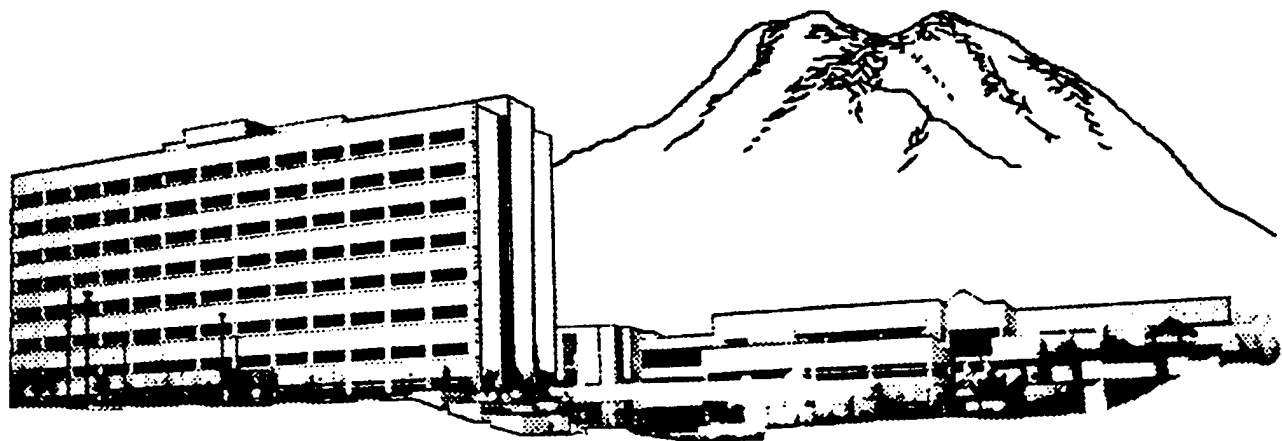
Associate Investigator(s): LTC James J. King, MC; MAJ James P. Olson, MC; LTC David T. Schachter, MC; MAJ Rosemary P. Peterson, MC

| | | |
|----------------------------------|--|--------------------------------|
| Start Date: 02/23/1999 | Est. Completion Date: Aug 99 | Periodic Review: N/A |
|----------------------------------|--|--------------------------------|

Study Objective: Primary objective of this study is to determine whether early interventional therapy with inodilator milrinone reduces the total number of days of hospitalization for cardiovascular events within 60 days following therapy. Secondary objectives: (1) reduces the proportion of treatment failures within the first 48 hours from randomization, (2) increases the proportion of patients achieving the target dose of ACE-inhibitor therapy and reduces the time to achieve target dose, (3) improves clinical outcome as measured by a patients visual analog scale and the overall personalized treatment effect questionnaire, measurements taken at admission, on discharge, day 30 and day 60, (4) improves heart failure score, measured at admission, day 3 and discharge, (5) reduces the length of initial hospitalization in number of days from the time of randomization to initial discharge, (6) reduces the number of days of hospitalization for primary cardiovascular disease post discharge and all cause admissions within 60 days following randomization, (7) reduces the number of days of hospitalization for cardiovascular events within 30 days of randomization, (8) influences the incidence of adverse events and (9) influences mortality.

Technical Approach: Subjects will be randomized within 48 hours of admission to receive either early intravenous milrinone therapy with conventional therapy and maintenance of oral therapy or early intravenous placebo with conventional therapy and maintenance of oral therapy (control care group). Study drug will be started at a dose of 0.5 mcg/kg/min without a loading dose and continued for a minimum of 24 hours. All efforts will be made to maintain the infusion for 48 hours and it may be maintained up to 72 hours at the discretion of the investigator. The control group will receive a placebo infusion. The heart failure score will be determined at day 3 and at discharge. Subjects will be seen (or telephone contact made) at 30 days and at 60 days following randomization.

Progress: One subject has been entered in FY 99 for a total of 1 subject enrolled.



Detail Summary Sheets

Endocrinology Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/124 **Status:** Ongoing

Title: The Effect of Partial Energy Restriction on the Changes in Metabolic and Kinetic Measures of Thyroid Hormone Metabolism During Antarctic Residence

Principal Investigator: COL H. Lester Reed, MC

Department: Medicine/Endocrinology **Facility:** MAMC

Associate Investigator(s): LTC Homer J. Lemar Jr., MC; CPT Nhan V. Do, MC;
Nancy S. Finney

Start Date:
07/18/1997

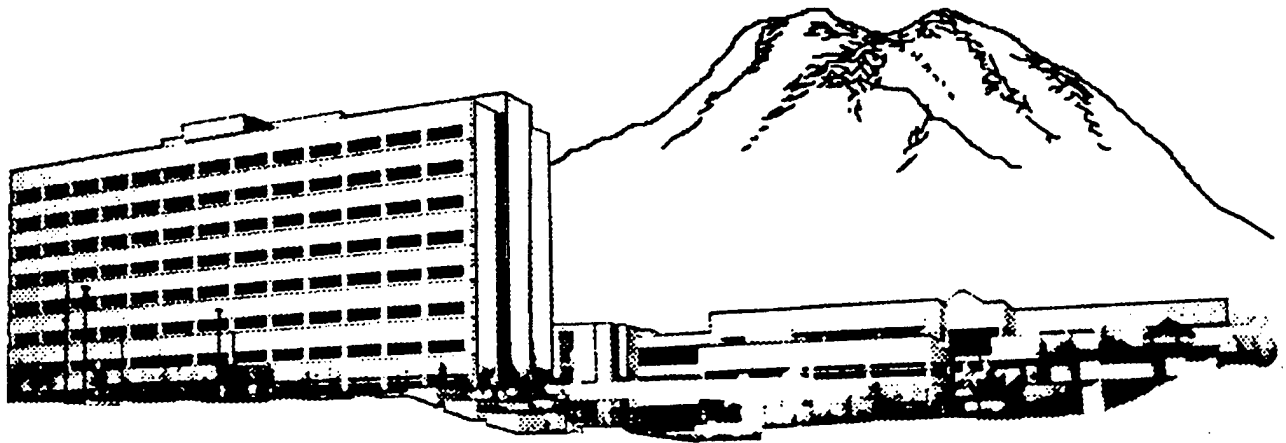
Est. Completion Date:
Oct 98

Periodic Review:
06/22/1999

Study Objective: 1) To evaluate the influence of circulating TSH and energy restriction upon the previously described increases in triiodothyronine (T3) plasma appearance rate and distribution volume (Vd) observed with extended Antarctic residence (AR). A reduction in serum TSH will be obtained by using 50mcg per day of thyroxine supplementation for the entire 11 month period, in contrast to our current study evaluating thyroxine supplement during the last 7 months of deployment. This dose schedule will allow an extension of our earlier findings regarding the effects of AR upon memory performance in this group. 2) To continue our previous mood and cognitive studies in the current study by contrasting placebo and thyroxine supplementation to insure the cognitive performance goal of supplementation has been achieved during the year as identified in our previous study.

Technical Approach: Sixteen military and civilian health care beneficiaries including men and women who are between 18 and 55 years old and are members of the winter-over crew in McMurdo, Antarctica will be recruited for the study. After recruitment subjects will perform monthly exercise, mood, and cognitive testing beginning one month prior to departure and continuing through their entire 11 month stay in McMurdo. The parameters that will be examined include changes in muscle oxygen utilization, changes in thyroid functions, and changes in cognitive, memory, and mood during the development of the Polar T3 Syndrome. One of the characteristics of the Polar T3 Syndrome is a low T4 state in the CNS that may be responsible for the characteristic declines in mood and memory during winter seasons in circumpolar regions. All subjects will receive either thyroxine 50mcg/day or daily placebo starting the day after October 1997 baseline studies and ending 11 months later in August 1998. Thyroid functions will be monitored monthly throughout the study. Subjects will serve as their own controls for analysis of kinetic parameters, mood and cognitive data. Comparisons will also be made between levothyroxine and placebo groups for the exercise, mood, cognitive testing, and kinetic parameters.

Progress: The worksite in McMurdo, Antarctica was closed and all equipment and materials used by the Project were shipped back to storage at MAMC after completion of all work directly with the subjects in McMurdo in September 1998 and return of all samples to relevant participating Centers/Investigators. Additional serum assays may still be performed on existing samples. This possibility was provided for in the IRB approved consent form for the protocol as signed by all subjects and witnessed.



Detail Summary Sheets

Gastroenterology Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/005 **Status:** Ongoing

Title: Intron A + Ribavirin for Treatment of Patients with Chronic Hepatitis C not Previously Treated with Interferon

Principal Investigator: MAJ William K. Hirota, MC

Department: Medicine/Gastroenterology **Facility:** MAMC

Associate Investigator(s): COL Amy M. Tsuchida, MC; LTC Robert H. Sudduth, MC; LTC Spencer S. Root, MC

Start Date:
10/17/1997

Est. Completion Date:
Dec 98

Periodic Review:
9/28/1999

Study Objective: To provide ribavirin for use in combination with Intron A for the treatment of Hepatitis C in patients who have not previously received interferon therapy; to obtain additional safety information of the combination on Intron A and ribavirin; to obtain additional information on different regimens of Intron A and ribavirin.

Technical Approach: Subjects will be randomized to either Intron A plus ribavirin or Intron A plus placebo. Treatment for the first 12 weeks will be double-blind. At 12 weeks, blood test for HCV-RNA will be done to assess response. If the test is positive, treatment will be unblinded and those on placebo will be offered to cross over to treatment with Intron A plus ribavirin. If they were on ribavirin, they will be finished with the study. If the test is negative, subjects will continue with their current blinded treatment.

Progress: No subjects have been entered in FY 99 for a total of 8 subjects enrolled. One serious adverse event was reported last year.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/006

Status: Ongoing

Title: Intron A + Ribavirin for Treatment of Patients with Interferon-Refractory or Interferon-Relapsed Chronic Hepatitis C

Principal Investigator: MAJ William K. Hirota, MC

Department: Medicine/Gastroenterology

Facility: MAMC

Associate Investigator(s): COL Amy M. Tsuchida, MC; LTC Robert H. Sudduth, MC; LTC Spencer S. Root, MC

Start Date:
10/17/1997

Est. Completion Date:
Dec 98

Periodic Review:
9/28/1999

Study Objective: To provide ribavirin for use in combination with Intron A for the treatment of Hepatitis C patients who failed previous interferon therapy or relapsed after treatment with interferon; to obtain additional safety information on the combination of Intron A and ribavirin; to obtain additional information on different regimens of Intron A and ribavirin.

Technical Approach: Patients will be treated throughout the study with open-label Intron A and ribavirin; dose dependent on weight. Safety and tolerance will be evaluated at weeks 1, 2, 4, 8, and then every 4 weeks during treatment and at weeks 4, 8, 12, and 24 until the end of therapy. Complete response will be defined as loss of detectable HCV-RNA by PCR.

Progress: No subjects have been entered in FY 99 for a total of 4 subjects enrolled. One serious adverse event was reported last FY.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/164 **Status:** Ongoing

Title: Epidemiology of Gallbladder Sludge and Stones in Pregnancy

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology **Facility:** MAMC

Associate Investigator(s): Sum P. Lee, M.D., Ph.D; MAJ Kazunori Yamamoto, MC; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC; Scott J. Schulte, M.D.; Beth W. Alderman, M.D., MPH; Gerard Schallenberg, M.D.; Edward J. Boyko, M.D., Ph.D.; Gail Jarvik, M.D.; Katherine H. Moore, Ph.D.

Start Date:
09/20/1996

Est. Completion Date:
Sep 02

Periodic Review:
10/20/1998

Study Objective: The primary objective of this NIH-funded study is to determine the incidence of gallstones and sludge during pregnancy. Other objectives are to: 1) identify behavioral and genetic risk factors for the development and regression of sludge and stones; 2) elucidate the mechanism by such risk factors may induce gallstones; and 3) predict the development and regression of sludge and stones.

Technical Approach: This cohort study will include serial ultrasound tests of the gallbladder during pregnancy and post-partum. All women presenting for prenatal care will be eligible unless they: (1) do not speak English; (2) have had gallbladder surgery; (3) are over 20 weeks pregnant; (4) do not expect to deliver at MAMC; and (5) are less than 18 years of age. Eligible women who agree to participate will complete Participation and Consent Forms and under waist and hip circumference measurements. The ultrasonographers will test participants for evidence of sludge and stones at 10, 18, and 28 weeks of gestation and 6 weeks postpartum. For each ultrasound test, the study radiologist will review selected ultrasound images saved by the ultrasonographer. Participants who have stones or sludge at 6 weeks postpartum will return in 12 year for a follow-up ultrasound. At her time of each ultrasound, participants will be asked to complete a one-hour questionnaire and interview. They will also be asked to give an extra fasting blood sample at 128 weeks of gestation. Medical data from the CIS and CHCS will be downloaded and linked to study data.

Progress: 1124 subjects have been entered in FY 99 for a total of 3469 subjects enrolled. To date 1005 subjects have completed the study; 1105 subjects were lost to follow-up for various reasons (PCS/ETS, miscarriage, non-compliance, medical reasons); 1359 subjects are still in some phase of the study, 13 subjects have had gallbladder surgery and 58 subjects have been referred to the GI clinic for further follow-up. Subject recruitment is on-going.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/012

Status: Ongoing

Title: A Pre-Clinical Research and Development Study to Evaluate Stool Specimens for Basement Membrane Fragments/Complexes and Cytoskeletal Proteins

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology

Facility: MAMC

Associate Investigator(s): LTC Robert H. Sudduth, MC; MAJ Kazunori Yamamoto, MC; MAJ John G. Carrougher, MC

Start Date:
11/15/1996

Est. Completion Date:
Oct 97

Periodic Review:
10/24/1999

Study Objective: Evaluate the clinical utility potential of the CoTA test strip assay in detecting basement membrane complexes in individuals with or without colorectal cancer, respectively. And to isolate sufficient amounts of colon BMC for additional antibody production and antigen characterization using the CoTA test strip assay and other antibody tests.

Technical Approach: This is a multicenter trial with MAMC providing stool specimens only from patients diagnosed with colorectal cancer. Following colonoscopy, eligible participants will be instructed to collect a stool specimen after their stools have returned to normal and prior to any other intestinal procedures. The specimen will be shipped directly to BARD Diagnostic Sciences, Inc.

Progress: 9 subjects have been entered in FY 99 for a total of 21 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/004

Status: Ongoing

Title: Epidemiology of Barrett's Esophagus

Principal Investigator: COL Amy M. Tsuchida, MC

Department: Medicine/Gastroenterology

Facility: MAMC

Associate Investigator(s): Diana C. Farrow, Ph.D.; MAJ William K. Hirota, MC; LTC Spencer S. Root, MC; LTC Robert H. Sudduth, MC

Start Date:

10/17/1997

Est. Completion Date:

Jun 01

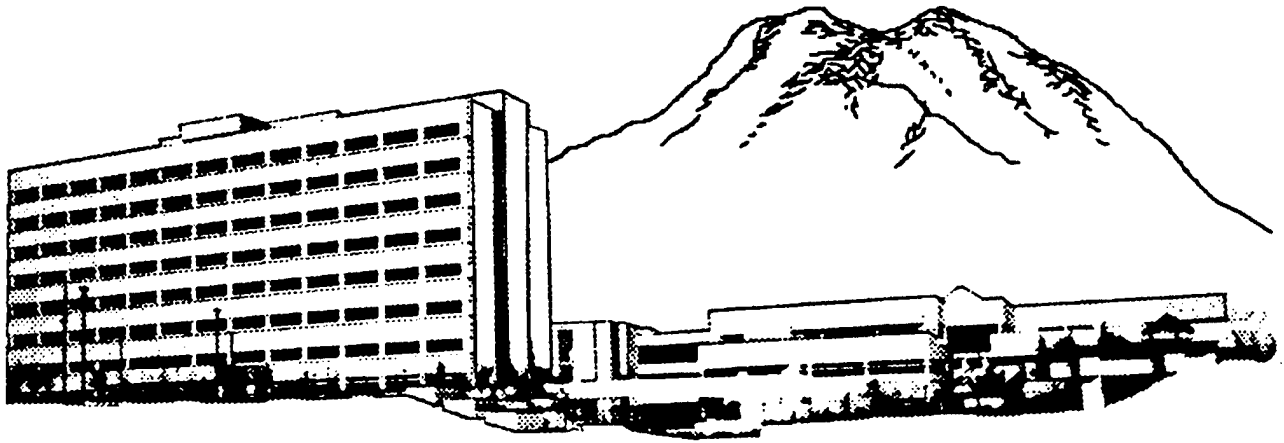
Periodic Review:

11/17/1998

Study Objective: To determine whether there are any specific environmental, dietary, or personal factors which increase the risk of developing Barrett's Esophagus.

Technical Approach: Patients who are undergoing an upper endoscopy for evaluation of their heartburn complaints will have four biopsies and a small amount of stomach fluid taken for research purposes. Information from the endoscopic findings will be abstracted from medical records.

Progress: 35 subjects have been entered in FY 99 for a total of 79 subjects enrolled.



Detail Summary Sheets

Hematology/Oncology Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/110 **Status:** Completed

Title: Double Blind, Double Dummy, Randomized, Multicenter, 2-Arm, Phase III Trial Comparing Letrozole 2.5 mg versus Tamoxifen 20 mg as First Line Therapy in Postmenopausal Women with Advanced Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: Medicine/Hematology & Oncology **Facility:** MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; James H. Timmons, MD; MAJ Matthew P. Jones, MC

Start Date:
06/20/1997

Est. Completion Date:
Aug 01

Periodic Review:
07/17/1998

Study Objective: To compare the efficacy, as evaluated by the primary variable of time to progression (TTP), and the secondary variables of objective response rate, duration of response, and time to treatment failure (TTF) between the two treatment arms (2.5 mg letrozole once daily and 20 mg tamoxifen once daily). Secondary: a) To compare the tolerability and toxicity of the two treatment arms; b) to determine the survival time in each of the two treatment arms; and c) to summarize time to progression, objective response rate, and time to treatment failure for the second-line therapy using the subset of patients in the cross-over treatment period.

Technical Approach: This is a double blind, double dummy, multicenter, randomized, 2-arm, cross-over, Phase III trial, comparing the efficacy of letrozole versus tamoxifen in first-line treatment of postmenopausal women with advanced breast cancer. Once patients have met the inclusion/exclusion criteria, they will be randomly assigned to one of the two treatment arms. The two treatments are randomly assigned according to a predetermined, computer generated randomization list using permuted blocks. Patients will be evaluated radiographically every three months for disease progression. If they remain disease free, they will be seen for an exam, laboratory tests and re-dispensing of blinded trial medication. Once disease progression has been documented, patients will be given the option of taking open label letrozole (if they were on prior treatment with tamoxifen) or open label tamoxifen (if they were on prior treatment with letrozole) and will continue to be followed every three months.

Progress: The protocol closed to patient enrollment 17 Dec 98 as the sponsor stated they had reached target enrollment. No patients were entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/026

Status: Completed

Title: A Phase II Trial of Thioplex Following Induction Chemotherapy to Decrease the Incidence of Brain Metastases in Limited Stage Small Cell Lung Cancer Patients

Principal Investigator: MAJ Matthew P. Jones, MC

Department: Medicine/Hematology & Oncology

Facility: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; LTC Kenneth A. Bertram, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; LTC Robert L. Sheffler, MC; MAJ David E. McCune, MC

Start Date:
11/15/1996

Est. Completion Date:
Jan 98

Periodic Review:
01/26/1999

Study Objective: The primary objective is to evaluate the effectiveness of Thioplex in the prevention of CNS metastases in limited stage SCLC subjects who have achieved a complete or partial remission following initial systemic chemotherapy and chest irradiation. Secondary objectives are to evaluate the treatment with respect to overall survival, incidence of systemic metastases, and safety.

Technical Approach: This is a multicenter, open label, Phase II pilot study designed to evaluate the efficacy of Thioplex following a standard Etoposide (VP-16)/platinum-based regimen for the prevention of CNS metastases in limited small cell lung cancer. Patients who have achieved a complete or partial remission following chest irradiation and four courses of standard induction chemotherapy will be eligible for the study. Subjects will receive Thioplex at a dose of 45 mg/m² IV each month for 3 cycles. Patients will be followed for up to 30 months for evidence of CNS metastases and survival.

Progress: Two patients were enrolled in this study at MAMC. One patient had several adverse events that were possibly related to the study drug. These were 3 episodes of upper respiratory infections (all resolved); fatigue (resolved), and elevated blood glucose (on-going but stable). This patient completed study drug and follow-up phase. The second patient died (of CVA) prior to receiving study drug. This study closed 14 Jan 99 by the sponsor due to poor enrollment at all sites.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/049

Status: Completed

Title: An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in Other OTFC Studies

Principal Investigator: MAJ David E. McCune, MC

Department: Medicine/Hematology & Oncology

Facility: MAMC

Associate Investigator(s): LTC Robert B. Ellis, MC; LTC Luke M. Stapleton, MC; LTC Robert D. Vallion, MC; MAJ James S. D. Hu, MC; MAJ John R. Caton, MC; LTC Robert L. Sheffler, MC; Rakesh Gaur, M.D.; MAJ Richard F. Williams, MC; MAJ Matthew P. Jones, MC; LTC Kenneth A. Bertram, MC

Start Date:
01/19/1996

Est. Completion Date:
Mar 97

Periodic Review:
02/23/1999

Study Objective: To establish the long-term safety and tolerance of OTFC in cancer patients experiencing breakthrough or incident pain while taking other opioids.

Technical Approach: The study will be conducted using an open-label, uncontrolled design in cancer patients. Cancer patients successfully completing other appropriate studies of OTFC will be eligible for this study. When patients experience breakthrough pain, they may treat up to 4 episodes each day with OTFC. Patients will be given a supply of OTFC units, all the same dosage strength, to treat breakthrough or incident pain for one month. The patient will be contacted at least weekly by telephone by a study physician or nurse and will be seen by study personnel at least monthly. After each contact, the investigator will decide whether or not the patient requires a larger or smaller dose of study medication to relieve breakthrough pain using a single OTFC unit. Patients may remain in the study for up to four months if they continue to experience breakthrough pain and are able to provide complete and accurate information on the safety and efficacy of the study medication. Patients will record in a daily diary the use of OTFC and any other medications, assess the performance of the study medication in relieving breakthrough or incident pain, and report any adverse events they experience. Demographics, medical history, physical exam, and laboratory results will be summarized using descriptive statistics.

Progress: This study closed to patient enrollment 2 Aug 99, per sponsor due to enrollment numbers having been met. Five patients were entered in previous years with three patients completing the study. One patient withdrew consent prior to receiving study medication and another patient withdrew secondary to adverse events not related to study drug.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/111

Status: Completed

Title: Protocol AC 600/001: Multicenter, Double-Blind, Crossover Study of Oral Transmucosal Fentanyl Citrate (OTFC) Compared to Immediate Release Morphine Sulfate for the Treatment of Breakthrough Pain in Cancer Patients Taking Stable Doses of Opioids

Principal Investigator: MAJ David E. McCune, MC

Department: Medicine/Hematology & Oncology

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; LTC Kenneth A. Bertram, MC

Start Date:
06/20/1997

Est. Completion Date:
Feb 98

Periodic Review:
07/17/1998

Study Objective: To demonstrate that Actiq™ (oral transmucosal fentanyl citrate) is more effective for the treatment of breakthrough pain than immediate release morphine sulfate in opioid tolerant cancer patients.

Technical Approach: This double-blind, double-dummy, multiple cross-over, multicenter study will be conducted in cancer patients who are currently using 60-100 mg per day of oral morphine (or morphine equivalent of another oral opioid) or 50-300 µg per hour transdermal fentanyl, on around-the-clock (ATC) schedule to control persistent pain. Patients will continue to use their ATC medication for persistent pain at a constant dose and regimen throughout the study. Patients who are currently using a stable dose of 15 mg, 30 mg, 45 mg, or 60 mg capsules of immediate release morphine sulfate (MSIR) to effectively treat breakthrough (BT) pain will be eligible for the study. In the open-label titration phase (Phase A), patients will be titrated to a dose of OTFC such that one unit of OTFC will successfully treat an episode of BT pain. Successfully titrated patients will enter the double-blind phase of the study (Phase B). In Phase B, patients will be supplied with ten sequentially numbered sets of study drug - each set containing one active OTFC unit and placebo capsule(s), or one placebo OTFC unit and immediate release morphine sulfate capsule(s). The dose of MSIR that the patient used prior to study will determine the number of capsules provided. Placebo and active drug will be prepared in a way to maintain the blind. Five of the study drug sets will contain active OTFC units, and five will contain active MSIR. The order of administration of active drug will be randomized. Patients will be instructed to take IN ORDER one set of study drug (one OTFC and capsules) for each episode of BT pain they experience until all ten sets have been administered, or until they have been in the double-blind phase for 14 days. Patients will be asked to rate their pain every 15 minutes for an hour after taking the study medication. In phase B, patients will be instructed not to use additional rescue medication within one hour of treating an episode of BT pain with study drug. Patients will also be instructed not to take study drug within 2 hours of previous rescue medication. Health changes, persistent and breakthrough pain, and use of concomitant and rescue medication will be assessed daily.

Progress: The study closed at MAMC, 4 Mar 99, per the sponsor due to enrollment numbers being met. Nine patients were consented in this study at MAMC. Three patients completed the study. Four patients were screen failures and two patients withdrew secondary to intolerance of MSIR.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/112 **Status:** Completed

Title: Protocol AC 600/002: An Open-Label, Long-Term, Multicenter Study of Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Breakthrough or Incident Pain in Cancer Patients Previously Enrolled in AC 600 Series Protocols

Principal Investigator: MAJ David E. McCune, MC

Department: Medicine/Hematology & Oncology **Facility:** MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.; MAJ Matthew P. Jones, MC; MAJ William B. Reece, MC; CPT Brent L. Kane, MC; MAJ Mark E. Shaves, MC; LTC Kenneth A. Bertram, MC

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| Start Date: 06/20/1997 | Est. Completion Date: Sep 98 | Periodic Review: 07/17/1998 |
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Study Objective: To establish the long-term safety and tolerance of Oral Transmucosal Fentanyl Citrate (OTFC) in cancer patients experiencing breakthrough pain while taking other opioids and to collect data regarding patients' preferences for OTFC versus immediate release morphine sulfate.

Technical Approach: This open-label, multicenter study will be conducted in cancer patients previously enrolled in other AC 600 series protocols. Patients who have complete an AC 600 series protocol will be eligible for this study provided that they safely tolerate OTFC and are enrolled within four weeks of completing the earlier study. Patients will choose either OTFC or IRM (immediate release morphine) for treatment of their breakthrough pain. Patients who choose to use OTFC will start therapy at a dose selected from experience in the earlier study. Patients who choose IRM will start therapy at a dose determined from their previous rescue dose. Patients must continue to take an opioid around the clock. Medication and dosage regimen can be changed at the discretion of the investigator. Contact every two weeks between the patient and study personnel will be used as the occasion to adjust the dose of study medication up or down, as needed. Dose adjustments may be made more frequently at the discretion of the investigator. In addition, patients will be asked to maintain a diary of the study drug usage. Patients will remain in the study for up to 6 months if they continue to experience breakthrough pain and are able to provide complete and accurate information on the safety and efficacy of the study medication. Eligibility will be evaluated monthly.

Progress: This study closed at MAMC 4 Mar 99, per the sponsor due to enrollment numbers being met. Three patients were enrolled in FY 98; however none of the patients completed the study. Disease progression in one patient led to weakness and inability to continue in the protocol. This patient was withdrawn from the study and died of the disease within a month. Another patient withdrew due to disease progression. The third patient withdrew secondary to dislike of OTFC sweetness (taste).

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/093

Status: Ongoing

Title: Phase II Trial of Gemcitabine and Herceptin in HER2 Overexpressing Metastatic Breast Cancer

Principal Investigator: MAJ David E. McCune, MC

Department: Medicine/Hematology & Oncology

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC; MAJ Ines J. Sanchez-Rivera, MC

Start Date:
08/24/1999

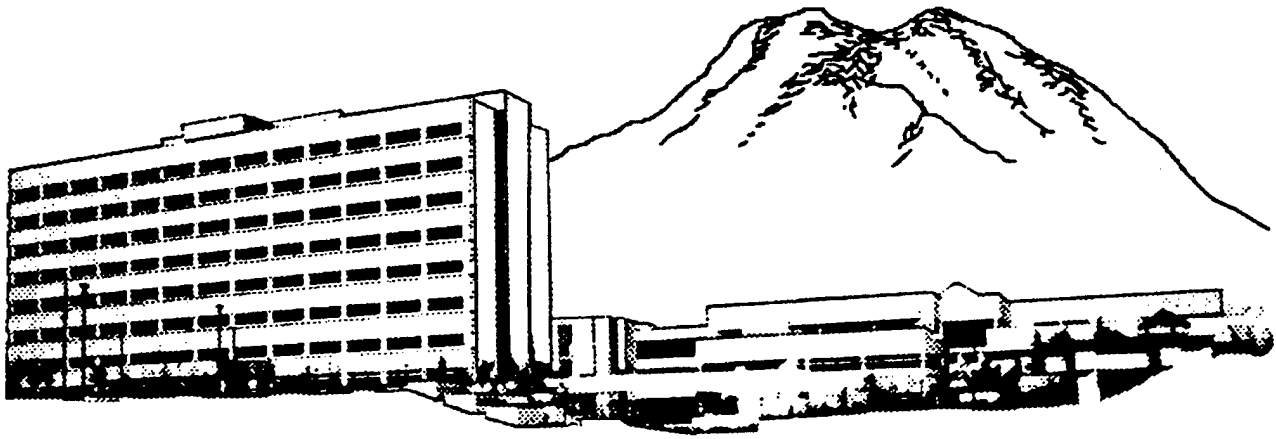
Est. Completion Date:
Jul 01

Periodic Review:
N/A

Study Objective: 1) To response rates of complete response, partial response, stable disease and progressive disease. 2) To document the median time to progression and median survival of disease. 3) To monitor toxicities of Grades 3 or higher to be reported (toxicities graded based on the NCI common toxicity grading scheme)

Technical Approach: This is a Phase II multicenter trial conducted in military medical centers experienced in the treatment of breast cancer. The study will investigate the response rate, time to treatment failure, overall survival and toxicity/safety profile of a novel combination of Gemcitabine and Herceptin in patients with metastatic breast cancer. Both of the drugs will be administered weekly in patients whose breast cancer overexpresses the BER2 proto-oncogene.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Infectious Disease Service,
Department of Medicine

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 98/058 | Status: Completed |
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Title: Linezolid for the Treatment of Methicillin Resistant Staphylococcus aureus (MRSA) Infections: An Evaluator Blinded Trial Comparing Linezolid with Vancomycin Alone and Vancomycin Followed by Oral Linezolid

Principal Investigator: LTC Joseph T. Morris III, MC

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| Department: Medicine/Infectious Disease | Facility: MAMC |
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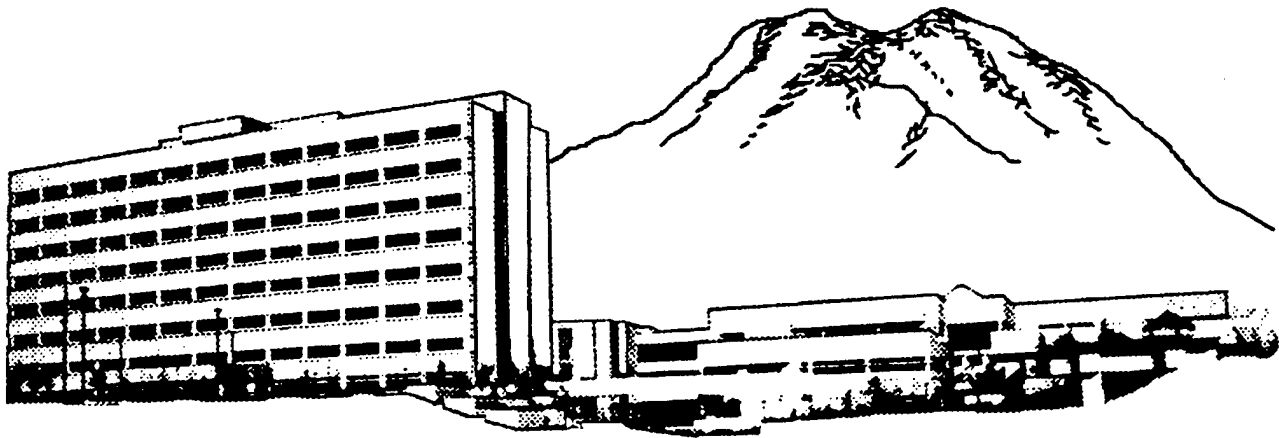
Associate Investigator(s): CPT Eric J. Messner, MC

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| Start Date: 03/20/1998 | Est. Completion Date: Nov 98 | Periodic Review: 04/27/1999 |
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Study Objective: To assess the efficacy (clinical and microbiological) safety and tolerance of intravenously and orally administered Linezolid when compared with vancomycin in the treatment of methicillin resistant Staphylococcus aureus (MRSA) infections,

Technical Approach: Patients with positive culture for MRSA will be randomized to receive one of three treatments, (1) Group 1 will receive IV Linezolid with optional oral Linezolid pills for follow-up, (2) Group 2 will receive IV Vancomycin and (3) Group III will receive a combination IV Vancomycin with oral Linezolid pills as follow-up.

Progress: This study closed to patient enrollment 31 May 99 per sponsor request. One patient was enrolled and completed the study with no serious adverse events.



Detail Summary Sheets

Internal Medicine Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/032

Status: Ongoing

Title: Cost Analysis of Prescreening for Hepatitis A Before Immunization in Patients with Chronic Liver Disease

Principal Investigator: CPT Marten B. Duncan, MC

Department: Medicine/Internal Medicine

Facility: MAMC

Associate Investigator(s): MAJ William K. Hirota, MC; COL Amy M. Tsuchida, MC; LTC Spencer S. Root, MC

Start Date:
02/23/1999

Est. Completion Date:
Feb 01

Periodic Review:
N/A

Study Objective: To define the prevalence of hepatitis A virus (HAV) in a population of patients with chronic liver disease (CLD) and to characterize demographic features of previously exposed patients. To perform a cost analysis of immunization for hepatitis a virus in those with CLD by comparing three strategies.

Technical Approach: 100 subjects with CLD will be recruited to clarify the prevalence of prior hepatitis A exposure. Subjects will complete a survey to identify which risk factors are most common among patients with CLD. Hepatitis A serology will then be determined using an anti-HAV elisa. Subjects will be asked to report for vaccination only if they are seronegative for prior exposure to the virus. A cost analysis will be done to identify the least costly way to provide immunity against the virus in this subgroup of patients using the prevalence of prior infection determined by this study. These strategies include: (1) to determine seropositivity and vaccinate only those without evidence of prior exposure, (2) to immunize all persons with CLD, or (3) determine antibody status and vaccinate in one visit with follow-up vaccination at 6 months only if the patient was seronegative for anti-HAV.

Progress: Data on 39 subjects have been collected during FY 99. Subject recruitment continues.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/074 **Status:** Completed

Title: The Prevalence of Hepatitis A in US Military Recruits

Principal Investigator: CPT Marten B. Duncan, MC

Department: Medicine/Internal Medicine

Facility: MAMC

Associate Investigator(s): MAJ William K. Hirota, MC; COL Amy M. Tsuchida, MC;
LTC Spencer S. Root, MC

Start Date:

06/22/1999

Est. Completion Date:

Jan 00

Periodic Review:

N/A

Study Objective: To determine the prevalence of hepatitis A in military recruits.

Technical Approach: The serum of approximately 1000 ROTC cadets will be tested to determine the prevalence of exposure to hepatitis A in incoming officers. This data will be linked to demographic information to establish characteristics common among individuals with prior exposure to hepatitis A. This data would be helpful in guiding future vaccination practices of the military by establishing the utility of prescreening for hepatitis A prior to vaccination.

Progress: Data on 1332 subjects have been collected during FY 99. Findings showed 13.3% of recruits had serologic evidence of hepatitis A. There was a statistically significant trend towards higher prevalence rates in minority populations, to include African Americans, Asians, Hispanics, and American Indians, with a rate of 17%. A cost analysis was performed confirming the results of another similar study conducted by the Dutch. Using a prescreening strategy for hepatitis A vaccinations, there was a cost saving if the prevalence was greater than 20%. Interestingly, this critical prevalence where a prescreening strategy becomes cost savings is reduced as the cost of vaccination increases or the cost of the clinic visit increases.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/016

Status: Terminated

Title: A Controlled Clinical Trial to Improve Housestaff Identification of and Attitudes Toward Mental Disorders in Primary Care

Principal Investigator: MAJ Robert B. Gibbons, MC

Department: Medicine/Internal Medicine

Facility: MAMC

Associate Investigator(s): CPT Jeffrey S. Strong, MC; MAJ Richard A. Jordan, MC; MAJ Jeffrey L. Jackson, MC

Start Date:
11/15/1996

Est. Completion Date:
Feb 96

Periodic Review:
02/23/1999

Study Objective: To determine whether simple educational intervention can increase the rate of recognition of mental disorders.

Technical Approach: As at least one third of all patients seen in an outpatient setting by primary care physicians have an underlying mental disorder, and the rate of identification of such problems by this group of physicians is generally under 50%, this educational intervention will attempt to improve housestaff attitudes toward recognition and management of psychiatric disorders.

Progress: This study was terminated by the PI, 12 Feb 99 prior to his PCS. No subjects were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/015 **Status:** Ongoing

Title: Use of Blood Cultures in the Evaluation of Febrile Episodes in Neutropenic Patients Receiving Broad Spectrum Antibiotics

Principal Investigator: CPT Brian P. Mulhall, MC

Department: Medicine/Internal Medicine **Facility:** MAMC

Associate Investigator(s): COL Ronald H. Cooper, MC; MAJ Robert B. Gibbons, MC; CPT Sue E. Fitzgerald, MC

Start Date:
11/21/1997

Est. Completion Date:
Jul 98

Periodic Review:
01/26/1999

Study Objective: To determine the prevalence of positive blood cultures in febrile granulocytopenic patients who are receiving antimicrobial therapy; whether blood culture results were used to modify antimicrobial therapy; the cost of obtaining blood cultures during these episodes and to determine, if possible, a population of patients in whom blood cultures are likely to be positive.

Technical Approach: The charts of febrile neutropenic patients admitted to MAMC from 1989 to 1997 will be reviewed with particular attention to blood culture results and antibiotic use. The cost of these blood cultures will be estimated. Data extracted will include: demographics, diagnoses, antibiotic use, chemotherapeutic regimen currently in use, daily ANC, blood cultures and clinical data.

Progress: No work has been done on this protocol during FY 99, due to PCS of associate investigators and time constraints of PI.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/080 **Status:** Completed

Title: Effect of Tricuspid Regurgitation on the Accuracy of Pulse Oximetry

Principal Investigator: CPT Michael W. Quinn, MC

Department: Medicine/Internal Medicine

Facility: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; MAJ Maureen A. Arendt, MC; MAJ Robert B. Gibbons, MC

Start Date:
05/22/1998

Est. Completion Date:
May 00

Periodic Review:
05/27/1999

Study Objective: To assess the effect of severe tricuspid regurgitation on the accuracy of pulse oximetric determination of SpO₂ compared to values determined by co-oximetry of arterial blood and to determine if there is a correlation between the following: tricuspid regurgitant jet velocity; tricuspid regurgitant jet distance, right atrial pressure, right ventricular systolic pressure, ejection fraction, cardiac output and stroke volume (as determined by echocardiography) as well as systolic blood pressure, diastolic blood pressure, mean arterial pressure, skin pigment, and pulse rhythm and any inaccuracy found between the SpO₂ values obtained by pulse oximetry compared to the oxygen saturation as determined by the co-oximetry of arterial blood.

Technical Approach: Patients referred for echocardiograms will be asked to participate. Following signing of informed consent, patients will fill out a questionnaire. Echocardiogram will be performed obtaining the parameters cited in the protocol. The patient will then undergo pulse oximetry, arterial blood gas, vital signs (temperature, pulse, and blood pressure).

Progress: 30 patients were enrolled in this study. Patients were grouped according to echocardiographic degree of TR; none, mild, moderate, moderate to severe and severe. Arterial blood was obtained by radial artery needle puncture while simultaneous measurement and graphing of the percent SpO₂ by pulse oximetry was obtained (Marquette Tramscope 12 system). **Conclusion:** The data confirm a small error in SpO₂ associated with TR. Findings suggest that as TR becomes more severe, pulse oximetry over-estimates the oxygen saturation of arterial blood and refute the findings of Stewart and Rowbottom.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/066 **Status:** Ongoing

Title: Spot Uric Acid/Creatinine Ratio vs. 24 Hour Collection for Evaluation of Uric Acid Excretion

Principal Investigator: CPT Naomi R. Sullivan, MC

Department: Medicine/Internal Medicine **Facility:** MAMC

Associate Investigator(s): MAJ David R. Finger, MC; CR LeBrun

Start Date:
04/27/1999

Est. Completion Date:
Sep 99

Periodic Review:
N/A

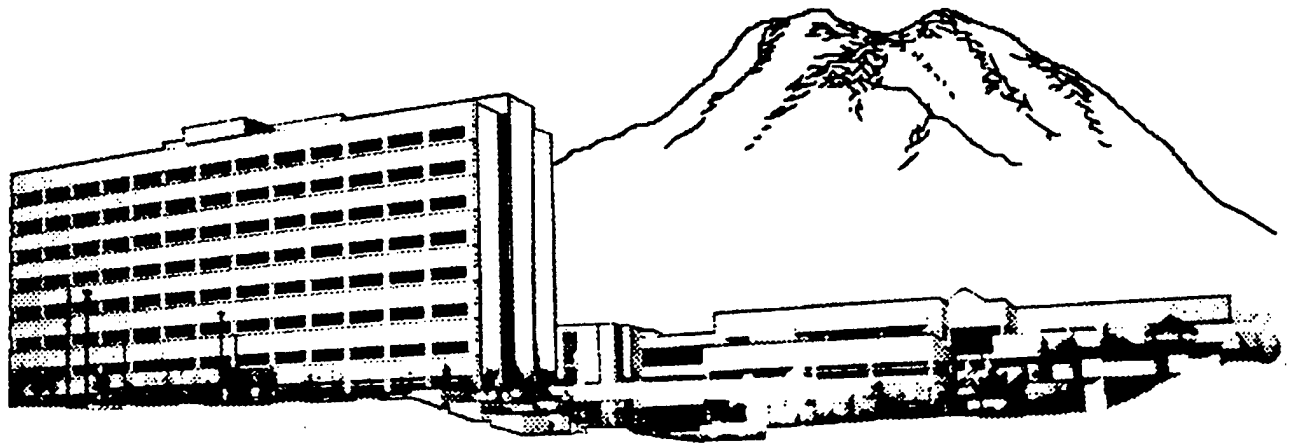
Study Objective: To determine if one time urine uric acid ratios strongly correlate with 24 hour urine collects in patients serving as their own controls.

Technical Approach: We are conducting a study of approximately 60 gout patients, 40 renal patients and 40 controls recruited from the Rheumatology, Nephrology and APC clinics to determine if one-time fractional excretion of uric acid is an accurate predictor of 24 hour uric acid excretion. Patients will be identified for the study by data abstraction from CHCS. Patients will be asked to perform a one-time serum and urine collection followed shortly by a 24 hour urine collection.

If they are willing to participate, a short history to determine age, sex, race, tobacco and alcohol use, diet, renal insufficiency, hyperlipidemia. Serum will be analyzed for creatinine and uric acid. Spot urine will be sent for uric acid and creatinine. A 24 hour urine sample will be analyzed for uric acid levels. Data collected will be made part of a permanent medical record.

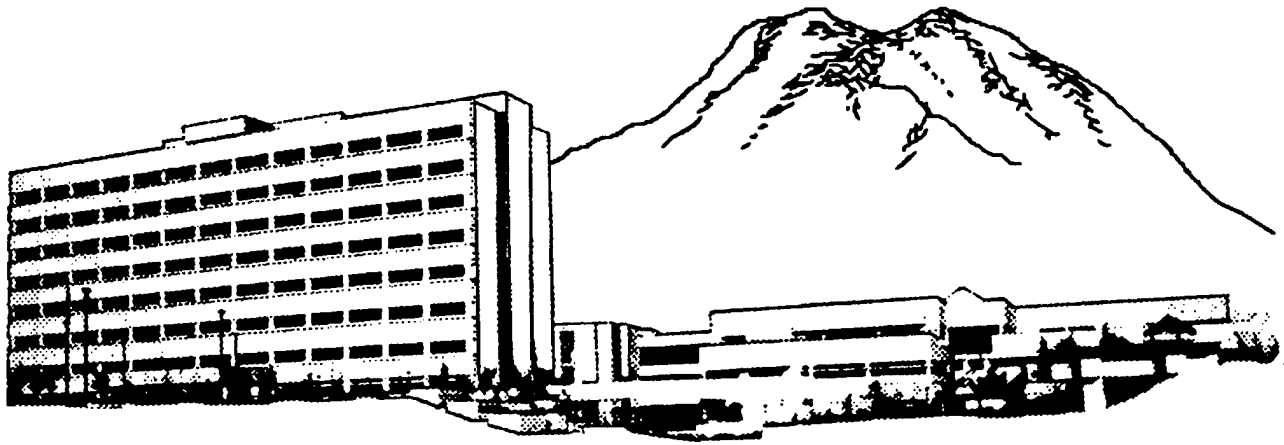
Our hypothesis is that fractional excretion of uric acid will accurately predict 24 hour urinary acid excretor status (high or low). Primary analysis will be for correlation of three ratios with 24 hour uric acid measurements: urinary uric acid/creatinine ratio, fractional excretion of uric acid ($UA(\text{serum}) \times \text{creatinine}(\text{urine}) / \text{uric acid}(\text{urine}) \times \text{creatinine}(\text{serum})$), and uric acid (urine x creatinine (serum)/uric acid (serum) ratio. Secondary analysis will be performed for factors that may interfere with this correlation (i.e. chronic renal insufficiency, high triglycerides). This analysis may identify a limited population in which spot urine/ serum measurements might suffice rather than 24 hour collections.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Neurology Service,
Department of Medicine



Detail Summary Sheets

**Pulmonary Disease & Critical Care Service,
Department of Medicine**

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/054 **Status:** Terminated

Title: The Use of Combined Ipratropium Bromide and Albuterol Given as Combivent MDI in COPD Exacerbation

Principal Investigator: LTC William E. Caras, MC

Department: Medicine/Pulmonary&Critical Care **Facility:** MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; Michael G. Winter, RRT

Start Date:
02/20/1998

Est. Completion Date:
Jan 99

Periodic Review:
04/27/1999

Study Objective: To compare the use of Combivent MDI with that of Albuterol MDI alone in patients admitted with COPD exacerbation.

Technical Approach: Once subjects are enrolled all inhaled bronchodilators will be held for four hours. During this time a respiratory therapist will obtain a FVC and a FEV-1 and the subject will be randomized to one of two groups. Group 1 will receive conventional metered dose albuterol under the supervision of a respiratory therapist. Spirometry will be checked (by a second respiratory therapist who was not present during the delivery of the inhaled medication) at 60, 90, 120 minutes, and at four hours following the bronchodilator. If the FEV-1 at four hours is within 15% of the baseline value the subject will crossover to the second treatment protocol which will consist of combivent containing albuterol and ipratropium bromide. Again spirometry will be obtained at 60, 90, 120 minutes and 4 hours following inhalation.

Group II will receive the exact same medication, but in reverse order of Group 1; combivent followed by albuterol. The major endpoint of the study is the FEV-1 response to the treatment combivent vs albuterol. Separately, the dyspnea scale between treatment groups will be analyzed.

Progress: This protocol was terminated, 17 Mar 99, per the PI, due to the inability to accrue a sufficient number of patients to make the study meaningful.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 94/029 **Status:** Ongoing

Title: A Prospective Study Using the Airway Occlusion Pressure (PO.1) To Predict the Outcome of Weaning From Mechanical Ventilation

Principal Investigator: COL Thomas A. Dillard, MC

Department: Medicine/Pulmonary&Critical Care **Facility:** MAMC

Associate Investigator(s): MAJ James D. Pike, MC; LTC George N. Giacoppe Jr., MC; MAJ Francis J. Landry, MC; CPT Jeremy R. Blanchard, MC; MAJ Lewis L. Low, MC; CPT Kurt W. A. Grathwohl, MC

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| Start Date: 12/17/1993 | Est. Completion Date: May 94 | Periodic Review: 11/19/1999 |
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Study Objective: The main objective of this study is to ascertain the usefulness of the PO.1 as a weaning parameter in predicting success or failure of patients upon extubation. The secondary objective is to validate the Rapid Shallow Breathing Index as described by Yang and Tobin.

Technical Approach: Weaning parameters will be obtained and documented by a Respiratory Care Practitioner (RCP) on patients in the surgical and medical ICU at MAMC. Individual progress toward weaning and extubation will be determined by the primary physician/team. When it is determined the patient is ready for extubation, a second set of weaning parameters will be obtained immediately prior to extubation. Weaning parameters will only be collected on patients at rest and who have not been stimulated within the prior 10 minutes. The parameters will be obtained by utilizing the Respiratory Mechanics Package on the Infrasonics Adult Star as required by MAMC policy. Only the data obtained from patients on the Infrasonic Adult STAR mechanical ventilator will be used so that our results are reproducible since other available ventilators do not easily measure the PO.1. The first 50 patient's will be used to form ROC curves to develop threshold values for the prediction of success or failure of extubation which can then be prospectively applied. A successful weaning/extubation will be defined as one in which the patient does not have to be reintubated within 24 hours.

Progress: 186 records were reviewed in FY 99, for a total of 323. Final data extraction is in progress before data analysis can begin.

Detail Summary Sheet

Date: 30 Sep 99

Number: 90/099

Status: Ongoing

Title: Comparison of the Serum Effusion Albumin Gradient to Traditional Criteria for Transudates in Patients with Pleural Effusions Secondary to Congestive Heart Failure

Principal Investigator: CPT Jennifer E. Jorgenson, MC

Department: Medicine/Pulmonary&Critical Care

Facility: MAMC

Associate Investigator(s): LTC William H. Cragun, MC; CPT Stephen M. Salerno, MC; CPT Donald M. Collins, MC; LTC Bernard J. Roth, MC

Start Date:
08/17/1990

Est. Completion Date:
Jun 96

Periodic Review:
9/28/1999

Study Objective: To determine if the albumin gradient is a more effective criterion than Light's criteria to distinguish transudates from exudates in patients with congestive heart failure that have been treated with diuretics.

Technical Approach: Fifteen patients with clinically suspected congestive heart failure and chest radiograph evidence of pleural effusion will be studied. A thoracentesis to remove 50 cc of fluid will be performed and the following laboratory tests will be done on the fluid: albumin, total protein, glucose, LDH, bilirubin, cell count with cyto-spin differential, gram stain, and routine culture. A simultaneous sample of serum will be measured for albumin, total protein, LDH, bilirubin, and glucose. After three to five days of therapy for the congestive heart failure a repeat chest radiograph with bilateral decubitus view will be done. If pleural fluid persists, a repeat thoracentesis and laboratory tests will be done. If no fluid persists after three to five days, then the patient will be dropped from the study. Bilirubin ratio will also be assessed. The classification of the patients as exudate or transudate by serum effusion, bilirubin ratio, and Light's criteria will be compared between the two thoracentesis. McNemar's test for matched-pair data will be used to compare the albumin gradient results to Light's criteria.

Progress: One patient was enrolled in FY 99 for a total of 16 patients.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/102

Status: Ongoing

Title: The Effect of Saphenous Vein Versus Internal Mammary Artery Bypass on the Mortality and Morbidity of Severe Chronic Obstructive Pulmonary Disease Patients

Principal Investigator: CPT Brian T. McKinley, MC

Department: Medicine/Pulmonary&Critical Care

Facility: MAMC

Associate Investigator(s): LTC Bernard J. Roth, MC; CPT Viki J. Leefers, AN; CPT Jamia E. Howell, MC; COL Thomas A. Dillard, MC; CPT Steven W. Krause, MC; CPT Claire S. Jenkins, MC

Start Date:
09/15/1998

Est. Completion Date:
Aug 98

Periodic Review:
7/27/1999

Study Objective: (1) To determine the effect the type of graft used has on the morbidity and mortality of patients with severe chronic obstructive pulmonary disease who undergo coronary artery bypass, (2) to re-examine the effect confounding variables have on COPD patients under CABG.

Technical Approach: Patients within the last five years with the diagnosis of COPD undergoing CABG, and a second group of sex and age matched non-COPD patients as controls will be computer selected for this retrospective cohort study. Confounding variables which will be examined include preoperative bronchodilator usage and cardiac ejection fraction, total bypass pump time, active smoking, number of vessels bypassed, type of bypass whether left main, left anterior descending artery (LAD) or other, placement of a thoracostomy type, steroid usage, abnormal preoperative chest x-ray, higher American Society of Anesthesiologist class, and comorbid disease as defined as the preoperative existence of diabetes, hypertension, and renal disease.

Progress: Approximately 200 subjects have been entered in FY 99 for a total of approximately 800 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/138 **Status:** Ongoing

Title: Active Inspiration/Expiration versus Tidal Volume Breathing During Transbronchial Biopsy

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary&Critical Care **Facility:** MAMC

Associate Investigator(s): MAJ Timothy R. Murray, MC; LTC Bernard J. Roth, MC; Suzette Gagnon-Bailey, M.D.; COL Thomas A. Dillard, MC; CPT Kurt W. A. Grathwohl, MC

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| Start Date: 08/16/1996 | Est. Completion Date: Aug 97 | Periodic Review: 9/28/1999 |
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Study Objective: To compare yield, results and complications of two currently used techniques for transbronchial biopsy.

Technical Approach: All patients referred in the pulmonary clinic for bronchoscopy will be enrolled. Bronchoscopy will be performed in the usual manner. Patients will have a minimum of 6 transbronchial biopsies performed. They will be randomized to have the first three biopsies performed by either the active inspiration/expiration method or the tidal volume breathing method. After 3 biopsies are performed, the patient will be crossed over to the method not previously performed to obtain the next three biopsies. If more biopsies are needed, the attending physician can utilize any method at their discretion although the subsequent biopsy samples will not be included in data analysis. The attending pulmonologist or nurse will record the number of attempts for each and the appearance and quantity of sample grossly. Hemorrhage, pain, dyspnea, change in vital signs, and need for stopping the procedure will be recorded after each attempt. Two containers will be identified to the investigators although the examining pathologist will be blinded to the method performed. The pathologist will identify the number and size of samples in each as well as note the presence of alveolar tissue and the pathologic diagnosis if any. We will enroll 100 patients over one year. The differences between number of adequate samples and size will be compared using the paired student t-test. Other variables such as presence of alveoli and presence of complications (i.e. chest pain, bleeding, dyspnea, etc.) will be compared using the chi square test.

Progress: No data have been collected during FY 99. The principal investigator on this study was changed from MAJ Kurt Grathwohl, MC, to MAJ Ramakrishna during FY 98. Since he is still consenting patients for the same patient population (extra biopsies) for protocol #98086, he will not be enrolling any patients until that study has accrued the planned number of subjects.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/055 | Status: Ongoing |
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Title: Telomerase Activity in Bronchial Washings, Pleural Fluid, Sputum, and Cerebrospinal Fluid (CSF)

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary&Critical Care

Facility: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; LTC William E. Caras, MC; CPT Wade K. Aldous, MS; Rakesh Gaur, M.D.; B Brown; LTC Jerome B. Myers, MC

Start Date:
03/20/1998

Est. Completion Date:
Sep 98

Periodic Review:
07/27/1999

Study Objective: To determine the sensitivity and specificity of telomerase activity as an indicator of malignancy in non-surgical pleuro-pulmonary tissue samples, and CSF.

Technical Approach: Samples of lung (bronchial) washings and sputum samples obtained at bronchoscopy, pleural fluid and CSF will be compared with samples submitted for cytological and histological examination from patients with lung and chest wall masses as a screening and possibly diagnostic tool for primary lung cancers as well as metastatic cancers to the lung and chest wall. The results of these will be analyzed to determine the sensitivity and specificity of telomerase as a screening and diagnostic tool for lung cancer. This is a pilot study.

Progress: Data on 90 samples from 80 subjects have been collected during FY 99. The data from this study has been combined with that from MAMC study #98055. Detection of telomerase activity in thoracic malignancies appears feasible from clinical diagnostic specimens. Prevalence of telomerase activity by gel electrophoresis was similar in small cell and non-small cell samples.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/086

Status: Ongoing

Title: Telomerase Activity in Non-surgical Specimens Obtained at Bronchoscopy and Fine Needle Aspiration

Principal Investigator: Ravi R. Ramakrishna, M.D.

Department: Medicine/Pulmonary&Critical Care

Facility: MAMC

Associate Investigator(s): COL Thomas A. Dillard, MC; LTC William E. Caras, MC; CPT Wade K. Aldous, MS; CPT Tommy A. Brown, MC; MAJ David P. Tracy, MC; MAJ Sean P. Murray, MC; LTC Jerome B. Myers, MC; CPT Michael C. Royer, MC

Start Date:
06/19/1998

Est. Completion Date:
Feb 99

Periodic Review:
07/27/1999

Study Objective: To determine the sensitivity and specificity of telomerase activity as an indicator of malignancy in non-surgical pleuro-pulmonary tissue samples.

Technical Approach: The type of samples submitted will be bronchial brushings, trans-bronchial biopsies, endobronchial biopsies and wang needle aspirates obtained during bronchoscopy. Other samples for evaluation will include pleural biopsies and fine needle aspirations of lymph nodes, chest and lung masses. The qualitative telomerase activity will be determined using the telomerase PCR ELISA kit supplied by Boehringer Mannheim. In those patients where there is activity an attempt will be made to quantitate the amount of activity. The telomerase activity will be compared with cytological and histological diagnosis from samples obtained by non surgical means and in those patients who undergo surgery with surgical samples.

Progress: Data on 90 samples from 80 subjects have been collected during FY 99. The data from this study has been combined with that from MAMC study #98055. Detection of telomerase activity tin thoracic malignancies appears feasible from clinical diagnostic specimens. Prevalence of telomerase activity by gel electrophoresis was similar in small cell and non-small cell samples.

Detail Summary Sheet

| | | |
|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 92/024 | Status: Terminated |
| Title: Resectable Bronchogenic Carcinoma: Value of Routine Contrast - Enhanced Cranial MRI in Preoperative Staging | | |
| Principal Investigator: LTC Bernard J. Roth, MC | | |
| Department: Medicine/Pulmonary&Critical Care | | Facility: MAMC |
| Associate Investigator(s): MAJ Kevin L. Quinn, MC; LTC Miquel J. Rovira, MC; LTC Steven S. Wilson, MC; MAJ Frank A. Zimba, MC | | |
| Start Date: 01/03/1992 | Est. Completion Date: Jan 93 | Periodic Review: 02/23/1999 |

Study Objective: To determine the incidence of clinically occult brain metastasis in patients with resectable primary bronchogenic carcinoma.

Technical Approach: The subjects (100) for this protocol will be patients >18 years of age with primary bronchogenic carcinoma, Stage IIIa or less as determined by chest CT, who are neurologically intact. The patient will undergo a complete clinical neurological history and physical exam and enhanced cranial MRI to screen for brain metastasis. Patients with evidence of significant CNS pathology will be divided into four groups: (1) solitary lesion amenable to neurosurgical resection (2) significant brain pathology other than metastatic disease that would delay or preclude therapy (3) brain metastasis and (4) metastasis outside the brain. Patients in group 1 or 2 will undergo neurosurgical and/or radiation therapy evaluation for possible curative or palliative therapy. Patients in group 3 or 4 will undergo radiation therapy and/or hematology-oncology evaluation for possible palliative therapy. Patients in whom MRI revealed suspicious areas which are not definitely characteristic for metastasis will undergo brain biopsy using stereotactic localization. Patients refusing brain biopsy will be followed closely with periodic follow-up enhanced cranial MRI every three months. MRI and clinical data will be evaluated to determine the overall incidence of clinically occult brain metastases and the presence (if any) of any significant differences among primary cell types.

Progress: No subjects have been entered in FY 99 for a total of 30 subjects enrolled. Recruitment of patients became very slow despite asking WRAMC and EAMC to help. Only 30 of a projected 100 cases were recruited after 5 years. A publication in Chest in the last few months basically did my protocol (one better because they randomized to CT) with more than 200 patients. The question was answered and we can't guarantee getting enough patients even in another 5 years, so this protocol has been terminated.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/132 **Status:** Ongoing

Title: Respiratory Care Team to Decrease the Misuse of Metered Dose Inhalers in Hospitalied Patients

Principal Investigator: LTC Bernard J. Roth, MC

Department: Medicine/Pulmonary&Critical Care **Facility:** MAMC

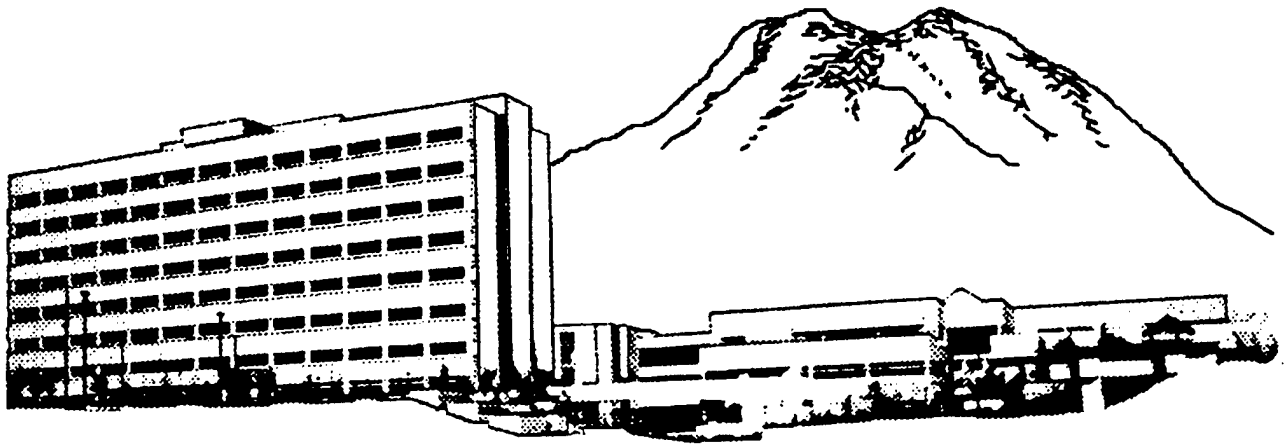
Associate Investigator(s): COL Thomas A. Dillard, MC; Michael G. Winter, RRT; Nora A. Regan; CPT John J. Mullan, MC; CPT Michael W. Quinn, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 09/19/1997 | Mar 96 | 10/20/1998 |

Study Objective: To determine if a respiratory team teaching proper metered dose inhaler (MDI) use to inpatients will improve the observed rate of proper MDI use at Madigan Army Medical Center (MAMC).

Technical Approach: In this study, a pulmonologist will interview 60 inpatients prescribed an MDI and observe their MDI technique to establish a baseline rate of misuse. Then a respiratory care team will receive a daily list from Pharmacy on all patients newly prescribed an MDI. They will provide direct teaching to the patients on correct use of their MDI. After the teaching program has been in place for 2- 6 weeks the same pulmonologist will interview 60 more patients and observe their MDI technique to establish the rate of misuse after the intervention. The patient will be asked if they have received education and this will be correlated to the chart documentation of education by the Respiratory Therapist. The major endpoint will be the change in the rate of MDI misuse observed.

Progress: 22 subjects have been entered in FY 99 for a total of 60 subjects enrolled.



Detail Summary Sheets

Rheumatology Service,
Department of Medicine

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/078 **Status:** Ongoing

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Prograf (Tacrolimus) in the Treatment of Rheumatoid Arthritis in Patients Who Have Failed One or More

Principal Investigator: LTC Thomas L. Irvin, MC

Department: Medicine/Rheumatology **Facility:** MAMC

Associate Investigator(s): MAJ David R. Finger, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 06/22/1999 | Jun 00 | N/A |

Study Objective: This protocol is designed to evaluate the efficacy and safety of the immunosuppressant tacrolimus in RA patients who are either resistant or intolerant of one or more DMARDs.

Technical Approach: This will be a 6 month multi-center, randomized, double-blind, placebo controlled study of adult patients, of either gender, with a diagnosis of rheumatoid arthritis for at least 6 months. Eligible patients will have demonstrated either resistance to or intolerance of one or more DMARDs. A total of 450 patients from approximately 50 centers will be randomized, with a maximum of 36 patients per center. Patients will be assigned to either the DMARD resistant or the DMARD intolerant stratum prior to randomization. Randomization to the three treatment arms will be at 1:1:1, tacrolimus (2 mg/day), tacrolimus (3 mg/day), or placebo respectively within each stratum at each center.

The primary efficacy endpoint will be the composite American College of Rheumatology (ACR) 20 success at six months for the combined 2 mg and 3 mg tacrolimus groups as compared to placebo. If the combined treatment group response is statistically significantly different from the placebo group response, then the pairwise comparisons between the placebo and the individual tacrolimus groups will be performed. Secondary efficacy endpoints are the ACR 20, 50, and 70 response rates at the end of the treatment, and the evaluation of change from baseline for the individual components of the ACR composite at end of treatment.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/079

Status: Ongoing

Title: An Open-Label, Long-Term Study to Evaluate the Safety of Prograf (tacrolimus) for the Treatment of Rheumatoid Arthritis

Principal Investigator: LTC Thomas L. Irvin, MC

Department: Medicine/Rheumatology

Facility: MAMC

Associate Investigator(s): MAJ David R. Finger, MC

Start Date:

Est. Completion Date:

Periodic Review:

06/22/1999

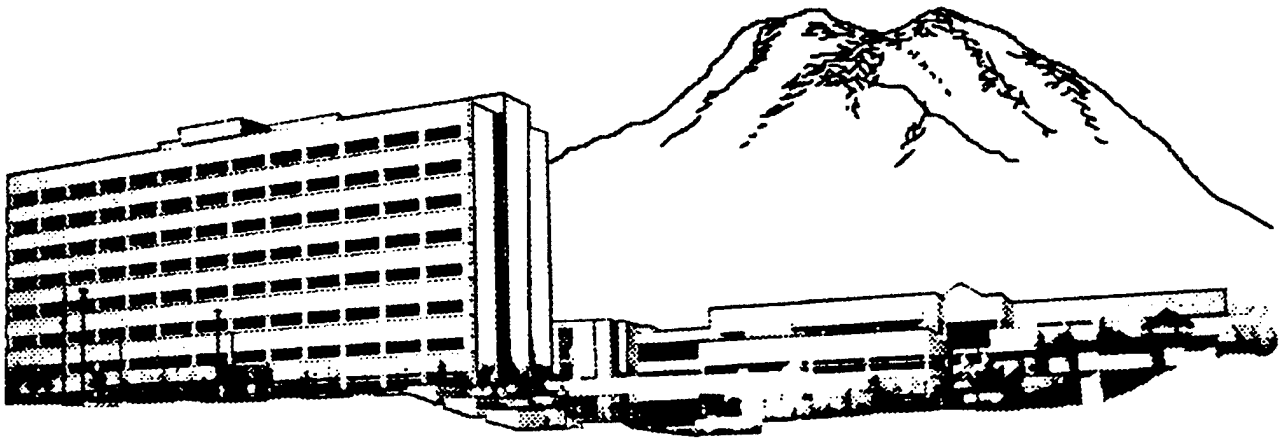
Jun 02

N/A

Study Objective: The primary objective of this study is to evaluate the long-term safety of Prograf in rheumatoid arthritis patients. A secondary objective of the study is to evaluate long-term efficacy of Prograf in RA patients.

Technical Approach: This will be a 12 month open-label, non-comparative, multi-center study. Eligible patients will have an RA diagnosis of at least six months duration and, in the investigator's opinion, require the use of a DMARD. A total of approximately 300 patients who have participated in previous Fujisawa protocols and approximately 500 patients who are entering this study directly will be enrolled at approximately 80 centers. All patients will receive a total daily dose of 3 mg of tacrolimus. Adverse events, including clinically significant laboratory abnormalities, will be recorded on the Case Report Forms. Treatment emergent adverse events during the 12 months of the open-label treatment will be determined and will be the primary assessment of risk. ACR 20, 50, and 70 will be assessed at 3, 6, 9, and 12 months as secondary endpoints of the study.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Department of Nursing

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/044

Status: Ongoing

Title: Physical Activity and Exercise in AD Female Soldiers

Principal Investigator: LTC Laura R. Brosch, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): Debra DePaul, RN; Lori A. Loan, MSN, RNC; COL Melissa A. Forsythe, AN

Start Date:

02/20/1998

Est. Completion Date:

Oct 98

Periodic Review:

1/13/1999

Study Objective: To examine the physical activity levels and habitual exercise patterns of active duty female soldiers and to identify factors that influence those habits in hopes of producing information to be used to improve the health of female soldiers.

Technical Approach: Each subject will complete an initial survey and APFT scores will be obtained for each service member consenting to be in the study. Focus groups will then explore the issues among subjects identified as belonging to subgroups at risk for low exercise participation.

Progress: 1103 subjects have been entered in FY 99 for a total of 1103 subjects enrolled. The response rate was 50% from the two survey mailings and 30% for the test-retest reliability.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/107 **Status:** Ongoing

Title: Nurses Influence on Patient Outcomes in US Army Hospitals

Principal Investigator: LTC Laura R. Brosch, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): COL Barbara Jo Foley; Dr. Carolyn C. Kee; Dr. Ptlene Minick; Dr. Susan Harvey; COL Bonnie M. Jennings, AN

Start Date:
09/15/1998

Est. Completion Date:
Sep 99

Periodic Review:
9/9/1999

Study Objective: To describe patient outcomes in active duty personnel, military retirees, and military dependents, associated nursing organizational structures and processes; and hospital characteristics.

Technical Approach: Interviews, questionnaires and short answer surveys will be used to gather information on (1) patient outcomes while in the hospital to include the occurrence of adverse events such as injury-sustaining falls, length of stay, and severity-adjusted mortality; (2) following discharge from the hospital, outcomes include patient satisfaction with nursing care, satisfaction with how symptoms were managed, and functional health status. (3) Nursing organizational structures include factors such as nursing practice model, nursing skill mix, and the education and experience level of registered nurses (RN); and (4) nursing organizational processes include RN job satisfaction, the degree of autonomy in nursing practice or the discretionary judgement accorded nurses in the work environment, the level of RN and physician collaboration, the degree of clinical expertise, and the extent to which an ethical work environment is present.

Progress: 51 subjects have been entered in FY 99 for a total of 51 subjects enrolled.

Detail Summary Sheet

| | | |
|--|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 99/028 | Status: Ongoing |
| Title: Factors Associated with Preventable Hospitalization in Older Military Retirees | | |
| Principal Investigator: LTC Laura R. Brosch, AN | | |
| Department: Nursing | | Facility: MAMC |
| Associate Investigator(s): COL Bonnie M. Jennings, AN; Suzanne K. Wilson, MSN, RN; Lori A. Loan, MSN, RNC | | |
| Start Date: 02/23/1999 | Est. Completion Date: Jun 01 | Periodic Review: 1/25/2000 |

Study Objective: To prospectively assess the relationship between patient-specific characteristics and the likelihood of preventable hospitalization for Tricare Senior Prime enrollees.

Technical Approach: All 3,300 Madigan Army Medical Center Tricare Senior Prime enrollees will be surveyed to obtain baseline predisposing (age, gender, race, education, living arrangements), enabling (income, tangible social support, perceptions of regular source of care, transportation, transportation time) and need factor (perceived physical health status, perceived mental health status, perceived functional limitations, chronic illnesses, past hospital use) data. These data will subsequently be linked to hospitalization data prospectively collected for the 12 month period following the survey. Each study participant's hospital use will be classified into one of three categories: (1) no hospital admissions, (2) at least one potentially preventable hospitalization, or (3) hospitalized, but not for a potentially preventable condition.

Descriptive statistics will be used to profile the sample in terms of the factors under study and summarize the frequency of occurrence of each type of hospital use. Multivariate polytomous logistic regression will be used to identify predisposing, enabling and need factors associated with the likelihood of potentially preventable hospitalization.

Progress: No subjects have been entered in FY 99. Funding for this study released 10 August 1999. Project director has been hired. Initial mailout of study questionnaires anticipated in Nov-Dec 1999. Project number of subjects is 3800 Tricare Senior Prime members.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/110 **Status:** Ongoing

Title: The Effects of Using Four Different Missing Data Imputation Methods on the Psychometric Property of the SF36

Principal Investigator: LTC Laura R. Brosch, AN

Department: Nursing **Facility:** MAMC

Associate Investigator(s): Qiuping Zhou, MS, RN; Lori A. Loan, MSN, RNC; 1LT Janet L. Hyers, AN

| Start Date: | Est. Completion Date: | Periodic Review: |
|-------------|-----------------------|------------------|
| 9/28/1999 | Oct 00 | N/A |

Study Objective: The purpose of this study is to determine the effects of using four different missing data imputation methods on the psychometric property of SF36, for different sample sizes, different length of the questionnaire, and different percentage of missing data.

Technical Approach: Background: Quality of life measure is an increasingly important endpoint in many clinical studies. SF36 is the most frequently used instrument with established reliability and validity. Since the length of the questionnaire and the health conditions of the respondents, missing items are frequently encountered. Missing data are usually ignored or replaced. It is unclear whether the different replacement methods alter the psychometric property of the measurement.

Objectives: The purpose of this study is to determine the effects of using four different missing data imputation methods on the psychometric property of SF36, for different sample sizes, different length of the questionnaire, and different percentage of missing data.

Design: This is a secondary data analysis. An existing data set with SF36 items included will be used to perform the simulations. The outcomes include the reliability and factor structure of the SF36 measure. Variables manipulated include 1) imputation methods (person mean, item mean, regression, and EM algorithm replacement), 2) length of the instrument (36 versus 12 items), 3) percentage of missing data (0%, 5%, 10%, 20%, and 30%) and 4) sample sizes (large, medium, and small).

Methods: Data were collected from 2800 patients in a military organization. SPSS 8.0 will be employed to analyze the data. Reliability and factor analysis will be performed on data sets with varying conditions. The results will be compared and summarized. Replacing methods with the minimum effect on the psychometric performance of the SF36 will be identified.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

| | | |
|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 96/132 | Status: Completed |
| Title: Pressure Ulcer Prevention: Comparing Support Surfaces | | |
| Principal Investigator: LTC Pamela J. Hildreth, AN | | |
| Department: Nursing | Facility: MAMC | |
| Associate Investigator(s): LTC Linda H. Yoder, AN; LTC Brenda I. Mygrant, AN; Gladys Cobb, BSN, MSN | | |
| Start Date: 06/21/1996 | Est. Completion Date: Sep 99 | Periodic Review: 07/27/1999 |

Study Objective: 1) Determine the demographic characteristics that differ between patients who do and those who do not develop pressure ulcers. 2) Compare the incidence of pressure ulcers between the patients on the KinAir® bed and patients on the EHOB WAFFLE® mattress. 3) Determine the difference in length of stay and monetary expenditure for individuals within the two support surface groups who do not develop pressure ulcers. 4) Determine the difference in length of stay and monetary expenditure for individuals within the two support surface groups who do develop pressure ulcers.

Technical Approach: The proposed study is a prospective, quasi-experimental design, in which subjects who are at risk for pressure ulcer development will be randomly assigned to one of two support surfaces. Data will be collected for a period of at least one week or until the subject is discharged, expires, or is no longer considered at risk. Data to be collected will include pressure sore risk using the Braden Scale for Predicting Pressure Sore Risk, daily skin integrity assessments, and information on pressure ulcer development and subsequent ulcer progression using the Pressure Sore Status Tool, as well as data on selected demographic variables. The study will be conducted in multi-site settings. The primary site for the study will be Madigan Army Medical Center and Brooke Army Medical Center (BAMC) is the study's secondary site.

Using data obtained from the Wound Care Specialists at both MAMC and BAMC, it is anticipated that approximately 4 eligible subjects will be admitted to BAMC per week. Because the proposed study offers daily care from a research team devoted to maintaining skin integrity, a 75% consent rate is predicted. This equates to enrollment of 3 subjects per week at MAMC and 2 per week at BAMC. An attrition rate of approximately 10% is anticipated based on preliminary data from the Tri-Services Nursing Research Group funded study "Pressure Ulcers: Patient Outcomes on Kinair Bed or EHOB Mattress." Recruitment will occur for twenty-eight months and enrollment of 560 subjects is anticipated.

Progress: This study was reported as completed, 13 Jul 99, without further enrollment in FY 99. A total of fifty-three patients were entered in year one from BAMC and MAMC. There were no statistically significant differences between patients who did and did not develop pressure ulcers for any of the demographic variables. There was no statistically significant difference in pressure ulcer development between support surfaces. No patients had a length of stay extended due to pressure ulcer development. Patients experiencing pressure ulcers had significantly more days in the ICU. Length of hospital stay approaches statistical significance. Cost expenditures were similar for patients with and without pressure ulcers. Patients in the Kin-Air group had statistically significantly more days in the ICU, longer hospital stays, and higher cost expenditures.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/077

Status: Completed

Title: Linking Nursing Care to ANA Quality Indicators

Principal Investigator: LTC Pamela J. Hildreth, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): Lori A. Loan, MSN, RNC; COL Bonnie M. Jennings, AN; Elizabeth Pulos, Ph.D.; COL Nancy Staggars, AN; Pamela H. Mitchell, Ph.D.

Start Date:
04/18/1997

Est. Completion Date:
Sep 98

Periodic Review:
04/27/1999

Study Objective: 1) To gain a better understanding of our ability to collect the ANA Nursing Quality Indicator data; 2) to assess the feasibility of collecting nursing care quality data and; 3) to examine the existence and strength of relationships between nursing care and the ANA Nursing Quality Indicators.

Technical Approach: Because nurses are an integral part of the health care delivery system, both in terms of patient contact and hospital spending, the ANA has initiated an endeavor to formulate a nursing report card which will include patient-focused outcome indicators chosen for their ability to link nursing care quality to patient-focused outcomes. The links between patient outcomes and the nursing care quality identified by the ANA Nursing Quality Indicators are not well understood. However, before these relationships can be tested, more information about the feasibility of collecting nursing care data and patient outcomes data is necessary. Using a variety of methods including expert panels, chart review and questionnaires, information related to the ANA Nursing Quality Indicators and nursing care quality will be gathered and evaluated. The final goal is to statistically determine whether the ANA Nursing Quality Indicators are sensitive to documented differences in the quality of nursing care patients receive using ANOVA. Further research on indicators sensitive to changes in nursing care quality will potentially improve the quality of patient care by promoting both the science of outcomes research and the practice of nursing. In addition, identifying quality indicators will provide valuable input for balancing administrative and clinical decision making.

Progress: The sample included the records of 872 adult inpatients from 2 adult ICU's, 1 step-down unit, 1 medical unit, and 1 surgical unit. A total of 5,082 patient records were reviewed. The nursing sample included 73 RNs, LPNs and unlicensed staff from the same inpatient units. The study demonstrated that nursing care quality data can readily be collected for compliance with patient education, skin care, patient safety and central line management standards. Nursing care quality data related to compliance with assessment standards is not easily obtained. Pain management nursing care quality data is obtainable, but only from verbal, responsive patients. Data for all ANA Nursing Quality Indicators could be collected at the study military facility. Study data suggest there may be a positive association between nursing staff satisfaction scores and nursing assessment scores. A positive association between patient satisfaction with nursing care scores and daily nursing skin care quality scores was also noted. The mix of RNs, LPNs and unlicensed staff caring for patients was positively correlated ($p < 0.05$) with nursing assessment and patient education quality scores. Finally, total nursing care hours provided per patient day was positively correlated a significant level with nursing assessment, patient education and central line care quality scores.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/022 | Status: Suspended |
| Title: Nurse Practitioner Manager Outpatient Heart Failure Program | | |
| Principal Investigator: MAJ Theresa A. Horne, AN | | |
| Department: Nursing | | Facility: MAMC |
| Associate Investigator(s): Lori A. Loan, MSN, RNC | | |
| Start Date: 01/26/1999 | Est. Completion Date: Jun 01 | Periodic Review: N/A |

Study Objective: To determine the best managed care model for providing care to patients with congestive heart failure.

Technical Approach: This study will use a randomized controlled clinical trial with two parallel arms to compare a cardiology NP-managed heart failure program to standard care provided by a primary care provider and cardiologist. A holistic nursing perspective and the Health Related Quality of Life (HRQL) Model provide the framework for conceptualization and measurement of patient and utilization outcomes. Primary outcomes are hospitalization, ER visits, clinic visits and disease specific quality of life. Secondary outcomes include functional status, self-perceived functional status, general health, health care provider adherence to effective drug therapy, self reported dietary sodium intake, deviation in weight, self-reported symptom scores, hospitalized days and cost for health care utilization. Data will be compiled using medical record reviews, patient logs, general and disease-specific instruments of HRQL, and telephone interviews. Chi-square, t-test, and Mann Whitney U tests will be used to compare group outcomes.

Progress: This protocol did not receive funding from TriService Nursing Research. The PI requested this protocol be suspended to allow time to pursue local funding.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/190

Status: Completed

Title: The Effects of Thermocouple Sensor Placement on Neonatal Skin Temperature Measurement

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing

Facility: MAMC

Associate Investigator(s): Lauran T. Taquino, RN, MS; Susan T. Blackburn, Ph.D., RN, FAAN; Karen A. Thomas, Ph.D., RN; Sue E. Chambers, RN

Start Date:
09/15/1995

Est. Completion Date:
Oct 96

Periodic Review:
08/20/1998

Study Objective: The objectives of this study are to compare temperature readings from probes placed on peripheral skin sites with readings of axilla temperature, and to compare temperature readings from probes placed on the abdomen and back during periods when the infant is lying on and not lying on the temperature probes. Also, to evaluate the effects of body size on accuracy of temperature probe measurements from selected sites, and when the infant is lying on versus not lying on the probe.

Technical Approach: This descriptive study is designed to objectively evaluate several common nursing practices and beliefs regarding the care of neonates and the placement of temperature probes. The study seeks to provide a physiologic basis to support and validate nursing practice. Four body sites will be studied simultaneously through the use of a small thermocouple sensor and two channel continuous readout device. Data will be collected for one hour with the subject in each of two common positions, supine and prone. Environmental temperature and basic demographic data will also be collected for each subject and study period. The study period will consist of approximately 2.5 hours for each study subject and will not interfere with or alter the standard neonatal nursing and medical care of that infant. This study is sponsored by the local chapter of the national professional association for neonatal nursing and is designated to support data collection in multiple hospital sites. Data from all sites will be aggregated for the purpose of analysis and reporting. Descriptive statistics will be used initially to examine differences in temperature readings from the four sensors. Further analysis will examine clinically and statistically significant changes in temperature between the four sites and between lying on and not lying on the sensors. Comparisons will also be made of differences in temperature values between sites and between infants of different weight groups.

Progress: 5 subjects have been entered in FY 99 for a total of 24 subjects enrolled. This study found abdominal and back temperatures differ based on position and probe placement. Lying on the probe raises the temperature by increasing skin insulation. Switching between lying on and not lying on the probe may result in variable skin temperature. In clinical practice, given the nature of skin temperature and effect of position on probe operation, assessment and interpretation should include the incubator air temperature, skin temperature, location of probe, infant position, as well as a separate source of infant temperature (axillary, rectal).

Detail Summary Sheet

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|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 96/125 | Status: Completed |
| Title: A Survey of Access to Care in the TRICARE Environment | | |
| Principal Investigator: Lori A. Loan, MSN, RNC | | |
| Department: Nursing | Facility: MAMC | |
| Associate Investigator(s): COL Frances D. Anderson, AN; COL Bonnie M. Jennings, AN; Suzanne K. Wilson, MSN, RN | | |
| Start Date: 06/21/1996 | Est. Completion Date: Sep 98 | Periodic Review: 06/22/1999 |

Study Objective: To describe access to health care in the TRICARE environment.

Technical Approach: Using a stratified sample of 7,680 military beneficiaries from the MAMC 40 mile catchment areas, this descriptive survey aims to describe access to health care in the TRICARE environment. The research questions are: 1) How do military beneficiaries (consumers) in the MAMC 40 mile catchment area evaluate access to health care? 2) How do military beneficiaries in each of the consumer groups evaluate access to health care? 3) How do members of each of the components of TRICARE evaluate access to health care? 4) Do consumer evaluations of access to care differ according to TRICARE component? Randomly selected beneficiaries from the four TRICARE components will complete and return a mailed questionnaire. Instruments selected for use in the study include the PSQ-III, the General Health Perceptions scale from the SF-36, and select sociodemographic questions from the 1994-1995 Annual Health Care Survey for DoD Beneficiaries. The instruments were chosen for their appropriateness and their high levels of reliability and validity. Data from the survey will be analyzed using descriptive statistics and one-way ANOVA.

Progress: No subjects have been entered in FY 99 for a total of 2,197 subjects enrolled. Interpretation of study findings and final report preparation are in progress.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/137 **Status:** Completed

Title: Single Woman's Breast Cancer Program

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing

Facility: MAMC

Associate Investigator(s): Nancy F. Woods, Ph.D., RN

Start Date:
07/19/1996

Est. Completion Date:
Jun 98

Periodic Review:
07/27/1999

Study Objective: There are five study purposes: to (1) test the effectiveness of a home-based counseling intervention for single women with early stage breast cancer with dependent children; (2) investigate the causal model underlying the intervention; (3) explore time related patterns of change in individual study participants; (4) develop a discriminant function that effectively categorizes women and children most able to benefit from the intervention; and (5) test the cost-effectiveness of the intervention. The goal of the intervention is to improve psychosocial adjustment and quality of life in single women with early stage breast cancer and their dependent children.

Technical Approach: This study will enroll 200 single females who have a recent diagnosis (11 months or less) of early-stage breast cancer (Stage 0, 1 or 2). Subjects will be inpatients or outpatients, from medical, surgical or radiation oncology departments. Subjects will be randomized prior to initial contact so that the woman is invited to participate in either the coached or evaluation group. When subjects have agreed to participate, an in-home appointment is made with the evaluation nurse. Consent is obtained on the first visit and questionnaires are administered. Child participation is desirable but not mandatory. Initial explanation to the child is always left to the mother, but the nurse will provide additional information and obtain written consent from the child, if willing. All families receive 4 evaluation visits. Women randomized to the coached group receive an additional 5 in-home visits by the coach. At the end of the study, all women receive thank you a letter and those who were randomized to the evaluation group receive \$20 for each visit and an informational packet about breast cancer. Data will be analyzed by 5 major methods: formal statistical tests of the effect of the intervention (MANCOVA); investigation of the explanatory model underlying the intervention (structural equation modeling); exploration of time-related patterns of change in individuals (trend analysis and latent growth model); discriminant analysis and cost-effectiveness analysis. All of these data analytic components constitute outcome analyses and there will also be a process evaluation component.

Progress: Study has been complete with no subjects from MAMC have participated in this study.

Detail Summary Sheet

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|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 97/068 | Status: Ongoing |
| Title: Effects of Stress Responses on Wound Healing | | |
| Principal Investigator: Lori A. Loan, MSN, RNC | | |
| Department: Nursing | | Facility: MAMC |
| Associate Investigator(s): JoAnne D. Whitney, Ph.D., RN; Margaret M. Heitkemper, Ph.D.; Stacey L. Heiner, BSN, RN; MAJ Susanne J. Clark, AN | | |
| Start Date: 03/21/1997 | Est. Completion Date: Sep 00 | Periodic Review: 03/23/1999 |

Study Objective: Compare measures of preoperative and postoperative psychological stress, SNS and HPA activation (STAI, RIES, PSQ-III GSS, urinary norepinephrine, epinephrine and cortisol) in subjects experiencing minor (e.g., outpatient arthroscopic) and major (e.g., total knee arthroplasty) surgical procedures.

Technical Approach: The proposed study will use a prospective, correlational design to explore relationships between pre and postoperative psychologic and physiologic stress and the defined wound healing indices. The study will enroll a total of 96 subjects over a three year period from populations experiencing minor and major orthopedic knee surgery. The relationship between each preoperative and postoperative measure of stress and each wound healing measure will be evaluated with the Pearson product moment correlation coefficient. Repeated measures analysis of variance will be used to compare the stress experienced by patients undergoing major surgery to those undergoing minor surgery at the eight times of measure.

Progress: 61 subjects have been entered in FY 99 for a total of 88 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/053 **Status:** Ongoing

Title: Improving Soldier Access to Urinary Incontinence Therapy

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing

Facility: MAMC

Associate Investigator(s): LTC Ann M. V. Bianchi, AN; LTC (Ret) Richard A. Sherman, MS

Start Date:
01/16/1998

Est. Completion Date:
Sep 98

Periodic Review:
1/5/1999

Study Objective: This study aims to compare access to care and patient satisfaction with care for female soldiers receiving biofeedback treatment for exercise-induced urinary incontinence in the troop medical clinic environment with those receiving similar treatments at a medical center.

Technical Approach: All subjects interested in participating in the study will be screened for evaluation of the lower urinary tract. If inclusion criteria is met, the subject will be randomized to treatment at either the TMC or MAMC and be scheduled for treatment visits every 2 weeks for 12 weeks. During the first visit, demographic and descriptive information will be gathered and subjects will learn how to do Kegel exercises using biofeedback. Subjects will be asked to keep daily logs and to practice the Kegel exercises for twenty minutes two times a day.

Subsequent visits to the treatment center will be to encourage continuation and the keeping of daily logs. At the final visit more demographic and descriptive information will be asked and a Patient Satisfaction Questionnaire will be filled out by each subject. The portable biofeedback equipment will be used to evaluate Kegel performance during this final visit.

Progress: Of 109 surveys returned, 99 soldiers have been enrolled in this study in FY 99. Of this 99, 12 soldiers completed the treatment cycle, 5 soldiers were disenrolled at their request and 12 were unable to begin treatment due to PCS or ETS. A second mailing is planned in hopes to enroll more participants for the target sample of 200.

Detail Summary Sheet

| | | |
|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/025 | Status: Ongoing |
| Title: The Effects of Postoperative Supplemental Oxygen on Tissue and Wound Healing | | |
| Principal Investigator: Lori A. Loan, MSN, RNC | | |
| Department: Nursing | | Facility: MAMC |
| Associate Investigator(s): JoAnne D. Whitney, Ph.D., RN; Stacey L. Heiner, BSN, RN; LTC Pamela J. Hildreth, AN; CPT Jeannie M. Padilla, MC; Candace Plumlee; LTC Jerome B. Myers, MC | | |
| Start Date: 01/26/1999 | Est. Completion Date: Jun 01 | Periodic Review: N/A |

Study Objective: Compare the effects of 36 hours of supplemental oxygen therapy provided postoperatively to patients having surgery to management of patients without supplemental oxygen on wound healing in test wound samples and subcutaneous tissue oxygen levels. Compare the incidence of wound complications between the two groups evaluated in the surgical wound on postoperative days 2 and 7. Compare clinical healing outcomes and describe complications that occurred in the two groups during the first 30 days post surgery.

Technical Approach: This study uses a randomized, two group, experimental repeated measures design. 160 essentially healthy subjects with a need for cervical spinal fusion and/or excision of a cervical intervertebral disc or excision of a lumbar intervertebral disc(s), will be recruited for the study. Subjects will be randomly assigned to receive only room air (control group) or supplemental oxygen at 28% via nasal cannula for 36 hours postoperatively (treatment group). PscO₂ will be measured at Hour 1, 18 and 36 using a tonometer/sensor system. Wound healing is evaluated by analysis of tissue cellularity and hydroxyproline from a tissue sample obtained from a small, polytetrafluoroethylene tube placed subcutaneously and removed on the 7th postoperative day. Wound complications/infections will be evaluated using the Wound Registry. Differences between groups will be tested using Analysis of Variance for repeated measures, Wilcoxon Rank Sum test, and Chi-square.

Progress: This protocol was suspended pending funding. Local funding for this study was approved Aug 99. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/029 **Status:** Ongoing

Title: Evaluation of the Clinical Status and Resource Utilization of Ventilated Patients with Acute Respiratory Failure in Intensive Care Units via a Longitudinal Observational Outcomes Database

Principal Investigator: Lori A. Loan, MSN, RNC

Department: Nursing **Facility:** MAMC

Associate Investigator(s): MAJ Mary S. McCarthy, AN

| | | |
|----------------------------------|--|--------------------------------|
| Start Date: 02/23/1999 | Est. Completion Date: Feb 00 | Periodic Review: N/A |
|----------------------------------|--|--------------------------------|

Study Objective: (1) To develop and maintain a detailed, longitudinal computer database of data on clinical and resource use outcomes in ventilated patients with acute respiratory failure, (2) to obtain a sample size of sufficient magnitude to permit statistically significant clinical and economic analyses, (3) to describe existing patterns of clinical management across a broad patient sample, (4) to use these data to conduct cohort studies that investigate in-depth patient outcomes in acute respiratory failure, including the prevalence of infectious complications and prolonged mechanical ventilation, (5) to identify treatment protocols associated with improved outcomes in patients with acute respiratory failure, and (6) to identify patient characteristics and treatment variables predictive of optimal or poor outcomes.

Technical Approach: This is a non-interventional study in which 150 subjects will be enrolled from participating sites over a one-year period of time. Chart review and direct observation will be used to collect demographic, clinical, and hospital data. Potential subjects will be identified by the PI during morning rounds in the ICU. Once it is determined that the patient meets the eligibility criteria the patient will be enrolled in the data collection group. The majority of data collection will be completed once the subject has been discharged; however, subject identification and documentation of processes that rely on direct observation must be done while the subject is in the ICU (e.g. rotational therapy). Analyses of these data may permit identification of interventions or patterns of patient care that are associated with a lower rate of respiratory infection, a shorter average ventilator time or other favorable outcomes in this high risk population.

Progress: 62 subjects have been entered in FY 99 for a total of 62 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/076

Status: Ongoing

Title: Gastric/Jejunal Feeding: Nutritional Outcomes and Pneumonia

Principal Investigator: MAJ Mary S. McCarthy, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): LTC Bernard J. Roth, MC; CPT Kurt W. A. Grathwohl, MC; 1LT Faith U. Watanabe, SP; MAJ Susanne J. Clark, AN

Start Date:
05/17/1996

Est. Completion Date:
Sep 98

Periodic Review:
04/27/1999

Study Objective: 1) To compare nutritional outcome between patients randomized to gastric or jejunal tube feeders as measured by: a) daily caloric intake, b) subjective global assessment, c) biochemical parameters, d) delayed cutaneous tests and e) indirect calorimetry. 2) To compare rates of nosocomial pneumonia between gastric and jejunal fed patients as measured by: a) new & persistent infiltrate on chest x-ray (CXR), b) fever, c) sputum culture, d) leukocytosis, and e) bronchoscopically directed protected specimen brush. 3) To compare colonization rates between a subset of gastric and jejunal fed patients, at three sites (oropharynx, trachea, stomach); specific focus being Gram-negative bacilli, as measured by quantitative and qualitative microbiology analysis.

Technical Approach: This proposed study is a replication of a prior study done by Montecalvo et al. (Appendix A) in the medical model. Areas of interest include modifiable and non-modifiable person factors, social and physical environmental factors, physiological factors, pathophysiological factors, behavioral factors, symptoms, cognitions/emotions, and drives/sensations. Infants who are prescribed a feeding tube in one of two places, the stomach or the small intestine. Both methods are commonly used in this hospital. If you are to receive tube feedings in the stomach your doctor will pass a soft, flexible tube down your nose or mouth into your stomach. If you are to receive tube feedings in the small intestine, a radiologist will pass a soft, flexible tube down your nose or mouth using a lighted scope to guide the tube placement into your small intestine. It is the policy of this hospital to confirm the placement of the tube by xray before feedings can begin. This is ordered by the physician and will be performed whether or not you participate in this study. Shortly after having the tube in place, the principal investigator or the project director will conduct a noninvasive metabolic test at the bedside to estimate your calorie needs for tube feeding. This test measures the amount of energy you use while you are ill in the ICU. It will be performed each week. In addition, specimens of blood, urine, sputum and stomach contents will be obtained to evaluate your nutritional status and monitor for infection or bleeding. Lastly, your health record will be examined by the investigator or the project director for the following information: pertinent medical history, admission vital signs, current medications, height and weight, and tube feeding regimen.

Progress: 16 subjects have been entered in FY 99 for a total of 50 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/063 **Status:** Ongoing

Title: Improving ALI/ARDS Patient Outcomes with Metabolic Support

Principal Investigator: MAJ Mary S. McCarthy, AN

Department: Nursing **Facility:** MAMC

Associate Investigator(s): CPT Maginia S. Morales, AN; Janet C. Chilton

Start Date:
03/20/1998

Est. Completion Date:
Sep 00

Periodic Review:
03/23/1999

Study Objective: 1) What are the differences in nutritional and physiologic responses between ARDS patients who receive a special formula (Oxepa) versus ARDS patients who receive a standard formula (Osmolite HN)? (2) What are the differences in patient outcomes between ARDS patients who receive a special formula (Oxepa) versus ARDS patients who receive a standard formula (Osmolite HN)?

Technical Approach: Subjects will be randomized to receive either immune-enhanced formula (Oxepa) or a standard stress formula (Osmolite HN) for a minimum of 4 days. Nutritional outcomes will be based on prealbumin values, nitrogen balance, and % caloric goal achieved. Physiologic outcomes will be measured by the oxygenation ratio respiratory quotient, and plasma interleukin-6 levels.

Progress: 5 subjects have been entered in FY 99 for a total of 5 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/106

Status: Completed

Title: Natural Killer Cell Activation and Apoptosis in Women with Early Stage Breast Cancer: Potential Measure for Nursing Research

Principal Investigator: MAJ Penny M. Moureau, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): Betty J. Gallucci, Ph.D., RN; LTC Thomas H. Miller, AN; Genevieve M. Fuller

Start Date:
06/20/1997

Est. Completion Date:
Apr 98

Periodic Review:
07/27/1999

Study Objective: 1) To explore the whole blood assay for the measurement of activation antigens on natural killer (NK) cells. 2) For our laboratory to select and gain experience with a measure of apoptosis or programmed cell death. 3) Describe and compare expression of NK cell activation antigens in women with hyperplasia and early stage breast cancer and women without breast disease, prior to and after IL-2 incubation. Expression of activation antigens is not normally detected in peripheral NK cells of healthy women, but is present in such illness states as chronic fatigue syndrome (40) and is also present after incubation with IL-2. 4) Explore the potential mechanisms for depression of NK cell cytotoxicity seen in women with breast cancer by determining the percent of apoptotic cells across all groups of women after activation by IL-2.

Technical Approach: NK cells play an important role in immune surveillance against tumor cells and are the first line of resistance against infections. NK cell activity is increased in individuals with healthy lifestyles and is depressed in individuals who experience acute or chronic stressors of disease symptomatology such as breast cancer. Activation of NK cells leads to the expression of activation antigens on the cell surface, initiates production of cytokines, increases levels of cytotoxicity, and promotes programmed cell death. The methodologic aims of our study are to gain experience in the laboratory with the whole blood assay for activation antigens and to determine which of the apoptosis assays will be the most rapid, reliable and sensitive. For nurse researchers, measurement of natural killer cell activation has the potential to monitor an immunologic outcome of primary and tertiary prevention strategies for breast cancer.

Progress: This past year data collection was completed with the total number of women enrolled was 28. To date, the fresh blood has been stained for the number and type of lymphocytes and determined the percentage of activation antigens, CD69 and HLA-DR on natural killer and T lymphocytes in whole blood. For the three healthy women, the percent of lymphocytes with CD69 antigens in whole blood was 1.73% and HLADR was 10.47%; while the percent CD69 was 3.79 and HLA-DR was 20.88 in the four women with a diagnosis of breast cancer. The activation antigens were approximately doubled in the women with breast cancer as compared to the healthy volunteers. In addition to the whole blood experiments, aliquots of lymphocytes from all volunteers were frozen and stored for activation and apoptosis experiments. Eight activation experiments have been completed to determine the percent increase of these antigens. For the two healthy volunteers, the mean percent increase of CD69 was 600%; for the three volunteers with fibrocystic disease, the mean increase was 345%; for one woman with hyperplasia, the mean was 700% and one woman with a diagnosis of cancer, the mean was 177%. In the next three months the activation experiments will be completed and the apoptosis experiments will begin. In addition, the questionnaire data will be entered and the appropriate statistical analysis will be done on the psychosocial variables.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/009

Status: Completed

Title: The Effect of Preoperative Administration of Ketorolac on Postoperative Bleeding in Anterior Cruciate Ligament Reconstruction

Principal Investigator: CPT Angela Quintanilla, AN

Department: Nursing

Facility: MAMC

Associate Investigator(s): MAJ Bryan D. Schmidt, AN; CPT Anne M. Silvasy, AN; LTC Patrick St Pierre, MC

Start Date:
11/17/1998

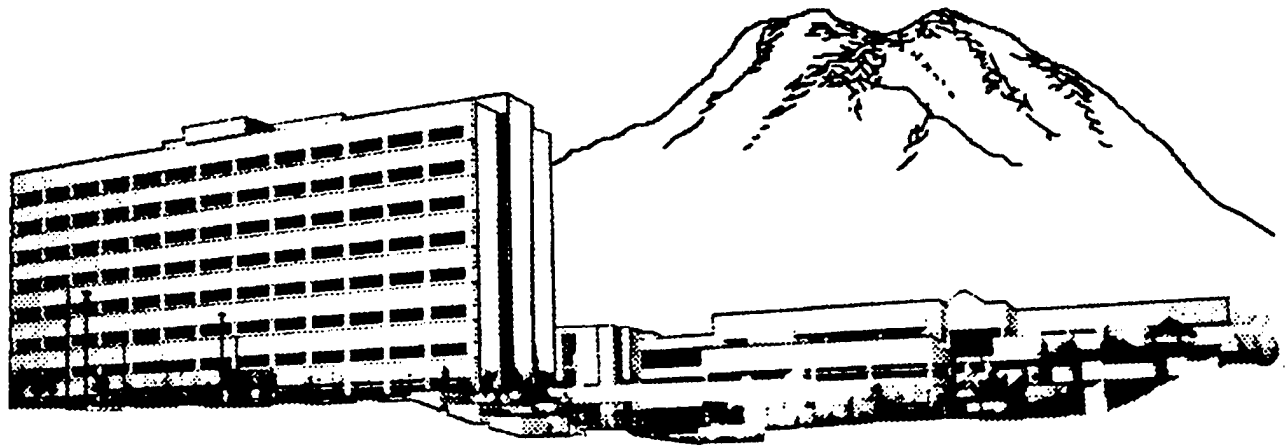
Est. Completion Date:
Aug 99

Periodic Review:
N/A

Study Objective: The purpose of this study is to examine the effects of a preoperative (preemptive) intravenous dose of ketorolac on platelet aggregation and measured postoperative blood loss on patients undergoing anterior cruciate ligament (ACL) reconstruction.

Technical Approach: This study is a prospective, randomized, double-blind, treatment versus control, experimental design. 40 orthopedic subjects, ages 18-65, undergoing ACL reconstruction will be randomized to receive either 30 mg of IV ketorolac or an equal volume of 0.9% normal saline preoperatively. Platelet aggregation studies will be obtained prior to the administration of the drug or placebo and at least 45 minutes later and after incision. Postoperative blood loss will be measured via a hemovac drain every 4 hours and as needed for a total of 18 hours. Nominal and ratio data will be collected. Demographic data will be collected to analyze any differences that may not be attributable to drug effect. Nominal data will be analyzed using Chi Square analysis. Platelet aggregation values are represented by ratio data and will be entered into the computer and analyzed using a two factor mixed ANOVA. Total blood loss values are also ratio data and will be analyzed using the Student's t-test. Differences between groups that were not anticipated will also be analyzed using the Student's t-test.

Progress: 31 subjects have been entered in FY 99 for a total of 31 subjects enrolled. Of the 7 subjects that received ketorolac in this study, not one demonstrated a statistically significant increase in postoperative blood loss. Platelet response to the agonists ADP and collagen were found to be different. In response to the ADP, platelets did not show a significant decrease in aggregation or ATP secretion. However, in response to the collagen, aggregation values were significantly inhibited by the ketorolac. These values did not correlate to a clinical significant difference in bleeding.



Detail Summary Sheets

Nutrition Care Division

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/082

Status: Ongoing

Title: Implementation and Evaluation of PEP (Personal Energy Plan) Health and Wellness Program Designed to Promote Healthy Eating and Physical Activity Among Adult Participants

Principal Investigator: 1LT Michelle D'Amico, SP

Department: Nutrition Care

Facility: MAMC

Associate Investigator(s): JC Hare; S Hite; L Kostner; J Spahn; P Jones; R Cavalcanti; M Perious; LTC Linda L. Rowbotham, SP

Start Date:
08/24/1999

Est. Completion Date:
Mar 00

Periodic Review:
N/A

Study Objective: 1) To determine if the implementation of CDC's PEP Program will make a difference in healthy eating and physical activity knowledge and behaviors within DoD. 2) To determine the factors (e.g., gender, beneficiary status, stage of readiness, rank, education level, type of worksite environment) that best predict whether or not an individual will experience a positive change in physical activity or eating.

Technical Approach: Study design is quasi-experimental, one group pre- and post-evaluation. Squadrons/units will be selected as potential sites for intervention. Site coordinator will meet with the commander and explain program and identify the amount of unit time that will be required to participate along with the expected benefits. Once commander's approval is obtained, the worksite audits must be done at either flight level prior to beginning the recruitment of participants. (Questionnaire will need to be identified as to what is "installation level" versus likely to change at flight to save evaluator time.) The PEP program consists of a promotional phase lasting approximately 8 weeks during which the program is marketed to recruit participants and a 12-week implementation phase. Participants that indicate an interest will be provided with an enrollment packet consisting of the informed consent form and PEP enrollment forms. The PEP enrollment forms will be analyzed to determine stage of change and registration log will be completed which assigns each participant an identification number (to maintain confidentiality). Only the on-site researcher will have access to the log with personal identification and identification numbers. Personal identification numbers will also be assigned to control group. Pretests will be distributed to all enrolled participants as well as control group from another worksite with similar composition. Instructions encouraging partners will be provided with the pretest. After all pretests are collected, partners will be assigned, kits will be distributed and dates recorded when each kit was provided to participant. Each month following the first month, a new calendar will need to be distributed to the participants. A telephone call will be made to all participants weekly to see how they are progressing and answer any questions about the PEP program. The telephone call will ask the participants to identify which part of the materials they have reviewed, provide encouragement for completing the next steps as outlined in the materials, ensure that they do not need additional program materials, and answer any questions that they may have.

Variables that will be assessed in the current study include physical activity stage, healthy eating stage, amount of physical activity, nutritional intake level, health knowledge, perceived energy, attitudes toward physical activity, attitudes toward healthy eating, environmental support, and worksite supportiveness. Participants will be classified according to their physical activity stage and healthy eating stage based on their: responses to the initial questionnaire (e.g., Precontemplation Stage, Preparation Stage, Late Preparation Stage; see description above); amount of physical activity, nutritional intake level, health knowledge, perceived energy score,

attitudes toward physical activity score, attitudes toward healthy eating score, environmental support score, worksite supportiveness score (based on the outcome of the worksite audit for his/her facility).

Descriptive statistics/frequencies for each of the major outcome variables will be tabulated. Statistics will be calculated separately for each of the two assessment points (pre- and post-PEP intervention). Pre- and post-intervention scores for each of the major outcome variables will be compared using a series of Wilcoxon-signed-rank tests. Logistic regression will be used to assess the factors that predict whether or not an individual will experience a positive change in stage after participating in the PEP program (e.g., going from the Contemplation Stage to the Preparation Stage). Independent variables that will be included in the model will be gender, age, beneficiary status, Pre-intervention Stage, and supportiveness of worksite environment. Separate models will be conducted for physical activity stage and healthy eating stage.

Progress: This protocol was recently approved and has not yet started recruiting subjects, study is on hold until 10 Jan 2000.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/111 **Status:** Ongoing

Title: An Evaluation of UPBEAT Weight Management Program

Principal Investigator: 1LT Susan Ann Jordan, SP

Department: Nutrition Care **Facility:** MAMC

Associate Investigator(s): None.

Start Date:
9/28/1999

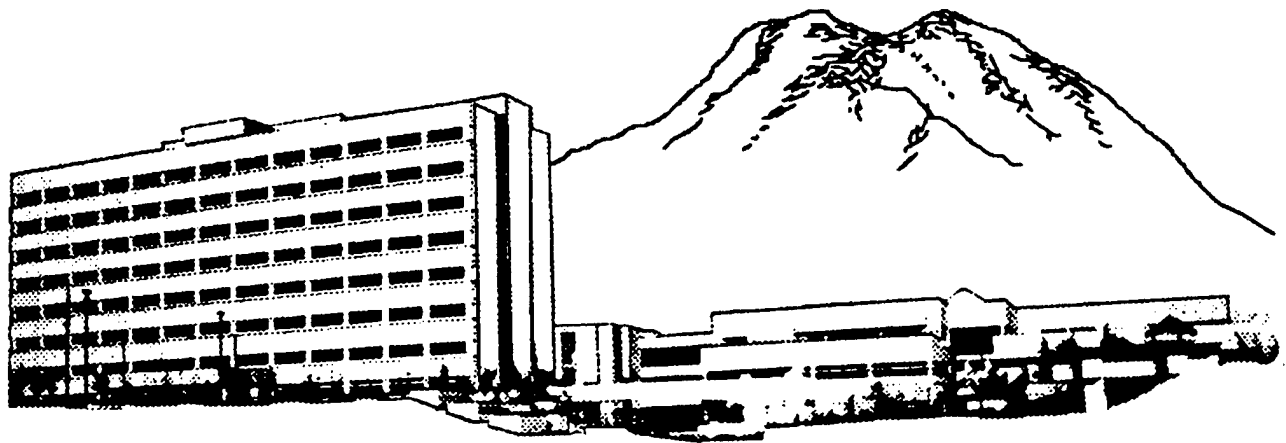
Est. Completion Date:
Nov 99

Periodic Review:
N/A

Study Objective: To educate soldiers about the mind and body drives that lead to overeating and inactivity. To increase soldier readiness through sustained improvement in overall health and fitness. To decrease losses in personnel due to AR 600-9.

Technical Approach: UPBEAT Program will consist of 4 phases: orientation/testing, personal interviews, Skill Training, Partnering for Change, and Maintenance and Relapse Prevention. This first phase will assess the soldiers' readiness to change, and develop individualized goals and outcomes. This phase will also identify if a soldier has an eating disorder. Based on the efforts of phase 1, the second phase will involve commanders and UPBEAT staff partnering for soldier success. The third phase will involve a 12- week intervention aimed at identifying the mind and body cues that will lead to permanent lifestyle changes and improved overall health. The fourth phase will focus on the maintenance of these skills and behaviors. This phase is essential in working through any relapses and is considered crucial in long term success. This phase will extend out to a full year.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Department of Obstetrics/Gynecology

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/031

Status: Ongoing

Title: Relationship of Cesarean Delivery for Arrest of Descent and Station at Onset of Maternal Pushing: A Case Control Study

Principal Investigator: CPT Richard O. Burney, MC

Department: OB/GYN

Facility: MAMC

Associate Investigator(s): C Frayer; S Wood; COL Roderick F. Hume Jr., MC; LTC Peter E. Nielsen, MC

Start Date:
02/23/1999

Est. Completion Date:
Apr 99

Periodic Review:
N/A

Study Objective: To determine the effect of station at onset of second stage on the rate of cesarean delivery in primiparous patients with epidural anesthesia.

Technical Approach: Using the 1996/1997 labor and delivery records of deliveries at MAMC, a case control study will be performed. All primiparous patients with epidural anesthesia who required a cesarean section for arrest of descent will be identified and labeled as cases. For each case, two primiparous patients with epidural anesthesia who progressed to spontaneous delivery will be identified and labeled as controls. For each case, respective controls will be matched for maternal age, gestational age, fetal weight and use of oxytocin in labor. During this period of labor management, all patients began pushing efforts at the onset of the second stage, which was defined as cervical progression to complete effacement and complete dilation irrespective of fetal station. The fetal station at the onset of second stage will be determined for all cases and controls.

A chi-square analysis will be performed to compare cases and controls with second stage maternal pushing efforts begun at fetal station 0 and higher. This will be conducted so as to allow the determination of an odds ratio for operative delivery when maternal pushing efforts are begun at fetal station higher or equal to 0. Additionally, each station will be assigned a value to allow for the performance of the Mann-Whitney Rank Sum Test in the comparison of cases and matched controls.

Progress: Using the 1995 labor and delivery log, the first ten patients who underwent primary cesarean delivery for arrest of descent were identified and matched with two controls each. The records of these thirty patients were pulled and data was collected using a study-specific data collection form. This data has been entered into a database for future statistical analysis. No preliminary conclusions have been drawn at this time.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/077 | Status: Ongoing |
| Title: Misoprostol for the Medical Management of Non-viable First Trimester Pregnancies | | |
| Principal Investigator: CPT Louis A. Dainty, MC | | |
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| Department: OB/GYN | Facility: MAMC | |
| <hr/> | | |
| Associate Investigator(s): COL Milo L. Hibbert, MC; LTC Peter E. Nielsen, MC; Troy H. Patience, B.S. | | |
| <hr/> | | |
| Start Date: 06/22/1999 | Est. Completion Date: Mar 01 | Periodic Review: N/A |

Study Objective: The purpose of this study is to examine the effectiveness of misoprostol (Cytotec; GD Searle and Co., Chicago, IL) for the management of non-viable first trimester pregnancies. Specifically, misoprostol (15-S-15-methyl PGE1) will be compared to a placebo with expectant management in who have documented non-viable gestations. We will examine the following outcome variables: time to resolution, number of patients requiring dilation and curettage, change in hematocrit, cost to the institution, patient satisfaction, and reported side effects.

Technical Approach: Patients presenting to the OB/GYN clinic with a nonviable gestation will be considered potentially eligible to participate in the study. The diagnosis of non-viable gestation will be documented by endovaginal ultrasound. Those patients entering the study will be directed to the OB/GYN clinic for evaluation, exam, counseling and to watch the video giving explanation of purpose of the study and the planned procedure, but also expected side effects and possible complications. An anembryonic gestation will be diagnosed in any patient with an irregularly shaped gestational sac and mean sac diameter of 16 or greater without an embryonic pole. Additionally any patient with an intrauterine fetal pole between 5 and 14 mm with no cardiac activity will be considered non-viable and will be considered for acceptance into our study. Ultrasonic findings will be verified by two of the resident staff from the obstetrics and gynecology department of Madigan Army Medical Center. After explanation of the study, verification that the patients meet the inclusion criteria, patients will be offered participation in the study and asked to view a short video to ensure consistency of counseling. Upon conclusion of the counseling and video, patients will be asked to sign a consent form for participation in the study.

Complete history and physical will be performed and initial laboratory will be obtained to include CBC, BUN, creatinine, quantitative BHCG and blood type to include Rh status. Patients will then be randomized into two groups: study group receiving misoprostol per vagina and the control group receiving a placebo per vagina.

Subjects will be issued an envelope and asked to report to the pharmacy where they will pick up their study medication, which will be blinded to them and the provider administering the medication. Additionally, they will be given Motrin and Phenergan to help alleviate undesired side effects. Subjects will have four 200 ug tablets of misoprostol in the posterior fornix of the vagina using a speculum under the direct visualization of the provider.

Patients will be asked to return in 24 hours for re-examination to include a pelvic ultrasound using a vaginal probe. If no evidence of an intrauterine pregnancy remains (i.e. gestational sac, fetal pole etc.), patients will be informed that their miscarriage was complete, given precautions and asked to make an appointment for follow-up in 4 weeks in addition to weekly visits to the lab for quantitative BHCG. All patients will be followed until the quantitative BHCG has fallen zero to ensure resolution of the pregnancy event.

Those patients with evidence of a gestational sac will be given a second dose of misoprostol or alternatively a D&C if they choose to withdraw from the study or surgical intervention is deemed clinically indicated by the attending staff. Again, the subjects will be given appropriate counseling and precautions and asked to follow up in an additional 24 hours for re-evaluation. At any point in the study, subjects may withdraw from the study as per the patient's wishes or removed from the study if the provider feels surgical intervention is indicated (i.e. excessive bleeding or side effects). Surveys will be given at each visit and follow up to evaluate patient satisfaction and also to query for unintended side effects and complications.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/084 **Status:** Ongoing

Title: Team Performance in Labor & Delivery: L&D MedTeams: Concept Phase

Principal Investigator: LTC Peter E. Nielsen, MC

Department: OB/GYN

Facility: MAMC

Associate Investigator(s): COL Matthew M. Rice, MC; COL Romeo P. Perez, MC; LTC Byron C. Calhoun, MC; Kathleen Judge; Robert Simon, EdD; COL Roderick F. Hume Jr., MC

Start Date:
08/24/1999

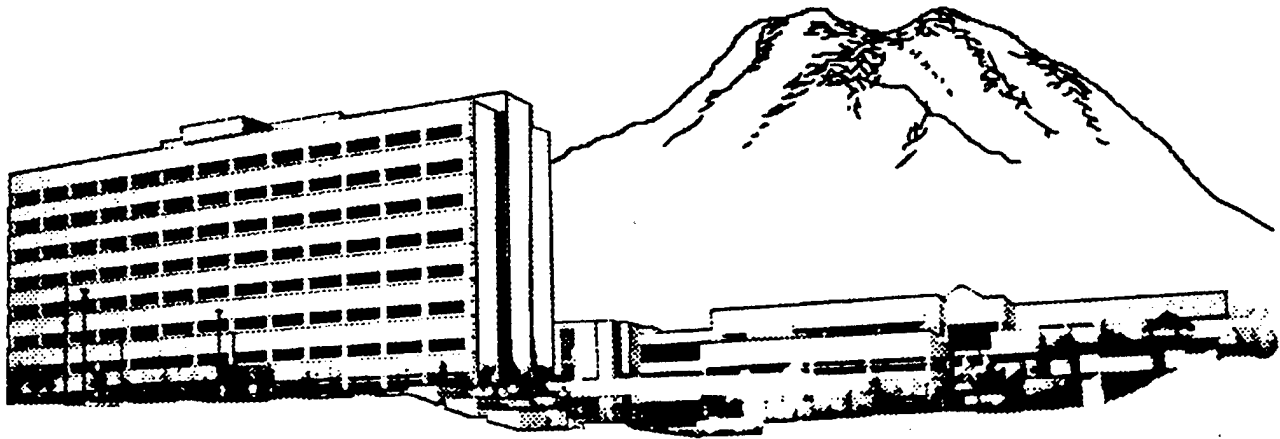
Est. Completion Date:
Oct 00

Periodic Review:
N/A

Study Objective: The proposed study, Concept Phase, is intended to develop an educational initiative in teamwork training (MedTearns) for Labor Delivery. Observational Study to determine components of curriculum and optimal training curriculum. Culmination in Experimental Phase pending successful Grant Application FY2000.

Technical Approach: This study is intended to demonstrate that an educational initiative in teamwork training (MedTeams) can be instrumental in improving labor & delivery caregiver performance and job satisfaction while reducing error patterns that are potentially dangerous to patients, mother and child. This initiative has its beginnings in the aviation community through team coordination training entitled "Cockpit Resource Management". Cockpit Resource Management in essence are rules of engagement that crew members abide by when communicating with one another, (i.e., check back, challenge, etc). This simple innovation was found to be a powerful one within the last several years and has contributed to a decrease in both civilian and military aviation mishaps. The successful multicenter educational trial involving the ETCC has proven that a similar initiative in medicine can reduce medication errors and other actions that are potentially harmful to patients. MedTeams has been funded by DA through ARL under a MOA with DRC and collaborating Medical Centers to test this hypothesis in emergency departments. A suite of both objective and subjective measures will be developed at MAMC under this expedited review protocol to pilot an L&D MedTeam educational initiative at MAMC. This program will serve as the core for the next phase, experimental phase, of a multicenter educational interventional trial which will parallel the ETCC trial. The Program will involve an eight-hour MedTeams didactic training, frequent refresher and reinforcement sessions, in addition to the administration of anonymous caregiver and patient survey tools. Commonly available continuing improvement and risk management data will be monitored to follow trends of error patterns, medication error, patient complaints, etc. Goal to develop Grant Proposal and Multicenter Trial by Oct 2000. CRDA with DRC, MAMC/CIRO through Geneva will develop concurrently.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Maternal-Fetal Medicine,
Department of Obstetrics/Gynecology

Detail Summary Sheet

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|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 98/068 | Status: Ongoing |
| Title: The Expression of Adrenomedullin and Its Receptor in the Human Placenta | | |
| Principal Investigator: MAJ Christina Apodaca, MC | | |
| <hr/> | | |
| Department: OB/GYN, MFM | Facility: MAMC | |
| Associate Investigator(s): MAJ Richard K. Wagner, MC; Katherine H. Moore, Ph.D.; LTC Byron C. Calhoun, MC; COL Roderick F. Hume Jr., MC | | |
| <hr/> | | |
| Start Date: 05/22/1998 | Est. Completion Date: Sep 98 | Periodic Review: 03/23/1999 |

Study Objective: To elucidate the expression of adrenomedullin (ADM) and its receptors in specific tissue components of the human placenta. This will be investigated by using placental tissue from both uncomplicated pregnancies and pregnancies complicated by chronic hypertension and pregnancy induced hypertension. Western blot analysis will be used to identify adrenomedullin expression. Reverse transcriptase-polymerase chain reaction will be used to identify the expression of adrenomedullin messenger ribonucleic acid for ADM and to identify presence of the ADM receptor. Immunocytochemical analysis will also be used to establish the expression of ADM in specific placental tissues.

Technical Approach: Adrenomedullin is a potent vasoactive peptide, whose vasoactive properties have been extensively described. It has been isolated from various human tissues, including pheochromocytoma, lung, heart and pancreas. Its presence in human plasma suggests that it functions as a circulating hormone, influencing the perfusion of various organs. The presence of adrenomedullin has recently been described in fetal membranes and amniotic fluid, suggesting its role in fetal perfusion. Increases of adrenomedullin in pathologic states have been described, including renal failure and hypertension in non-pregnant individuals, and in pregnant women with preeclampsia. To date there exist no studies demonstrating the isolation of adrenomedullin and its receptor in specific placental tissues.

We will isolate samples of amnion, cotyledon, umbilical artery and umbilical vein from women with uncomplicated pregnancies and pregnancies complicated by pregnancy induced hypertension. Western blot analysis will be used to identify the presence of the adrenomedullin protein. Reverse transcriptase-polymerase chain reaction will be used to isolate total messenger ribonucleic acid for adrenomedullin and its receptor. Histochemical staining will be used to identify adrenomedullin in the tissue samples.

Categorical analysis will be performed describing the distribution of adrenomedullin and its receptor in both normal placentas and the placentas from patients with chronic hypertension and pregnancy induced hypertension.

Progress: Data on 25 placentas (125 tissue samples) have been collected during FY 99. Finished rtPCR for adrenomedullin receptor probing. Protein extraction of remaining tissue for adrenomedullin western analysis and membrane extract of remaining tissue for adrenomedullin binding assay will be performed shortly and protocol will be completed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/035 **Status:** Ongoing

Title: Comparison of Elective Labor Induction and Spontaneous Labor: A Randomized, Controlled Clinical Trial

Principal Investigator: MAJ Christina Apodaca, MC

Department: OB/GYN, MFM **Facility:** MAMC

Associate Investigator(s): CPT Robert H. G. Holland, MC; COL Paul N. Smith, MC; CPT Brian T. Pierce, MC; MAJ Richard K. Wagner, MC; LTC Peter E. Nielsen, MC; LTC Byron C. Calhoun, MC; COL Romeo P. Perez, MC; Kathleen Judge; Roxanne Piecek

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| Start Date: 02/23/1999 | Est. Completion Date: Feb 00 | Periodic Review: N/A |
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Study Objective: The purpose of this study is to compare cesarean section rates between patients delivered at term with a favorable cervix by elective induction with patients allowed to enter labor spontaneously. Additional maternal and neonatal outcomes will also be compared between the two groups.

Technical Approach: Between 38 and 39 weeks, subjects presenting with a favorable cervix and consenting to be in the study, will be randomized into either the labor induction group or the spontaneous labor group. Labor induction will follow MAMC Labor and Delivery protocol. Those subjects assigned to labor induction will be scheduled within 72 hours for admission including routine admission labs, establishment of intravenous access and fetal monitoring. Subjects in the control group will continue in the Obstetric Clinic until the onset of spontaneous labor. Their labor will also follow MAMC Labor and Delivery protocol.

Subject information sheets for the health care providers managing the subjects will capture complete documentation of labor and delivery information. These data will be entered into a computer database for analysis and the data sheets will not be part of the subject's medical record. Subjects will also be asked to fill out a questionnaire, the Labor and Delivery Satisfaction Index, to assess satisfaction with their labor and delivery.

Chi-square analysis will be used to assess for differences in nominal variables (epidural use, oxytocin use, chorioamnionitis, postpartum complications, NICU admissions, meconium stained amniotic fluid, neonatal or maternal complications, neonatal or maternal birth trauma). The paired Student's t-test will be used to compare groups of continuous variables (cesarean section rate, vaginal delivery rate, operative vaginal delivery rate, duration of first and second stage of labor, maternal and neonatal lengths of stay, birth weight, Apgar scores).

Progress: Data has been collected on 16 subjects during FY 99. Recruitment of subjects continues.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/051

Status: Ongoing

Title: The Use of Transvaginal Sonography in Predicting Preterm Delivery in Patients with Preterm Contractions

Principal Investigator: MAJ Christina Apodaca, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): CPT Lisa M. Foglia, MC; CPT Brian T. Pierce, MC; MAJ Richard K. Wagner, MC; LTC Peter E. Nielsen, MC; LTC Byron C. Calhoun, MC; Troy H. Patience, B.S.

Start Date:
03/23/1999

Est. Completion Date:
Aug 99

Periodic Review:
N/A

Study Objective: Primary: To investigate the accuracy of transvaginal cervical ultrasound in predicting the occurrence of preterm delivery, in patients presenting to Labor and Delivery with complaints consistent with preterm contractions.

Secondary: We will also compare the abilities of transvaginal sonography and digital cervical exam in predicting preterm delivery within one week from examination.

Technical Approach: Despite recent advances in modern obstetric care, the incidence of preterm delivery has not decreased, and remains a leading cause of neonatal morbidity and mortality. Due to the refractory nature of preterm labor to effective management, early diagnosis is essential. Definitive diagnosis of legitimate preterm labor remains difficult, however, and results in over-diagnosis and treatment of what is most likely innocuous preterm contractions.

Early cervical effacement and dilation may be subtle changes that may not be identified on digital examination. Transvaginal cervical ultrasonography is a precise, reproducible, modality that can provide an objective means by which to evaluate the cervix for early effacement and dilation.

While studies have identified the utility of transvaginal cervical sonography in predicting preterm delivery, its role in assessing patients with preterm contractions is less clear.

We propose to evaluate the utility of transvaginal cervical sonography in predicting subsequent preterm labor and delivery. We will also compare the efficacy of cervical sonography with digital examination in predicting the incidence of preterm delivery.

We hope to identify a cervix length in a patient with preterm contractions, at which a physician can feel comfortable sending her home, with a 98 to 100 percent assurance that she will not deliver within the next week (eg, that cervical length which yields a 98 to 100 percent negative predictive value for preterm delivery within a week).

Progress: No data on subjects have been collected during FY 99. Recruitment of subjects continues.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/075 **Status:** Ongoing

Title: Fetal Macrosomia in a Military Population

Principal Investigator: LTC Byron C. Calhoun, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): CPT Curt A. Misko, MC; MAJ Elisabeth Hancock, MC; CPT Lisa M. Foglia, MC

Start Date:
06/22/1999

Est. Completion Date:
Sep 99

Periodic Review:
N/A

Study Objective: To determine the incidence of macrosomia (> 4500 gm) in the military population and evaluate for co-morbidities.

Technical Approach: We wish to show that macrosomic fetuses are increased in incidence in the military population with variables of interest to include, fetal and maternal morbidities associated with macrosomic fetuses. The inherent risks associated with fetal macrosomia at delivery we wish to evaluate are: shoulder dystocia, fetal hypoglycemia, hypercalcemia, hyperbilirubinemia, trauma to maternal birth canal, maternal hemorrhage and increased risk of cesarean section. This will be done by chart review for 200 patients to be compiled with 100 patients from a similar study by Keesler AFB for publication and presentation. We will review charts starting at the end of 1998 and going back until 100 macrosomic infants are found. At the same time 100 patients will be used as controls by choosing the nearest non- macrosomic patient (birth weight <4000gms) to the macrosomic patient.

Progress: 100 subjects have been entered in FY 99 for a total of 100 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/100

Status: Ongoing

Title: Comparison of First and Second Trimester Screening for Prenatal Detection of Down Syndrome and Other Birth Defects

Principal Investigator: LTC Byron C. Calhoun, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): MAJ Christina Apodaca, MC; CPT Brian T. Pierce, MC; LTC Peter E. Nielsen, MC; Laura S. Martin, M.D.; COL Roderick F. Hume Jr., MC; V Souter

Start Date:
9/28/1999

Est. Completion Date:
Jul 01

Periodic Review:
N/A

Study Objective: 1) To determine the effectiveness of first trimester screening in detection of fetal chromosome abnormalities as well as other birth defects and to compare the accuracy of first trimester screening with second trimester screening; and 2) To evaluate patient assessment of perceived risk compared to calculated risk of fetal Down syndrome and other birth defects.

Technical Approach: Patients will be enrolled between 10.5 and 14 weeks. They will be asked to complete a questionnaire to evaluate their perceived risk of fetal Down's syndrome and their attitudes toward patient screening. First trimester ultrasound with maternal-blood sampling in will be performed 10 3/7 weeks and 13 6/7 weeks looking for nuchal (neck thickness) with a follow-up ultrasound in the second trimester between 15 and 20 weeks.

First trimester laboratory testing will include maternal-serum for free Beta-human chorionic gonadotropin and pregnancy associated plasma protein-A (PAPP-A). The second trimester testing will include alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) as well as inhibin-A. Further, the patients who screen positive in either first or second trimester analyte screening will have maternal blood sent to be included in the "National Institute of Child Health and Human Development Fetal Cell Isolation Study (NIFTY). This study seeks to explore the ability to extract fetal cells from maternal blood for possible detection of abnormal chromosomes.

Progress: This protocol was recently approved and has not yet started recruiting subjects and awaiting funding.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/023 **Status:** Ongoing

Title: Delayed Maternal Pushing with Labor Epidural Analgesia: Effects on Operative Vaginal Delivery

Principal Investigator: LTC Peter E. Nielsen, MC

Department: OB/GYN, MFM **Facility:** MAMC

Associate Investigator(s): CPT Richard O. Burney, MC; CPT Brian T. Pierce, MC; MAJ Christina Apodaca, MC; MAJ Richard K. Wagner, MC; S Wood; Thomas W. Overly; LTC Byron C. Calhoun, MC

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| Start Date: 01/26/1999 | Est. Completion Date: Feb 00 | Periodic Review: N/A |
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Study Objective: To determine the effect of delayed maternal pushing on the rate of operative vaginal delivery.

Technical Approach: Following consent, subjects will continue to be managed according to standard of care. When study eligibility criteria is met, subjects will be randomized into one of two treatment groups after the placement of epidural analgesia; early pushing and delayed pushing.

Early pushing group: Subjects will be allowed to push at the first maternal urge once the cervix is completely dilated.

Delayed pushing group: Subjects will begin pushing when the vertex is distending the perineum. The subjects in this group will be given 0.25% bupivacaine epidural boluses to delay the maternal urge to push.

Cervical examinations in both groups will occur at either maternal urge to push, or at 2 hours following complete cervical dilation. If no maternal urge to push at 2 hours, and the descent of the vertex is > 1 cm/hr, then continue management as randomized. If descent < 1 cm/hr, then begin oxytocin infusion per protocol for hypo tonic contractions and reexamine cervix in 2 hours, or at the onset of urge to push. If uterine activity is adequate, then begin pushing in both groups. Reexamine cervix in 2 hours and evaluate for arrest of descent. This management may allow the length of the second stage to be extended to approximately 5 hours, exceeding the generally accepted length of 3 hours in nulliparas and 3 hours in multiparas with epidural analgesia. The type of operative intervention (forceps, vacuum or cesarean delivery) will be the decision of the attending physician to ensure a safe and effective delivery.

Progress: 16 subjects have been entered in FY 99 for a total of 16 subjects enrolled.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/024 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: Extending the Duration of Active Phase Arrest: Effects on Cesarean Delivery

Principal Investigator: LTC Peter E. Nielsen, MC

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| Department: OB/GYN, MFM | Facility: MAMC |
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Associate Investigator(s): CPT Amy J. Asato, MC; CPT Brian T. Pierce, MC; MAJ Christina Apodaca, MC; MAJ Richard K. Wagner, MC; Thomas W. Overly; LTC Byron C. Calhoun, MC

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| Start Date: 01/26/1999 | Est. Completion Date: Feb 00 | Periodic Review: N/A |
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Study Objective: To determine the effect of extending the length of active phase arrest of dilation from 2 to 4 hours on the rate of cesarean delivery.

Technical Approach: Following consent, subjects will continue to be managed according to standard of care. When study eligibility criteria is met, subjects with active phase arrest, despite 2 hours of adequate uterine activity and continuous labor epidural analgesia, will be randomized to either cesarean delivery or 2 additional hours of labor. All subjects at the end of this 2 hour study period who fail to demonstrate cervical change (< 1 cm progress in 2 hours) will be delivered by cesarean section. All other patients will continue the labor process. Cesarean delivery for non reassuring fetal heart rate tracing will be performed based on routine obstetric indications.

Progress: One subject has been entered in FY 99 for a total of one subject enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/060

Status: Terminated

Title: Random Urine Protein/Creatinine Ratio for Quantification of Proteinuria in Pregnancy: An Outcomes Based, Cost Consequences Analysis

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; MAJ Christina Apodaca, MC; MAJ Richard K. Wagner, MC; COL Howard M. Cushner, MC; LTC Curtis L. Yeager, MS; COL Bonnie M. Jennings, AN; LTC Byron C. Calhoun, MC; COL Roderick F. Hume Jr., MC; LTC Peter E. Nielsen, MC

Start Date:
03/20/1998

Est. Completion Date:
Apr 99

Periodic Review:
03/23/1999

Study Objective: 1) Evaluate the use of random urine protein to creatinine ratios utilized for accurate quantification of proteinuria in MAMC's unscreened pregnant population, (2) the random urine testing of P/C ratios yields a shorter turnaround time and therefore a shorter time to diagnosis and treatment of medical complications of pregnancy, (3) patient compliance and satisfaction with testing are much improved by using random samples as compared with 24 hour urine collections, and (4) both direct and indirect medical costs are much decreased.

Technical Approach: Patients will be enrolled at the MAMC OB orientation for new OB patients. Testing for study purposes will be scheduled to coincide with regularly scheduled testing. We will assess random urine protein/creatinine ratios and 24 hour urine protein during each trimester of pregnancy and at 6 weeks postpartum. Blood urea nitrogen and serum creatinine levels will also be drawn at the same time for assessment of overall renal function.

Progress: This study was never implemented due to funding.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/018

Status: Completed

Title: Fetal Outcome Following Single Umbilical Artery Diagnosis

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): MAJ Richard K. Wagner, MC; CPT Vanessa D. Dance, MC; MAJ Christina Apodaca, MC; LTC Peter E. Nielsen, MC; LTC Byron C. Calhoun, MC

Start Date:

01/26/1999

Est. Completion Date:

Jun 99

Periodic Review:

N/A

Study Objective: To report the frequency of associated congenital abnormalities in fetuses with a single umbilical artery, the sensitivity of ultrasound for detecting associated abnormalities and obstetrical and neonatal outcome for fetuses diagnosed with a single umbilical artery.

Technical Approach: Antepartum maternal charts will be reviewed of all pregnancies complicated by a single umbilical artery, followed by neonatal/newborn chart reviews for evidence of associated structural anomalies and aneuploidy. Ultrasound data and fetal outcome will be recorded on a coded data sheet.

Progress: Data on 65 subjects have been collected during FY 99. Found consistently worse perinatal outcome for fetuses with single umbilical artery and other abnormalities.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/026

Status: Ongoing

Title: The Relationship Among Fetal Karyotype, Intrauterine Fetal Death, and Histologic Villous Mineralization

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): COL Roderick F. Hume Jr., MC; Laura S. Martin, M.D.; MAJ Sandra Carter, MC; LTC Peter E. Nielsen, MC; LTC Byron C. Calhoun, MC; CM Salafia

Start Date:
01/26/1999

Est. Completion Date:
Dec 99

Periodic Review:
N/A

Study Objective: To describe the relationship between fetal death and degree of villous mineralization of the placenta in aneuploid fetuses.

Technical Approach: Records of all chromosomal analysis obtained on fetuses and newborns at Madigan AMC will be reviewed (from Jan 1992 through Jul 1998). Available placentas will be sampled according to standard protocol and reviewed by a pathologist for evidence of villous mineralization. The reviewing pathologist will be blinded to both the karyotype of the placenta and the clinical history (liveborn or stillborn).

Progress: Data on 18 subjects have been collected during FY 99. Aneuploid fetuses have more histologic villous mineralization compared to euploid fetuses.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/046 **Status:** Ongoing

Title: Outcome of Infants Born at 22-28 Weeks Gestation: A Retrospective Review in Military Care Facilities

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): MK Yancey; GC Sharpe; MAJ Peter G. Napolitano, MC; MAJ Wanda A. Barfield, MC; G Marinkovich; MAJ Christina Apodaca, MC; MAJ Richard K. Wagner, MC; LTC Byron C. Calhoun, MC; LTC Peter E. Nielsen, MC

Start Date:
03/23/1999

Est. Completion Date:
Feb 00

Periodic Review:
N/A

Study Objective: To analyze and report neonatal morbidity and mortality in early gestation in military care facilities.

Technical Approach: All neonates born between 22 and 28 weeks EGA, inclusive, will be identified through hospital coding systems. A chart review will be performed on both the mother and neonate. Data will be collected to include: Gestational age at delivery, delivery weight antepartum betamethasone administration, neonatal surfactant administration, maternal age and race, and specific neonatal complications to include: death, RDS, WH (grade 3 and 4), periventricular leukomalacia, NEC, hyperbilirubinemia requiring phototherapy or exchange transfusion, retinopathy of prematurity, hypoglycemia, and sepsis. Maternal medical problems and ante/intrapartum complications will also be recorded. A follow-up study is planned to report long term follow up in these premature infants, specifically at 2 years of age and 5 years of age. The data will be collected on a separate data sheet (attached), with the patient being identified by a code number. The principle investigator will be the sole keeper of the names of the patients as well as the code to which they are assigned.

Progress: Five charts have been reviewed during FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/064 **Status:** Completed

Title: The Effects of Shear Stress on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon

Principal Investigator: CPT Brian T. Pierce, MC

Department: OB/GYN, MFM

Facility: MAMC

Associate Investigator(s): MAJ Richard K. Wagner, MC; MAJ Christina Apodaca, MC; Katherine H. Moore, Ph.D.; COL Roderick F. Hume Jr., MC; LTC Peter E. Nielsen, MC; LTC Byron C. Calhoun, MC; James R. Wright, M.T.

Start Date:
05/25/1999

Est. Completion Date:
Apr 00

Periodic Review:
N/A

Study Objective: To determine the effects of shear stress on placental production of interleukin-6 (IL-6).

Technical Approach: This study will evaluate the effect of shear stress on IL-6 production in the isolated dually perfused placenta cotyledon. Paired cotyledons from 10 placentas obtained from uncomplicated vaginal and cesarean deliveries in MAMC's labor and delivery will be used. A perfusate consisting of Hank's balanced salt solution, bovine albumin, heparin, and gentamicin will be used to perfuse both the maternal and fetal circulations of the cotyledons. One cotyledon will have the fetal circulation infused at 1 cc/min. The other cotyledon will have the fetal circulation perfused at 10 cc/min. After establishing perfusion of an intact fetoplacental circuit, effluents will be collected at hourly intervals for four hours. These samples will be stored for determination of IL-6 levels by ELISA. The fetoplacental vascular tone will be continuously monitored throughout the experiment and recorded at 10-min intervals. Data will be analyzed using repeated measure analysis of variance.

Progress: Data on 5 subjects have been collected during FY 99. Increasing shear stress resulted in decreased placental IL-6 production. Accepted for poster presentation Feb 2000 @ SMRM meeting.

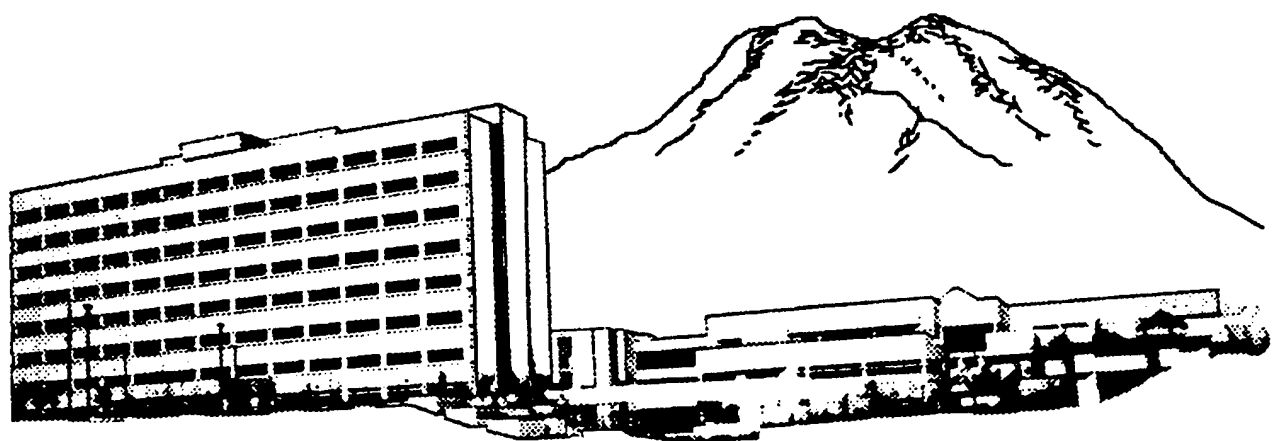
Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/105 | Status: Completed |
| Title: The Effects of Magnesium Sulfate on Placental Production of Interleukin-6 in the Isolated Dually Perfused Placental Cotyledon | | |
| Principal Investigator: MAJ Richard K. Wagner, MC | | |
| Department: OB/GYN, MFM | | Facility: MAMC |
| Associate Investigator(s): MAJ Roger M. Hinson, MC; MAJ Christina Apodaca, MC; CPT Brian T. Pierce, MC; Katherine H. Moore, Ph.D.; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC | | |
| Start Date: 09/15/1998 | Est. Completion Date: Nov 98 | Periodic Review: N/A |

Study Objective: To determine the effects of magnesium sulfate, a commonly used tocolytic, on placental production of interleukin-6 (IL-6).

Technical Approach: Paired cotyledons from 5 placentas obtained from uncomplicated vaginal and cesarean deliveries in MAMC's labor and delivery will be used. A perfusate consisting of Hank's balanced salt solution, bovine albumin, heparin, and gentamicin will be used to perfuse both the maternal and fetal circulations of the cotyledons. The Mg²⁺ concentration of the base solution is approximately 1.97 mg/dl. The maternal circulation of the study cotyledon will contain additional MgSO₄, with a magnesium ion concentration of 8 mg/dl. After establishing perfusion of an intact fetoplacental circuit, effluents will be collected at hourly intervals for four hours. These samples will be stored for determination of IL-6 levels by ELISA. The fetoplacental vascular tone will be continuously monitored throughout the experiment and recorded at 10-min intervals. Data will be analyzed using repeated measure analysis of variance.

Progress: All placental perfusion experiments necessary for this protocol have been completed. Treatment with MgSO₄ does not appear to affect placental production of IL-6 or fetoplacental vascular tone.



Detail Summary Sheets

Urogynecology,
Department of Obstetrics/Gynecology

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/107

Status: Terminated

Title: The Effectiveness of Mechanical Devices in the Prevention of Exercise Induced Urinary Incontinence in the Female Soldier

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG

Facility: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; COL Milo L. Hibbert, MC; COL Lawrence A. Decker, MC; COL Romeo P. Perez, MC; LTC (Ret) Richard A. Sherman, MS

Start Date:
06/20/1997

Est. Completion Date:
Nov 97

Periodic Review:
06/22/1999

Study Objective: To determine the effectiveness of mechanical devices in the prevention of exercise induced incontinence in the female soldier.

Technical Approach: Our recent study of urinary incontinence among female soldiers revealed that 30 percent use precautions of various types to help prevent urinary incontinence in the field or during exercise. We propose to study the effectiveness of four types of mechanical devices for the prevention of urinary incontinence in female soldiers by comparing perineal pad weights after exercise with and without the mechanical devices. Multichannel urodynamic parameters will also be compared with and without the mechanical devices in place. This will objectively document the effectiveness of each device in the treatment of urinary incontinence during exercise.

Progress: No patients have been entered. The investigators are still attempting to get the devices for the study acquired through their departmental budget, so study has been terminated.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/108

Status: Ongoing

Title: A Pilot Study for Transanal Ultrasonography (TAUS) in the Repair of Episiotomy Anal Sphincteroplasty

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG

Facility: MAMC

Associate Investigator(s): CPT Jerome L. Buller, MC; COL Milo L. Hibbert, MC; COL Lawrence A. Decker, MC; LTC George McClure, MC; LTC Frederick B. Brown, MC; COL Romeo P. Perez, MC; LTC (Ret) Richard A. Sherman, MS; CPT Patrick J. Woodman, MC

Start Date:
06/20/1997

Est. Completion Date:
Nov 97

Periodic Review:
07/27/1999

Study Objective: To assess the efficiency of intra-operative transanal ultrasound (TAUS) in the repair of the anal sphincter at episiotomy.

Technical Approach: Transanal ultrasonography (TAUS) has proven to be an effective means of assessing the structure and function of both the internal and external anal sphincters. Preliminary studies at Madigan Army Medical Center have shown that the intra-operative use of TAUS provides rapid and precise identification of both the internal and external anal sphincters, as well as immediate assessment of sphincter continuity and the success of sphincteroplasty. We propose to determine if the intra-operative use of TAUS will improve the anatomical and functional outcome of (a) episiotomy repair and (b) sphincteroplasty. (a) One hundred obstetric subjects at 28 weeks gestation or greater will be evaluated by endoanal ultrasound, pudendal nerve velocity and anal manometry to obtain initial. Episiotomies will be rendered only if obstetrically indicated. Those subjects requiring episiotomies at delivery will be randomly assigned to one of two groups. Those who will receive TAUS, and those who will not receive TAUS for episiotomy repair if episiotomy is indicated at delivery. Those subjects not requiring episiotomy will be dropped from the study. (b) In addition, twenty gynecologic subjects scheduled to undergo and sphincteroplasty will receive identical pre-operative evaluations of anal manometry, pudendal nerve velocities and endoanal ultrasonography to establish pre-operative values. They will be randomly assigned to one of two groups, those having repair with the aid of TAUS, and those undergoing sphincteroplasty without the aid of TAUS. All subjects (both obstetric and gynecologic) will be evaluated six weeks after surgery with repeat and manometry, pudendal nerve velocity and endoanal ultrasound. Pudendal nerve velocities, internal and external and sphincter length and width, manometric pressures, and pelvic organ prolapse quantification (POPQ) scores will be compared.

Progress: 4 subjects have been entered in FY 99 for a total of 32 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/102

Status: Ongoing

Title: Comparison of Tolterodine and Oxybutinin for the Treatment of Urinary Incontinence among Female Soldiers

Principal Investigator: COL Gary D. Davis, MC

Department: OB/GYN, UG

Facility: MAMC

Associate Investigator(s): CPT Patrick J. Woodman, MC; COL Milo L. Hibbert, MC; CPT Vanessa D. Dance, MC; MAJ Stephen D. Seymour, MC; COL Romeo P. Perez, MC; CDR (Res) Dennis A. Kelly, Ph.D.; LTC (Ret) Richard A. Sherman, MS

Start Date:
10/26/1999

Est. Completion Date:
Sep 01

Periodic Review:
N/A

Study Objective: 1) To determine the relative effectiveness of Tolterodine and Oxybutinin in the treatment of urinary urge incontinence in female soldiers during exercise. 2) To determine incidence and severity of anticholinergic side effects of Tolterodine and Oxybutinin in female soldiers. 3) To determine whether Tolterodine and Oxybutinin have significant cognitive effects on work performance tasks. 4) To determine changes in quality of life and work performance during treatment of urinary urge incontinence with Tolterodine and Oxybutinin.

Technical Approach: Sixty active duty female soldiers with urge incontinence will be recruited through a letter sent to all female soldiers at Fort Lewis, Washington. Each subject will initially undergo a standard evaluation of the lower urinary tract. The urodynamic evaluation will include uroflometry, with post-void residual urine volume measurement, retrograde provocative water cystometry, resting and stressed urethral axis determination, and direct visualization testing of fluid loss with stress. Urethral pressure profilometry with urethral closure pressures will also be performed. The subjects will then be evaluated one week later with ambulatory cystometric recordings. The subjects will be fitted with the UPS 2020 ambulatory measurement system. The intravesical and intravaginal pressures will be recorded with flexible 3mm microtip inserted 6cm from the urethral meatus and above the levator plate vaginally. The subjects will be given instructions to record events on the keyboard of the UPS 2020 ambulatory urodynamic recording system as they occur, and to proceed with the work or exercise which commonly produce their urinary incontinence. All subjects will be asked to complete a standard questionnaire which will assess the number and severity of the incontinent episodes they are experiencing. In addition they will complete a standard questionnaire which will assess job satisfaction and a standard quality of life survey. Once baseline values for the number and magnitude of detrusor contractions have been obtained, the subjects will be randomly assigned to one of three groups: Group I - Twenty subjects will receive placebos (one tablet twice a day), Group II - Twenty subjects will receive Oxybutinin (5mg twice a day), Group III - Twenty subjects will receive Tolterodine (1 mg twice a day). All subjects will be re-tested after one week of therapy by both stationary and ambulatory urodynamic studies. Comparison will be made among the groups as to the reduction of the amplitude and frequency of uninhibited detrusor contractions. The subjects will repeat the standard questionnaire, which assess the number and severity of incontinent episodes as well as job satisfaction and quality of life. They will also list the number of times as well as rate the severity of which they experienced (1) dry mouth, (2) headache, (3) visual disturbances, and (4) inability to perspire during exercise. All subjects who still complain of urinary urge incontinence at the end of one week of therapy will have their medication increased as follows: Group I - Increased to two tablets twice a day, Group II - Oxybutinin increased to 5 mg three times a day, Group III - Tolterodine 2mg twice a day. All subjects will be re-tested at the end of the second week of therapy by both stationary and ambulatory urodynamics as well as with the cognitive test battery and the questionnaires. Comparisons will be made among the groups as to the reduction of the amplitude

and frequency of inhibited detrusor contractions. The subjects will repeat the standard questionnaire, which assess the number and severity of incontinent episodes as well as job satisfaction and quality of life. They will also list the number of times as well as rate the severity of which they experienced (1) dry mouth, (2) headache, (3) visual disturbances, and (4) inability to perspire during exercise.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/144

Status: Ongoing

Title: Operative Endoscopy and Surgical Management of the Bowel and Urinary Tract Injuries in Gynecologic Surgery in the Pig (*Sus scrofa*)

Principal Investigator: COL Mark E. Potter, MC

Department: OB/GYN, UG

Facility: MAMC

Associate Investigator(s): COL Lawrence A. Decker, MC; COL Gary D. Davis, MC; COL Roderick F. Hume Jr., MC; LTC Byron C. Calhoun, MC; MAJ Elisabeth Hancock, MC; MAJ Richard K. Wagner, MC; MAJ Martin L. Ladwig, MC; MAJ Christina Apodaca, MC; CPT Patrick J. Woodman, MC; MAJ Stephen D. Seymour, MC; MAJ Gregory E. Chow, MC; MAJ Peter G. Napolitano, MC

Start Date:
09/19/1997

Est. Completion Date:
Sep 00

Periodic Review:
10/26/1999

Study Objective: To familiarize residents in OB/GYN with techniques of management of bowel and urinary tract injury with suturing or stapling techniques. To familiarize residents with techniques for colostomy, ileostomy, ureteroneocystostomy and vascular injury repair. To expand the operative endoscopy experience of OB/GYN Residents and Staff, prior to utilization in humans. Familiarity with these techniques will allow an increased margin of safety for patients in gynecologic surgery and better prepare the gynecologic surgeon to assist in general surgery patients when bowel or urinary tract procedures or repair are required. Increased operative endoscopy experience will minimize operating time and potential complications when utilized in the clinical setting.

Technical Approach: With the animal in the supine position, a midline incision will enter the abdomen and repair of lacerations and anastomosis will be performed by standard techniques. Additional surgical procedures may include ureteroneocystostomy. The abdomen will be closed. A second episode of surgery will occur 3-4 weeks later and additional procedures including colostomy, loop ileostomy, and vascular injury repair will be carried out. Following the second surgical episode, the animal will not be allowed to recover from anesthesia. In some cases an animal may be used for a single training episode. When this occurs, euthanasia will be carried out at the completion of the session. When follow-up evaluation of a surgical procedure is desired, no more than one procedure will be done on that animal during the first episode. The animal will then be allowed to recover and will be re-anesthetized and reoperated 3-4 weeks later. During the second surgical episode, more than one procedure may be performed. The animal will be euthanized at the end of the episode while still under general anesthesia. Procedures which would normally involve any postoperative care beyond normal husbandry will only be performed during the last surgical episode to which that particular animal is subjected. The animal will be euthanized while still under general anesthesia.

Progress: No training sessions have been held the last two years. The protocol has recently received its annual review, has been updated, and training sessions are planned in the future.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/103 **Status:** Ongoing

Title: Prevalence of Anal Incontinence in New Mothers Trial (PAINT)

Principal Investigator: CPT Patrick J. Woodman, MC

Department: OB/GYN, UG **Facility:** MAMC

Associate Investigator(s): COL Gary D. Davis, MC; MAJ Ronald J. Place, MC; CPT Vanessa D. Dance, MC; COL Romeo P. Perez, MC; James M. Nelson

Start Date:
9/28/1999

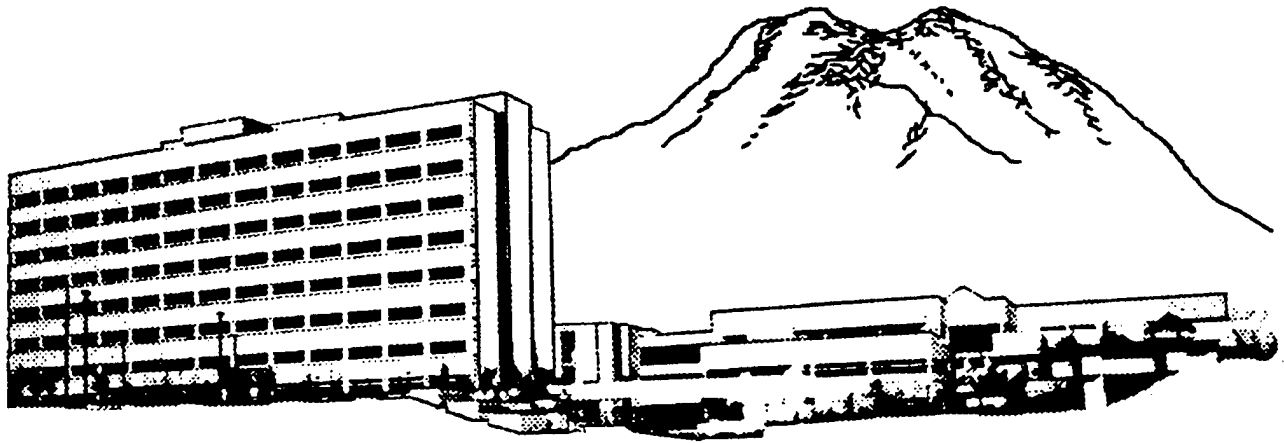
Est. Completion Date:
Aug 00

Periodic Review:
N/A

Study Objective: To discover ways to prevent recognized and occult anal sphincter rupture and improve long-term primary closure outcome; thereby helping to prevent the development of future fecal and flatus incontinence.

Technical Approach: This study will investigate the occult anal sphincter disruption rate as a result of a variety of delivery types in primigravid women. The predominant method of episiotomy at MAMC is midline, which may affect the occult anal sphincter disruption rate. Primigravid women will be recruited from the OB/GYN clinic population and asked to participate postpartum. They will fill out a questionnaire, which will ask about their deliveries, their medical, surgical, colorectal histories and some randomization information. The investigator, who is blinded to the type of delivery, whether the patient had an episiotomy or tear, and other pertinent history, will perform an endoanal ultrasound of the anal musculature at approximately 6 weeks postpartum. Thickness and morphology of the internal and external sphincter and perineal body will be performed and recorded on a data sheet (attached). Those patients in which defects are found will be asked to return at approximately 6 months for repeat examination. At a later date, a second investigator will compare and verify the information requested in the patient questionnaire and obtain information about diagnoses, malposition, degree of episiotomy and extension, and labor augmentation. This will be recorded on the verification sheet. The patients will be identified by coded numbers, cross-classified to FMP/SS#. All data will be entered and analyzed using SPSS, Primer of Biostats, or similar statistical package. A small group of women (approximately 10) will be recruited to participate in an investigation on how the anal sphincter musculature morphology changes during the three trimesters of pregnancy. Each woman will undergo a series of three anal ultrasonographic examinations, one per trimester. These subjects would also the patient questionnaire, and the same data points would be obtained: Thickness and morphology of the internal and external anal sphincter and the perineal body. At the end of the trial, each woman will be asked if she would like to continue with the main study protocol, which would require a separate consent form.

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

Department of Pathology

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/070 **Status:** Completed

Title: The Stability of Reagents Used in A DEPMEDS Clinical Chemistry Analyzer

Principal Investigator: CPT Arthur A. Russell, MS

Department: Pathology

Facility: MAMC

Associate Investigator(s): None.

Start Date:
05/22/1998

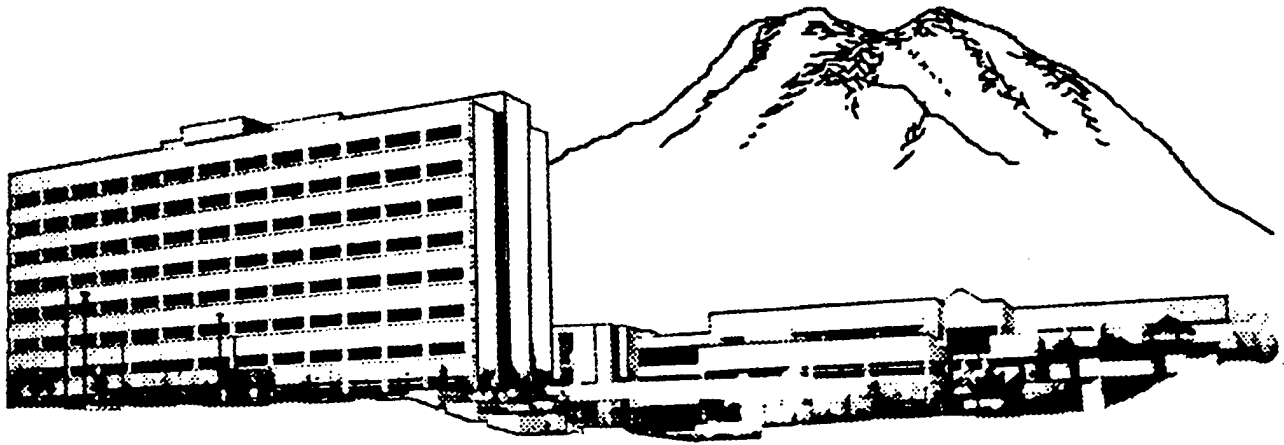
Est. Completion Date:
May 99

Periodic Review:
06/22/1999

Study Objective: To determine the stability of reagents for a clinical chemistry analyzer used by field units of the United States Army when the reagents are not refrigerated or frozen according to the manufacturer's specifications.

Technical Approach: The performance of clinical reagents for the DT-60 clinical chemistry analyzer will be tested for stability at ambient temperatures and compared to the performance of reagents stored according to the manufacturer's recommendations. Periodically the manufacturer's controls will be run 5 times using reagents that have been refrigerated or frozen (control group) or exposed to an ambient temperatures in a laboratory environment (experimental arm). The change in mean (bias) and precision (coefficient of variation) observed will be subjected to a t-test to determine the significance of the changes observed.

Progress: Conclusions: Total protein reagent is predictably robust, since its primary constituents are inorganic reagents. Reagents with enzyme constituents presumably degrade faster at room temperature because of the susceptibility of enzymes to oxidation and denaturation. Nevertheless, these results show that the degradation of solid phase reagents is not inevitable when refrigeration is unavailable. At least one assay on the DT60 analyzer shows great robustness with reagents stored at room temperature.



Detail Summary Sheets

Department of Pediatrics

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/111 **Status:** Terminated

Title: Validation of the Symptom-Free Days Instrument in Children with Asthma

Principal Investigator: LTC Edward R. Carter, MC

Department: Pediatrics

Facility: MAMC

Associate Investigator(s): COL Donald R. Moffitt, MC; Dana Winter, RCP; Jetta C. Joseph, Pharm.D.; Sean D. Sullivan, Ph.D.; David Blough, Ph.D.; Jocan Fagan, M.S.; Kevin B. Weiss, MD, MPH

Start Date:
09/15/1998

Est. Completion Date:
Feb 88

Periodic Review:
N/A

Study Objective: To determine the reliability and the validity of the Symptom-Free Days (SFD) instrument (questionnaire) as an asthma outcomes measure in children ages 6-17 years-old with mild or moderate persistent asthma and whether the responses derived on the questionnaires concerning asthma outcomes and quality of life from asthmatic children >10 years-old are similar to those obtained from their parents. We want to determine whether patient self-reporting and parental reporting of their child's symptoms are similar.

Technical Approach: This is a one year prospective study of children, ages 6-17 years old, with mild-moderate persistent asthma. Both the children and their parents will be asked to participate. They will be randomized into one of two groups; Group 1 will be followed two 2-week intervals and Group 2 will be assessed during two 4-week intervals. The only difference between the study groups will be the length of study time intervals. Initial visit, all patients will undergo spirometry, asthma severity assessment and given a peak flow meter and diary in which to record peak flow measurements. Group 1 patients will receive a phone call one week after the initial visit and then return for a second clinic visit two weeks after the initial visit. The asthma questionnaires will be filled out by the study investigators and spirometry repeated at this second visit. Patients will be given one month off and then repeat the process. Group 2 patients will have the initial visit followed by phone calls the next 3 weeks and return for their second clinic visit at week four. At this second visit, questionnaires will be completed concentrating on the last 2 weeks before the clinic visit. Thus, patients in both groups will be recalling symptoms from a 2-week period. After one month off, the process is repeated.

Progress: This study was completed without enrolling patients from MAMC; therefore, the PI terminated this study 26 Feb 99.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/049 | Status: Terminated |
| Title: National Standardization Study of the Brigance Infant-Toddler Screen | | |
| Principal Investigator: MAJ Beth E. Davis, MC | | |
| Department: Pediatrics | Facility: MAMC | |
| Associate Investigator(s): COL William O. Walker, Jr., MC; COL Russell D. Hicks, MC | | |
| Start Date: 04/27/1999 | Est. Completion Date: Apr 99 | Periodic Review: N/A |

Study Objective: To validate a new method to developmentally screen infants and toddlers.

Technical Approach: The study involves testing 12-25 children in the 0-2 year age range. A Guide for Examiners is included in the distribution packet along with the parent questionnaires and the examiner score sheets. Toys are provided for use in specific age appropriate tasks of the Brigance Infant Toddler Screen (BITS). Examiners are the Madigan PI and AI's for two-half day sessions. Interviews and screens will occur in the Developmental Pediatrics clinic. No nursing personnel or extra supplies are needed. When parents bring infants and toddlers to their normal well baby checks at the MAMC Well Baby Clinic, the nurse practitioner and physicians will distribute a flyer to explain the developmental screen and how the parent can enroll their child in the study. If parents have questions prior to enrollment, the MAMC PI is the point of contact. If not, parents are instructed to call the clinic manager and request a "Little BITS" appointment. On the day of the screen, parents and infants will arrive in the Developmental Clinic at 45 minute intervals. Inside the parent questionnaire packet is a full consent form for parent and examiner signature. About 15 minutes is needed to administer the screen and document observations. Another 10-15 minutes is set aside for the parent interview and clinical judgment items. The parent forms are written at the 4th grade level so most of this form can be completed independently. If not, the examiner has a few more minutes to finish administering the parent form as an interview. If the MAMC examiners have any concerns about the child's development based on the BITS, the parents will be offered a follow up developmental appointment to perform traditional standardized screening measures.

Progress: 12 children were enrolled in this study at MAMC in FY 99. All 12 completed the evaluation. However, the principal investigator felt the tool was inadequate and not age-appropriate for the subject's evaluation. This information was relayed to the study sponsor and the protocol was terminated at MAMC, 24 Jun 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 90/092 **Status:** Ongoing

Title: Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses

Principal Investigator: LTC Mary P. Fairchok, MC

Department: Pediatrics **Facility:** MAMC

Associate Investigator(s): COL James S. Rawlings, MC; MAJ Thomas A. Perkins, MC; LTC Joanna C. Beachy, MC; COL Marvin S. Krober, MC

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|----------------------------------|--|---------------------------------------|
| Start Date: 07/20/1990 | Est. Completion Date: Sep 91 | Periodic Review: 07/27/1999 |
|----------------------------------|--|---------------------------------------|

Study Objective: To analyze laboratory assays for detection of HIV infection in children and to correlate the results with the clinical status of the child.

Technical Approach: Technical Approach: This will be a multicenter study funded by Walter Reed Army Medical Center. The plan of this protocol is to evaluate the usefulness of new assays as they are developed, using blood from HIV-infected or high risk children. Blood will be sent to the laboratory for standard HIV testing using those tests that are most developed. Surplus will be utilized for less well developed assays or stored for future analysis. Results from the tests will be compared to conventional assays used to diagnose adult HIV infection, such as ELISA, western blot, and culture, to determine their usefulness in children. These specimens will also be used to develop improvements and new methods for HIV testing in children. This analysis will be done in 120-150 individuals at three month intervals to determine if changes in these tests correlate with changes in the patient's clinical or immunological status. Most of the data generated in this protocol will be qualitative and will be correlated to quantitative clinical data using Spearman's Rank Correlation. Logistic regression will be used for correlating the numerical data to noncontinuous clinical measures. Analysis of data from different clinical groups (patients who remain asymptomatic versus those who develop AIDS) will be compared using two-way ANOVA to determine significant differences between clinical groups.

Progress: One new patient was entered in this study in FY 98 with no adverse events. No patients enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/056

Status: Ongoing

Title: Physiological, Behavioral, and Feeding Effects of Neonatal Physical Therapy Procedures on Preterm Infants in a Neonatal Intensive Care Unit Setting

Principal Investigator: Jane K. Sweeney, Ph.D., PT, PCS

Department: Pediatrics

Facility: MAMC

Associate Investigator(s): MAJ Roger M. Hinson, MC; MAJ Wanda A. Barfield, MC

Start Date:

02/21/1997

Est. Completion Date:

Oct 99

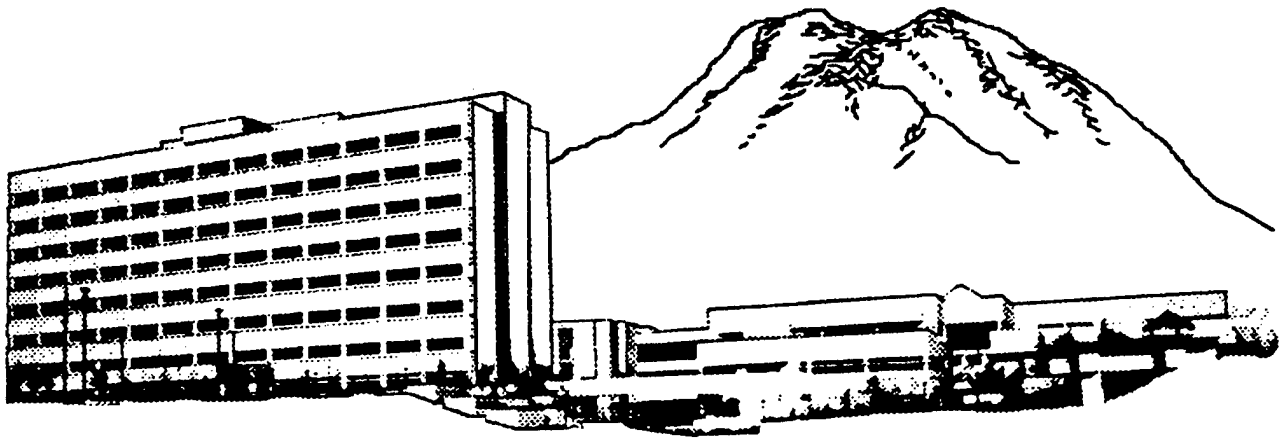
Periodic Review:

03/23/1999

Study Objective: 1) To study and compare the physiological tolerance of medically stable, preterm infants to three interventions: neonatal hydrotherapy, infant seat positioning with social stimulation, and a control intervention of no physical handling or social stimulation; 2) to investigate and compare the behavioral tolerance of medically stable, preterm infants to three interventions in a neonatal intensive care unit: neonatal hydrotherapy, infant seat positioning with social stimulation, and a control intervention of no physical handling or social stimulation; 3) to evaluate and compare the effects of neonatal hydrotherapy, infant seat positioning with social stimulation and a control condition of no handling or social stimulation on oral feeding performance in medically stable, preterm infants; 4) to compare the length of hospital stay among subjects in the three intervention groups.

Technical Approach: This is a prospective, quasi-experimental study of the physiological, behavioral, feeding, and cost effects of neonatal physical therapy procedures on 60 medically stable, preterm infants (31 to 35 weeks post-conception) in a neonatal intensive care unit setting. A randomized block design is used with postconceptual age as the blocking variable. After an 10 minute initial baseline phase, subjects are randomly assigned to a physical therapy intervention followed by oral feeding and concluded by a 10 minute recovery baseline phase. The intervention conditions are a 15 minute session of neonatal hydrotherapy (20 subjects), infant seat positioning with social stimulation (20 subjects), or a control condition of no handling (20 subjects). The physiological measures of heart rate, respiratory rate, mean arterial pressure, temperature, intracranial pressure, and oxygen saturation are recorded continuously and will be compared across intervention groups among the four phases of the study using a repeated measures analysis of variance. The behavioral responses of behavioral state, motor stress cues (finger splay, arm salute, trunk arch), and autonomic stress cues (hiccoughs, sneezes, yawns, regurgitation) are measured continuously by videotape and scored at two minute intervals. Between group comparisons of behavioral responses will be analyzed by analysis of variance (ANOVA). Feeding performance of volume ingested, duration of feeding, transition from gavage to oral feedings and weight gain will be reported descriptively and compared across intervention groups with ANOVA. The length of hospital stay and estimated cost of hospitalization in the NICU will be calculated and compared among all intervention groups using ANOVA.

Progress: 38 subjects have been entered in FY 99 for a total of 40 subjects enrolled.



Detail Summary Sheets

Pharmacy

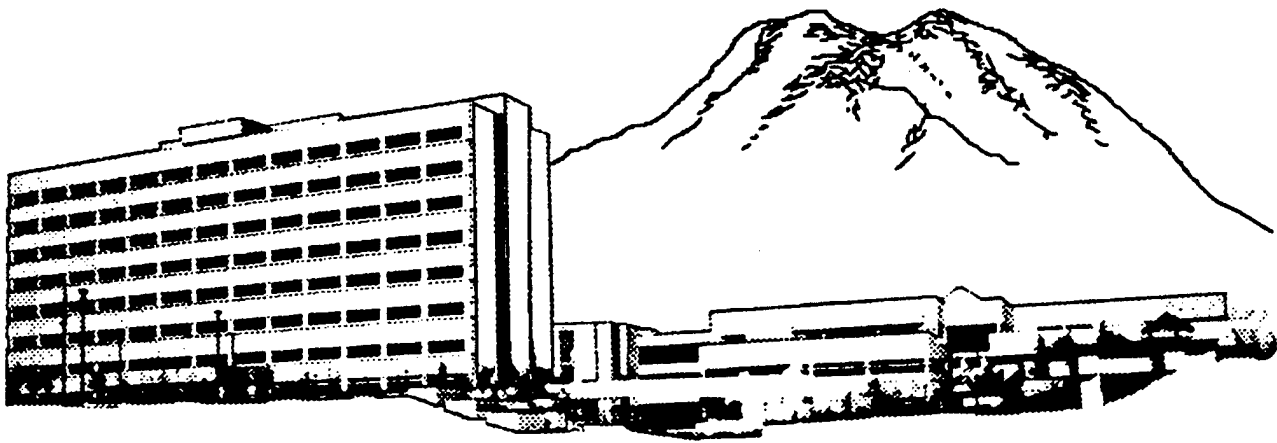
Detail Summary Sheet

| | | |
|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/106 | Status: Ongoing |
| Title: Pilot Study to Determine the Effectiveness of Glutamine in the Treatment of Paclitaxel Induced Myalgia, Arthralgia and Neuropathy | | |
| Principal Investigator: COL Dennis R. Beaudoin, MS | | |
| Department: Pharmacy | | Facility: MAMC |
| Associate Investigator(s): MAJ Matthew P. Jones, MC; MAJ David E. McCune, MC; MAJ Ines J. Sanchez-Rivera, MC | | |
| Start Date: 9/28/1999 | Est. Completion Date: Dec 00 | Periodic Review: N/A |

Study Objective: To determine the efficacy of glutamine in treating the common, non-hematological, dose-limiting toxicities (myalgia, arthralgia and neuropathy) associated with the use of paclitaxel.

Technical Approach: All patients receiving paclitaxel (doses ≥ 135 mg/M²) will be asked to participate in the study. Those consenting will be provided pain scales (arthralgia / myalgia / neuropathy) and counseled how to complete them prior to their first paclitaxel dose. Patients reporting arthralgia, myalgia or neuropathy will be provided glutamine at time of next paclitaxel dose. Post treatment pain scales completed by the patient will then be collected. Comparison of pre and post treatment observations will be completed to determine if glutamine was effective in relieving paclitaxel induced toxicities (arthralgia / myalgia / neuropathy).

Progress: This protocol was recently approved and has not yet started recruiting subjects.



Detail Summary Sheets

**Physical Therapy,
Physical Medicine & Rehabilitation Service**

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/094

Status: Terminated

Title: A Prospective Randomized Trial of Controlled Compression Cryotherapy versus Institutionalized Cryotherapy in Post-Operative Anterior or Posterior Cruciate Ligament Reconstruction Patients

Principal Investigator: CPT Roger W. Dougherty, SP

Department: PMRS/Physical Therapy

Facility: MAMC

Associate Investigator(s): LTC Patrick St Pierre, MC; COL (ret) Joseph R. Dettori, SP; Jeffrey T. Hermsmeyer

Start Date:
07/17/1998

Est. Completion Date:
Apr 99

Periodic Review:
07/27/1999

Study Objective: Determine if controlled compression cryotherapy (Aircast/Cryocuff) is better at reducing pain and edema and enhancing weight-bearing and range of motion versus standard cryotherapy care in post-operative ACL/PCL patients.

Technical Approach: Subjects will be randomly assigned to two study groups. Group A will serve as the control group and undergo the standard post-operative care which includes an ice-bag on top of the bulky dressing while in the PACU, followed by cryotherapy at home and in PT per standard protocol. Group B will serve as the study group and will receive less post-operative dressing in order to accommodate the Cryocuff cooling system. Group B will receive the cryosystem while in the PACU and will receive a unit for home use once discharged from the hospital. All subjects will be required to apply their respective cryotherapy for twenty minutes QID for the fourteen days post surgery and to annotate their cryotherapy times each day on the compliance log. Subject data will be collected at post-operative days three, seven and fourteen.

Progress: 15 subjects have been entered in FY 99 for a total of 25 subjects enrolled. The study was terminated do to the ETS of the PI.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/027 **Status:** Ongoing

Title: Mandatory Physical Training and Physical Readiness in Postpartum Soldiers

Principal Investigator: COL Nancy E. Henderson, SP

Department: PMRS/Physical Therapy **Facility:** MAMC

Associate Investigator(s): COL Roderick F. Hume Jr., MC; CPT Mary C. Adams, MC

Start Date:
01/26/1999

Est. Completion Date:
Jan 02

Periodic Review:
N/A

Study Objective: (1) To compare the proportion of MPPPT trained soldiers who pass the Army Physical Fitness and body-fat standards at 6 and 12 months postpartum to the proportion of non-pregnant controls who pass during the same time interval, (2) to compare injury rates in MPPPT trained soldiers during the postpartum period to the injury rates in non-pregnant controls during the same time intervals, (3) to compare postpartum fitness, body-fat and injury rates in MPPPT trained soldiers to postpartum soldiers exempt from MPPPT and (4) to compare postpartum fitness, body-fat and injury rates in MPPPT trained soldiers to non-MPPPT trained postpartum soldiers (an historical control).

Technical Approach: Subjects will be scheduled for 3 appointments during this one year study; day 1, 6 months and one year. At each appointment body composition will be measured and subjects will be asked to complete a questionnaire, to include questions about age, ethnic background and exercise patterns. Medical records will be reviewed for injuries or illness. PT scores from the last PT test taken and from the next 2 PT tests will be recorded.

Progress: No subjects have been entered, awaiting funding from study sponsor.

Detail Summary Sheet

| | | |
|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/094 | Status: Completed |
| Title: Injury Rates and Interventions in the 75th Ranger Regiment | | |
| Principal Investigator: COL Nancy E. Henderson, SP | | |
| <hr/> | | |
| Department: PMRS/Physical Therapy | Facility: MAMC | |
| Associate Investigator(s): CPT Daniel C. Norvell, SP; COL (ret) Joseph R. Dettori, SP; CPT Daniel C. Norvell, SP | | |
| <hr/> | | |
| Start Date: 9/28/1999 | Est. Completion Date: Jul 99 | Periodic Review: N/A |

Study Objective: 1) To describe and compare the impact of a battalion level Sports Medicine Clinic on regimental readiness as determined by injury rates, severity of medical profiles, and rates of medically non-deployable personnel. 2) To describe and compare absolute risk of injuries occurring in Rangers by battalion. 3) To describe and compare relative risk of injuries occurring in 2nd Battalion verses 1st and 3rd Battalion. 4) To describe and compare profile days and severity of profile by battalion. 5) To describe and compare relative risk of profile days and severity of profiles in 2nd Battalion verses 1st and 3rd Battalion. 6) To describe risk factors for injury.

Technical Approach: This study is designed to follow all three combat battalions of the 75th Ranger Regiment prospectively through their Joint Readiness Operational Cycle (JORT). This is a 39-week cycle divided into three phases that culminates with the assumption of duties as the primary alert battalion. The primary alert battalion is ready for deployment to a designated target within 18 hours of an alert. Demographic data will be obtained on all soldiers who volunteer for the study. Personnel rosters will be available to compute person-time data. Injury will be obtained daily during sick call.

Progress: Data on 605 subjects have been collected during FY 99. Data suggest that there are less medically non-deployable soldiers in 2nd battallion verses 1st and 3rd battalions. In fact, the risk of being medically non-deployable in 2nd battalion is 50 percent less than in the comparison battalion.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/030

Status: Ongoing

Title: Physical Therapy Treatment Effectiveness for Osteoarthritis of the Knee: A Prospective, Randomized, Controlled Comparison of Supervised Clinical Exercise and Manual Therapy Procedures versus A Home Exercise Program

Principal Investigator: MAJ Robert L. Matekel, SP

Department: PMRS/Physical Therapy

Facility: MAMC

Associate Investigator(s): COL Gail Deyle, SP; COL Nancy E. Henderson, SP; Skyeann Allison; MAJ Jeremy Hutton, SP; CPT John Stang, SP; CPT David Gohdes, SP; CPT Mike Ryder, SP; CPT Matt Garber, SP

Start Date:
12/18/1997

Est. Completion Date:
Oct 98

Periodic Review:
12/15/1998

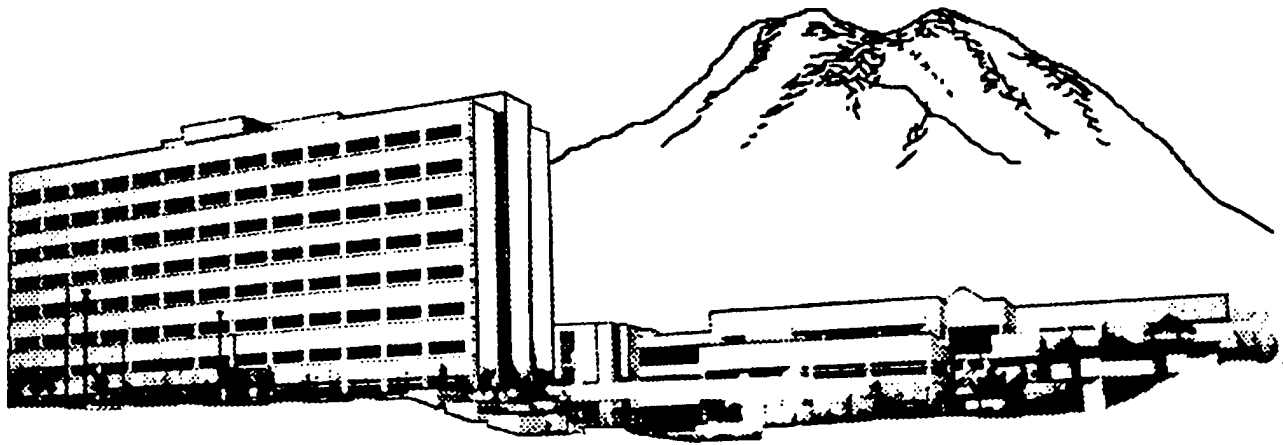
Study Objective: To evaluate the effectiveness of manual physical therapy treatment for osteoarthritis of the knee compared to a home exercise program.

Technical Approach: Subjects will be randomly assigned to one of two treatment groups. Subjects will undergo a thorough clinical examination by the treating physical therapists and then turned over to a trained research assistant (tester) blinded to the group assignment. The tester will obtain measurements of the dependent variables using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and a six-minute walk test. The subjects will be returned to the treating therapist and treatment will begin as per group assignment.

Group 1 will perform an in-clinic series of closely supervised exercises. Subjects will also receive manual physical therapy as indicated by examination and do home based exercise on the days when they are not in clinic. At the end of eight sessions the subject will be retested with the tester 2 days after the last exercise session and at the same time of day as the pretest.

Group 2 will receive a home based exercise program, instructed to the subject by the treating physical therapist, and a detailed supporting handout and compliance log. Subjects will return to the clinic 2 weeks later to ensure proper execution of the exercises and compliance with the program. After completing 4 weeks the subject will be retested with the tester 2 days after the last exercise session and at the same time of day as the pretest.

Progress: One subject has been entered in FY 99 for a total of 33 subjects enrolled.



Detail Summary Sheets
Preventive Medicine Service

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/061 **Status:** Completed

Title: MAMC Stethoscopes and Methicillin Resistant Staphylococcus Aureus (MRSA)

Principal Investigator: LTC Leon B. Bybee, MC

Department: Preventive Medicine

Facility: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC

Start Date:
03/23/1999

Est. Completion Date:
May 99

Periodic Review:
N/A

Study Objective: To determine the frequency of MRSA found on the diaphragms of MAMC stethoscopes.

Technical Approach: Procedures: On a predetermined hospital day, as specified by the MAMC Commander, a large contingent of pre-trained investigative personnel from 62nd Medical Group will make a previously-unannounced sweep of all MAMC wards and clinics to culture all personal stethoscopes as well as all stethoscopes on nursing carts/screening rooms. In order to ensure maximum cooperation from all, the hospital commander or a designated representative will announce over the hospital public address system that tag-identifiable personnel will be in all MAMC wards and clinics to culture all personal and hospital stethoscopes. An appeal for restraint by those using personal stethoscopes not to immediately clean them will then be made (Explaining that they will be asked when the stethoscope was last cleaned may also serve as a deterrent against immediate remedial cleansings). All designated investigators will then swab for culture (using recappable throat swabs) each and every stethoscope in current use. Investigators will annotate the job title (no names) of those bearing individual stethoscopes (ones in use each day by the same individual) on the appropriate swab casings as they are employed. They will also annotate information concerning the approximate day and time the stethoscope was last used and last cleaned, as reported by the owner of the stethoscope. Lastly, they will annotate the ward or clinic in which the culture was taken. Nursing cart/screening room stethoscope cultures will be performed on stethoscopes in current use as declared by the wardmasters concerned. Culture casings for this category of stethoscope cultures will be annotated with ward or clinic name only. When all culture swabs are completed in their assigned areas, investigators will assist those needing help, and then return all products to the clinical investigation laboratory for transfer to appropriate growth medium and incubation, per normal protocol. After sufficient time for incubation lapses, colonies will be counted and analyzed with information provided on swab casings. Should results suggest a need for remedial education of hospital personnel in proper attention to maintaining clean stethoscopes, a second study under an identical plan will be performed after that education (unknown requirements as yet) is complete. Should results suggest no need for remedial education, the a report of that will be made to all hospital personnel involved. No attempt will be made to incriminate any individuals by tracing any MRSA infection to an individual stethoscope.

Progress: Swabs were collected from the stethoscopes of house staff, attending staff, and nursing personnel in various departments of Madigan. Samples were administered to culture media and transported to the laboratory. All of the isolates were negative for MRSA. This study suggested that the levels of MRSA transmitted by stethoscopes at Madigan during the study period was low to none.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/062

Status: Completed

Title: Personal Cleanliness, Hygiene, Privacy, and Related Health Concerns of Female Soldiers in the Field Environment

Principal Investigator: LTC Leon B. Bybee, MC

Department: Preventive Medicine

Facility: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC

Start Date:
03/23/1999

Est. Completion Date:
Mar 99

Periodic Review:
N/A

Study Objective: To determine the current concerns of female soldiers in the FSB field environment as it pertains to personal cleanliness, hygiene, privacy, and related health.

Technical Approach: Survey questions will first cover demographic questions such as gender, race/ethnicity, marital status, number of children, number and length of past field exercises and deployments. Also a history of contraceptive use and past sexual activity in the field environment will be gathered for analysis. Statements requiring graded agree-vs.-disagree responses will include topics focusing specifically on hygiene issues, such as availability, condition, and relative privacy of latrines, both enroute and after arrival at past field destinations. Additional statements for graded response will include behavioral tactics taken when latrines were unavailable or deemed unacceptable, attitudes of gender resentment for those prone to make more of a mess, and perceptions of risk for acquiring a sexually-transmitted disease from a dirty latrine. Further statements for graded response will also include those concerning privacy for bathing when showers are not available as well as privacy for changing one's clothing when wet or soiled. Female-specific graded responses will also measure individual frustrations and general tactics (such as change of contraceptive) taken to address menstrual period problems in the field environment. Past male-female peer, immediate supervisor, and field health care provider attitudes concerning discrepant conditions- to include women's health issues in general- will also be individually assessed, again by way of specific graded-response statements. With this, additional graded response statements will inquire about the necessity (if any) to temper the "train as you fight" doctrine, when it comes to female health and hygiene challenges. Of course, discretion will be used to phrase graded-response statements so as not to be unnecessarily obtrusive or overly explicit in nature. Since 68 responses may be required for individual completion of the survey, a one-hour block of time should be needed for participant orientation and administration of the survey. No attempt will be made to determine what problems occurred during what field exercises/deployments in the past. Rather, a valid assessment of current experience and general attitudes is the ultimate goal of the survey.

Progress: 323 subjects have been entered in FY 99 for a total of 323 subjects enrolled. Substantial differences were found between male and female soldiers in several domains of field hygiene, focusing primarily on their "level of concern" and on their "coping behaviors".

Detail Summary Sheet

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|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 99/076 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: Immune Response to Community-Acquired *Campylobacter jejuni* Infection in United States Military Personnel on Deployment in Korat, Thailand (Cobra Gold 99)

Principal Investigator: COL James E. Cook, MC

Department: Preventive Medicine

Facility: MAMC

Associate Investigator(s): D Tribble

Start Date:
06/22/1999

Est. Completion Date:
Aug 99

Periodic Review:
N/A

Study Objective: 1) Characterize the immune response to community-acquired *C. jejuni* infection in U.S. military personnel deployed to Korat, Thailand during Cobra Gold 99. 2) Compare the ranges of immune response found in community-acquired and experimental *C. jejuni* infections.

Technical Approach: Volunteer enrollment will occur at the 47th Combat Support Hospital in Korat during the period of the Cobra Gold 99 exercise (May 10-30). Stool and blood samples will be processed and stored in the field laboratory in Korat and transported to AFRIMS and NNMC for analysis at exercise completion. Stool specimens will be cultured and bacterial diarrheal pathogens will be presumptively identified in the field laboratory in Korat. Further evaluation will be completed at AFRIMS. All *C. jejuni* isolates will be archived and transported to NMRC. Post-deployment blood specimen collection (during July 1999) for enrolled volunteers will occur at both Ft. Lewis, Washington and Schofield Barracks in Hawaii with on-site processing prior to transport to NMRC.

Progress: 30 subjects have been entered in FY 99. Major findings of this study thus far include the predominant role played by *Campylobacter* spp. as a cause of deployment-associated diarrhea in Thailand, an observed increase in clinical severity and recovery time in campylobacter-associated cases, and increasing rates of fluoroquinolone-resistant *Campylobacter* spp. Immunologic studies are ongoing and are expected to generate critical information needed in the effort to develop an effective *Campylobacter* vaccine.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/033

Status: Ongoing

Title: Breast Cancer Risk Assessment Among Women Beneficiaries Eligible for Medical Care in the Pacific Northwest, Region 11

Principal Investigator: LTC Jeffrey D. Gunzenhauser, MC

Department: Preventive Medicine

Facility: MAMC

Associate Investigator(s): MAJ Heidi P. Terrio, MC; Troy H. Patience, B.S.

Start Date:
02/23/1999

Est. Completion Date:
Dec 99

Periodic Review:
N/A

Study Objective: To measure the prevalence of major breast cancer risk factors among female DOD beneficiaries in TRICARE Region 11, to estimate mammography usage rates among female beneficiaries in TRICARE Region 11 and to advise female beneficiaries that there is a genetics screening program available to all through the Breast Cancer Initiative in Region 11.

Technical Approach: 16,000 women beneficiaries will be mailed a one-page anonymous questionnaire on risk factors for breast cancer, and preventive screening prevalence with regard to self-breast exam, clinical breast exam and mammogram. Three mailings will be sent out in an effort to try and get a better than 70% response rate. All recipients of this questionnaire will be offered genetic counseling.

Progress: 11,000 subjects have been entered in FY 99 for a total of 11,000 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/063 **Status:** Completed

Title: Attrition Rates for Military Recruits Receiving A Medical Waiver for Skin Conditions Compared to Those Without a Waiver

Principal Investigator: LTC John M. Wempe, MC

Department: Preventive Medicine **Facility:** MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC; RL Erickson; K Clark; LTC Margot R. Krauss, MC

Start Date:
04/27/1999

Est. Completion Date:
Mar 99

Periodic Review:
N/A

Study Objective: 1. Determine if military personnel who receive entry waivers for pre-existing skin conditions have a different attrition rate than military personnel who do not receive a waiver.

2. Determine if military personnel who receive entry waivers for pre-existing skin conditions have different hospitalization rates than military personnel who do not receive a waiver.

Technical Approach: The design is a matched cohort study of military personnel entering active duty between August 1996 through December 1997. Data on which individuals received entry waivers for pre-existing skin conditions will be obtained from Accession Medical Standards Analysis Research Activity (AMSARA) located at Walter Reed Army Institute of Research. Denominator, demographic and length- of-service information for each individual will also be obtained from AMSARA data sets. Survival analysis and the Generalized Wilcoxon Test will be used to determine if there is a difference in attrition rates between the two groups.

Progress: Most skin waivers were due to the following conditions; contact dermatitis, atropic dermatitis and nevus syndrome. Marines were 2.9 times as likely to have a medical event if granted a waiver for a dermatological condition. Although there was a significant statistical difference between recruits granted a waiver compared to those without a waiver with respect to a medical event, the actual difference was only 20 events over a two year period.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/030 **Status:** Completed

Title: Characteristics and Correlates of Asthma in the Military Population of the Northwestern United States

Principal Investigator: CDR Sylvia Y. N. Young, MC, USN

Department: Preventive Medicine

Facility: MAMC

Associate Investigator(s): LTC Jeffrey D. Gunzenhauser, MC; Kathleen E. Malone, Ph.D.; Anne McTiernan, M.D.

Start Date:
02/23/1999

Est. Completion Date:
Mar 99

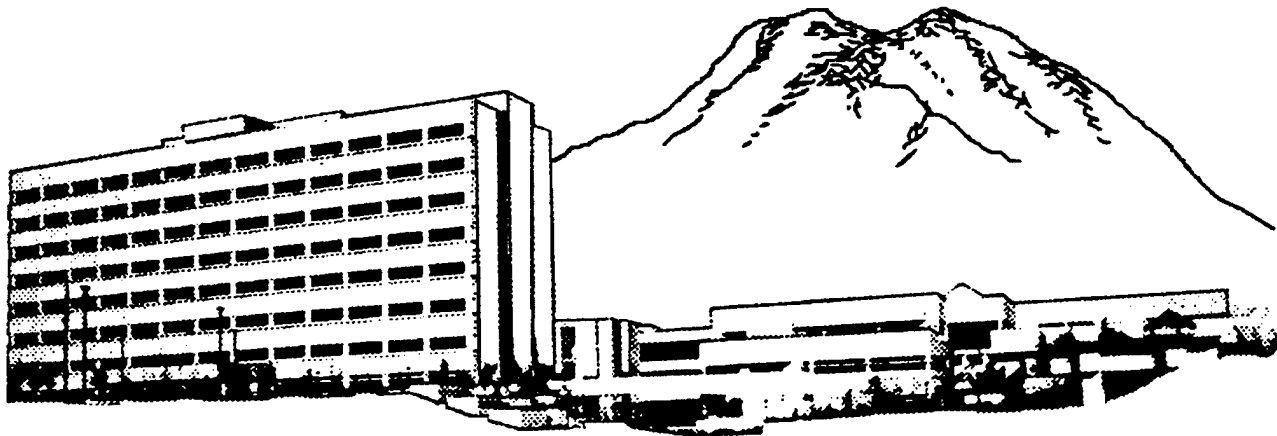
Periodic Review:
N/A

Study Objective: To study military population-based data, to examine comorbidity factors, primarily obesity, in patients with asthma compared to patients without asthma, and to measure the associations of these comorbidities with asthma controlling for potential confounders, such as smoking and physical activity. A second purpose is to examine health care utilization in patients with asthma with increasing body mass index compared to asthmatic patients with low body mass index, controlling for potential confounders.

Technical Approach: Patients enrolled in TRICARE Region 11, January 1997 to October 1998 (estimated 45,000), will be studied through the TRICARE Health Enrollment Assessment Review (HEAR) questionnaire. Asthma cases will be identified as those cases self-defined on the HEAR questionnaire and verified as having been prescribed asthma medications on the Composite Health Care System (CHCS). Controls will be identified as those cases indicating on the HEAR questionnaire that they have not been diagnosed with asthma. Using a case control study design, odds ratios for the primary exposures of interest, overweight and obesity, will be calculated from self-reported height and weight from the HEAR questionnaire, in patients with asthma compared to patients without asthma. Odds ratios will be calculated for the following secondary exposures of interest: hypertension, heart attack, liver disease, kidney disease, stomach ulcer, anxiety or personality disorder, and depression, all self reported in patients with asthma compared to patients without asthma.

Data will be analyzed to determine the prevalence of obesity and asthma for different age groups, sex, racial/ethnic groups, marital status, and military status, and possible confounding factors such as smoking and physical activity. For univariate analysis, the unadjusted association of asthma with other factors will be determined. Proportions will be compared using the chi-square test with Yates' correction or Fisher's exact test. Significance will be determined at the 0.05 level. Multiple logistic regression analysis will be performed using SPSS to determine the odds of the dependent variable asthma, given the predictor variable of body mass index plus confounders such as smoking. Additionally, the data will be analyzed to see if a dose-response relationship may be determined such that with increasing body mass index, there is increasing severity of asthma, as measured by the following indices: increase in number of different prescription medications taken, increase in the frequency of visits to an emergency room or urgent care clinic over the prior year, and an increase in frequency of hospitalizations over the prior year.

Progress: 2,788 subjects with asthma were compared to 39,637 controls. Increasing body mass index is a key determinant predicting prevalence of asthma, and if determined to be etiologically related asthma incidence, is a potentially modifiable risk factor for asthma.



Detail Summary Sheets

Department of Psychiatry

Detail Summary Sheet

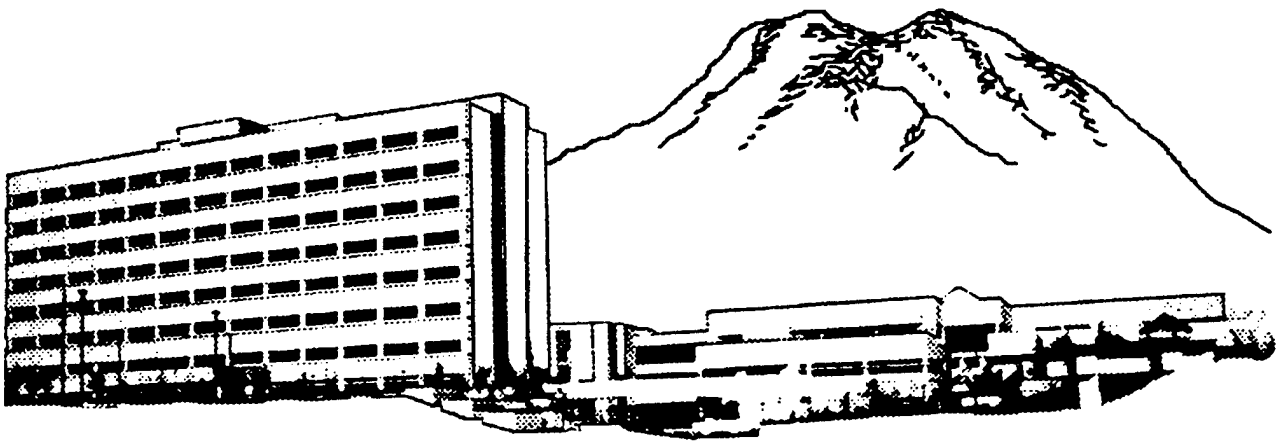
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|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 98/029 | Status: Completed |
| Title: Migraine Prevention with Magnatherm Pulsing Electromagnetic Fields | | |
| Principal Investigator: COL Russell D. Hicks, MC | | |
| <hr/> | | |
| Department: Psychiatry | Facility: MAMC | |
| Associate Investigator(s): LTC (Ret) Allyn Woerman, MMSC,TP; LTC (Ret) Richard A. Sherman, MS | | |
| <hr/> | | |
| Start Date: 12/18/1997 | Est. Completion Date: Dec 97 | Periodic Review: 12/15/1998 |

Study Objective: Evaluating the effectiveness of a small, light weight pulsing electromagnetic field generating device for use in patient's homes in preventing onset of most migraine headaches.

Technical Approach: 1) Open trial study: 20 subjects will use the PEMF unit in their homes one hour per day for ten days. Effectiveness will be determined by comparing headache frequencies reported on month long headache log made before and after exposure of the inner thighs to the fields at half power setting. 2) Double Blind study: 20 subjects (10 per group) will be randomized to receive, in their homes once a day five days per week for two weeks, treatment with a PEMF generator or a non-working (placebo) generator. Effectiveness will be determined by comparing headache frequencies reported on month long headache logs made before and after exposure to the fields. Subjects with no change in their headaches may come into the clinic for treatment with a working generator. 3) Minimal effective dose study: To determine whether the SSP unit set to its minimum power is still effective in preventing headaches in order to permit development of a minimal size/weight home-use unit specialized for treatment of migraine headaches which would have a simplified arm and only one head. Same design as "1" above using ten subjects at the lowest dosage and possibly an additional ten at a higher dosage if not effective. 4) Large scale, long-term effectiveness trial: To produce data from 100 migraine subjects using the minimized device developed in "3" above with the open design from "1" above but with an eight month follow-up to provide convincing evidence that (a) the device works for a significant number of patients, (b) that the decrease is maintained beyond the six month placebo period, and (c) that side effects are either minimal or non-existent.

Progress: Ten patients completed the following protocol: 3 weeks of daily (5X/wk) exposures at 12/12 using one head on each inner thigh sequentially (1/2 hour per thigh for a total of one hour of exposure per day). At one month follow-up, none showed excellent improvement, two showed good improvement, three showed minor improvement, three showed no change, and two were a bit worse. The two with worsening symptoms showed changes small enough as to describe this change as probably random; therefore, you could say that actually half showed no change. An eleventh patient did not keep the post-treatment log but verbally reported (by phone) that she had no headaches for the first month and then returned to baseline levels for the next three months. We were able to obtain follow-up logs beyond the first post-treatment month for 5 of the patients with one patient's results changing from no change to a minor decrease, another from good to minor and one other patient from minor to good. The rest remained stable.

Six additional patients completed the following protocols: Three patients did three weeks of daily exposures (21 days total) of each thigh sequentially (not simultaneously) for 1/2 hour per thigh with two using a power of 8/8 all the way through the hour and three used 8/8 for the first twenty minutes and 1/12 for the remaining ten minutes. At one month follow-up, one showed excellent results (no migraines at all for the entire three months we have followed her for so far), three showed minor decreases, and two showed no change.



Detail Summary Sheets

Department of Psychology

Detail Summary Sheet

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|--|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 98/091 | Status: Terminated |
| Title: Prevention of Tension Headaches with Microcurrent Electrical Stimulation: A Placebo Controlled Pilot Study | | |
| Principal Investigator: Mary Brencick, MSW | | |
| Department: | Facility: MAMC | |
| Associate Investigator(s): Nancy E. McLaughlin; Anita Millmann-Thorndike | | |
| Start Date: 07/17/1998 | Est. Completion Date: Dec 98 | Periodic Review: 1/27/1999 |

Study Objective: To perform a double-blind, placebo controlled pilot study which will provide sufficient information to determine whether a full study is warranted to determine whether two weeks of exposure to microcurrent electrical stimulation for one hour per day can prevent at least 50% of the expected tension headaches among at least 50% of the subjects receiving actual stimulation.

Technical Approach: Twenty subjects of either sex between the ages of 18 and 70 years, diagnosed as having uncomplicated tension headaches, will keep a one month initial baseline of headache activity. They will then be randomized into real or placebo microcurrent electrical stimulation at home for one hour per day for two weeks. Subjects will keep a headache log throughout this period. This is followed by a one month follow-up during which subjects continue to keep the log every time they get a headache.

Progress: 12 subjects have been entered in FY 99 for a total of 12 subjects enrolled. This protocol is having inordinate difficulty recruiting subjects and maintaining them in the study. Only 2 of the 12 subjects have completed their post-trial logs due to compliance issues. It takes many hours of phone calls and letters to remind the subjects to complete their initial and final logs. Because of this extensive time output and little data input, we decided to terminate the study.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/130 **Status:** Completed

Title: MMPI-2 Profiles in Korean Military Dependents

Principal Investigator: CPT Kathleen S. Lester, MS

Department: Psychology

Facility: MAMC

Associate Investigator(s): None.

Start Date:
06/16/1995

Est. Completion Date:
Aug 95

Periodic Review:
08/20/1998

Study Objective: To determine the normative scores for the Minnesota Multi-phasic Personality Inventory-2 (MMPI-2) in Korean dependent wives of active duty soldiers.

Technical Approach: In order to determine the norms for the Korean female spouses of service members, the MMPI-2 will be administered to 50 subjects, age 20 to 70. Subjects will be recruited from the primary care clinics at MAMC by means of referral by their physician and through recruitment advertisements posted in community areas of Ft. Lewis. Subjects consenting to participate will be given a questionnaire, a brief, structured psychiatric interview (mini-SCID), a screening test of English proficiency and the MMPI-2. The mean and standard deviation of the clinical and validity scales will be derived for the group. These scores will be compared with existing norms and, where differences exist, t-tests of significance will be performed. Results will be examined for covariance of factors of age, number of years in the U.S., and proficiency in English language.

Progress: During this study, a total of 10 Korean-born women married to active duty soldiers were recruited to take a standardized test of personality, Minnesota Multiphasic Personality Inventory (2nd Edition). The results indicate that scores for these women were no different than scores from a normalized population used in establishing scoring criterion. For purposes of medical/psychological evaluations, the results of this study would suggest that any elevations in scores should be interpreted within the guidelines of the psychometric properties of the test. Drawbacks to this study are certainly the limited number of subjects.

Detail Summary Sheet

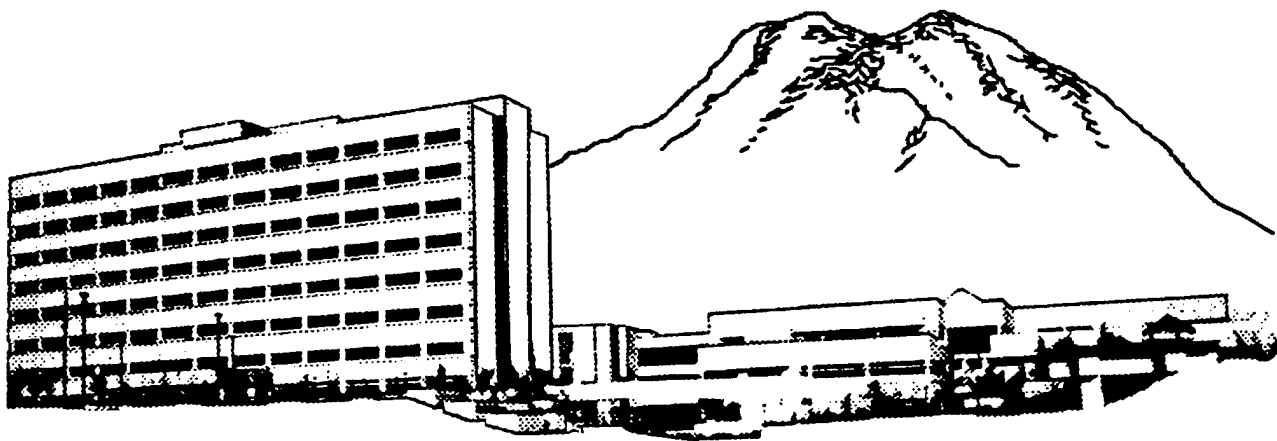
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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/016 | Status: Ongoing |
| Title: Prevalence of Anxiety Symptoms in General Pediatric and Specialty Pediatric Populations | | |
| Principal Investigator: CPT Kathleen S. Lester, MS | | |
| Department: Psychology | Facility: MAMC | |
| Associate Investigator(s): MAJ Kenneth A. Miles, MS | | |
| Start Date: 01/26/1999 | Est. Completion Date: May 99 | Periodic Review: N/A |

Study Objective: To determine the rate of anxiety symptoms occurring among pediatric patients in a general population and in pediatric populations being evaluated/treated for asthma, GI complaints, neurologic disorders, diabetes and cancer.

Technical Approach: A valid and reliable instrument of self-report symptoms (Multidimensional Anxiety Scale for Children) will be given to pediatric patients with identified medical disorders of asthma, ADHD, diabetes, abdominal pain, headaches or cancer. Rates of anxiety symptoms within these medical populations will be ascertained and comparisons will be made between general and specialty populations as well as between medical subgroups. Correlation will be made between the medical subgroups with and without symptoms of anxiety and measure of medical utilization (number of clinic visits, ER visits and medications) and severity of illness.

Progress: A total of 151 children between the ages of 8 and 18 were recruited for the study. Subjects fell into the following categories: General population, 70; Diabetes, 22; Asthma, 26; ADHD, 21 and Oncology, 12. Subjects reported clinically significant levels of anxiety at the following rates: General population, 11% (8/70); Diabetes, 0%; Asthma, 24.5% (7/26); ADHD, 19% (4/21) and Oncology, 0%. The rate of 11% for the general population is consistent with that reported for general non-medical, non-military populations. When groups are examined among themselves for significant differences in rates of reporting, only the population with asthma differed significantly from the other groups on total MASC scores ($p=.018$). There were no significant correlations between anxiety scores (Anxiety Disorder Index or MASC Total) for numbers of medical visits, numbers of medications or severity of illness within any of the medical specialty groups.

Results of this study suggest that significant anxiety symptoms are likely to be present in 11% of all children who attend a general pediatric clinic for non-anxiety related illnesses. This rate is consistent with that reported for the general population. Being treated for clinical asthma is associated with greater risk for symptoms of anxiety although the causal nature of this correlation is not established by this study. Surprisingly, children with serious illnesses such as cancer and diabetes do not report higher incidences of anxiety. Results within the oncology groups may be related to the fact that anxiety symptoms were measured after treatment was completed and children were in remission.



Detail Summary Sheets

Department of Radiology

Detail Summary Sheet

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|---|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 99/007 | Status: Completed |
| Title: Pseudo-dissection of the Main Pulmonary Artery by CT | | |
| Principal Investigator: CPT Adam J. Benson, MC | | |
| Department: Radiology | Facility: MAMC | |
| Associate Investigator(s): MAJ Sean P. Murray, MC; MAJ Robert E. Morgan, MC; MAJ Scott C. Williams, MC | | |
| Start Date: 11/17/1998 | Est. Completion Date: Dec 99 | Periodic Review: 9/28/1999 |

Study Objective: Retrospective study evaluating chest computed tomograms (CT) for dissection-like artifact in the pulmonary artery believed to be motion artifact arising during image acquisition.

Technical Approach: Chest CT scans of patients who received a contrast enhanced CT will be evaluated over a two month period to determine the incidence of artifact simulating pulmonary artery dissection. Data will be collected anonymously. A determination will be made of the incidence, location, and appearance of pulmonary artery abnormalities. Data will be categorized of these abnormalities into obvious artifacts versus artifacts simulating pulmonary artery dissection.

Progress: 102 subjects have been entered in FY 99. Seven percent of CT scans exhibit artifacts highly suggestive of pulmonary artery dissection. Another 32% exhibit abnormalities in the pulmonary artery which are clearly artifactual. Artifacts within the main pulmonary artery are more common than previously reported. Pseudo-dissection of the main pulmonary artery is a previously unreported artifact, and is likely related to motion of the main pulmonary artery during CT scan. Knowledge of this artifact may avert further invasive or noninvasive testing.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/081 **Status:** Terminated

Title: Pulmonary Manifestations of Gastro-esophageal Reflux Disease: HRCT Findings

Principal Investigator: CPT David M. Keadle, MC

Department: Radiology **Facility:** MAMC

Associate Investigator(s): MAJ Cristopher A. Meyer, MC; MAJ Kazunori Yamamoto, MC; CPT Matthew D. Gilman, MC; CPT Manish K. Varma, MC

Start Date:
03/15/1996

Est. Completion Date:
Jan 96

Periodic Review:
09/30/1998

Study Objective: To investigate the pulmonary high resolution CT findings of patients with GERD. By categorizing HRCT findings in patients with GERD, a distinction may be made between pulmonary manifestations of GERD and other entities which often have similar plain film findings. This would allow clinical decisions regarding therapy, e.g. steroid therapy in UIP versus anti-reflux measurements to be facilitated.

Technical Approach: Gastroesophageal reflux disease is very common in Western Countries and is associated with significant morbidity. Based on symptoms alone, up to 44% of adult Americans experience GERD. The Gastroenterology Department has a proven population of patients with gastroesophageal reflux disease using the gold standard - 24 hour pH probe monitoring. 25 patients will be selected from the patient population after screening out those patients with prior lung disease, smoking, pregnancy, etc. that may interfere with pulmonary findings of GERD. High Resolution Computed Tomography of the lung will be performed in an attempt to categorized findings unique to GERD that are not discernible on plain film examination. CT and CXR findings will be reviewed by a radiologist and radiology resident. A grading system will be devised on the findings of the first five patients which will consist of five normal volunteers with normal pHs and no GERD. These findings will facilitate treatment options, e.g. steroid treatment in UIP verses anti-reflux precautions in GERD, in diseases that have similar plain film findings.

Progress: The original PI PCS'd in Jun 98 and CPT David Keadle, MC, was appointed to be the PI. The protocol remained in suspended status pending possible revisions; however, Dr. Keadle chose to terminate this study as it was written to pursue other research projects.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/088 | Status: Ongoing |
| Title: Comparison of Computed Tomography Angiography and Digital Subtraction Angiography for the Pre-Operative Evaluation of Carotid Artery Disease | | |
| Principal Investigator: CPT David M. Keadle, MC | | |
| Department: Radiology | Facility: MAMC | |
| Associate Investigator(s): CPT Christopher R. Spence, MC; MAJ Sean P. Murray, MC; MAJ Stephen M. Yoest, MC; James H. Timmons, MD; COL David F. J. Tollefson, MC; LTC Stephen B. Olsen, MC; Troy H. Patience, B.S. | | |
| Start Date: 08/24/1999 | Est. Completion Date: Jul 00 | Periodic Review: N/A |

Study Objective: To evaluate the accuracy of Computed Tomography Angiography (CTA) in the evaluation of patients with atherosclerotic carotid artery disease. Comparison will be made with the with the accepted gold standard evaluation, digital subtraction angiography.

Technical Approach: The study sample will be obtained from consecutive patients who have had clinical evaluation and a duplex ultrasound examination in the vascular surgery clinic and who were referred for conventional angiographic examination of the carotid arteries. The plan is to evaluate 40 patients, although a preliminary statistical analysis will be performed after the first 20 patients to assure adequate sample size. Patients will be counseled regarding the risks of the procedure by Dr Keadle, Dr Yoest, or Dr Timmons. Patients who agree to participate in the study will have CTA performed at least 72 hours prior the conventional angiography. These studies will be read by two radiologists. Conventional angiography will then be performed and will be read by two different radiologists. The physicians performing and reading the angiogram will be blinded to the results of the CTA study. Percent stenosis of the carotid artery will be computed using the North American Symptomatic Carotid Endarterectomy Trial method. The results of the CTA will be compared with the conventional angiogram using paired T-test analysis.

The CAT scan protocol used for the CTA exams is as follows: a non-contrast scan will be done first from the skull base to the aortic arch. These will be true axial images at 5 mm slice thickness and intervals using settings of 120 kV and 200 mA. Next, a contrast-enhanced study will be performed. 125 ml of non-ionic contrast material will be injected at a rate of 4ml per second. During the dynamic administration of this contrast material, a scan will be performed from the skull base to the aortic arch. These images will be acquired helically with a pitch of 2 and a slice thickness of 3 mm, and will use settings of 120 kV and 250 mA. These images will be reconstructed at 1 mm thickness, and will be reformatted in sagittal and coronal planes. In addition, 3 dimensional and maximum intensity projection (MIP) images will be obtained. The projected CT weighted dose (weighted 2/3 peripherally and 1/3 centrally) is 9.78 mGy for the contrast scan and 14.76 mGy for the non-contrast scan.

If the ultrasound and the CTA show only unilateral disease, the angiogram on the contralateral side will be abbreviated and will consist of only one contrast run as opposed to three. This will decrease the catheter time in that artery, which is suspected to decrease the chance of stroke. In addition, the decrease in radiation from excluding the two runs will likely exceed the extra radiation from the CTA.

Progress: Awaiting RPO approval statement before study can be started.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/085

Status: Ongoing

Title: Radiographic and Clinical Correlation of the Outcome of Calcaneal Osteotomy for Talocalcaneal Valgus

Principal Investigator: CPT Gina J. Kim-Ahn, MC

Department: Radiology

Facility: MAMC

Associate Investigator(s): Rush A. Youngberg

Start Date:
08/24/1999

Est. Completion Date:
Dec 99

Periodic Review:
N/A

Study Objective: Review the literature regarding radiographic determination of talocalcaneal valgus and assess the three standard radiographic measurements of talocalcaneal alignment from the Cobey view. Introduce the Cobey view to the radiology community. Correlate the clinical outcome of patients undergoing calcaneal osteotomy for talocalcaneal valgus with each of the three measurements.

Technical Approach: Review of charts of patients who have had the Cobey view will be performed. For each patient's Cobey view, three measurements for the talocalcaneal valgus will be made independently by two radiologists. These measurements will be compared to each other and correlated with clinical assessment and selection for surgery. The readers will be blinded to patients' subsequent clinical management. Both initial and follow-up Cobey views will be assessed. Charts of post-operative patients will also be reviewed to assess outcome.

Progress: This protocol received final approval 8 Aug 99 and has not yet begun.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/093 | Status: Ongoing |
| Title: Magnetic Resonance Imaging of the Sternum | | |
| Principal Investigator: CPT Andrea R. Manzo, MC | | |
| Department: Radiology | Facility: MAMC | |
| Associate Investigator(s): Rush A. Youngberg; LTC John D. Pitcher Jr., MC | | |
| Start Date: 07/17/1998 | Est. Completion Date: May 99 | Periodic Review: 7/27/1999 |

Study Objective: To determine the magnetic resonance imaging characteristics of the normal sternum and anatomical variations.

Technical Approach: We propose to study 25 adults with no prior history of trauma using a torso array coil. MR images will be obtained in T1-weighted sequences in the sagittal and coronal planes. The patients we propose to study will be patients scheduled for MR imaging for other indications.

Progress: 15 subjects have been entered in FY 99 for a total of 15 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/047 **Status:** Completed

Title: Clinical Evaluation and Diagnostic Tests for Suspected Pulmonary Embolic Disease: A Survey of Physician Attitudes and Correlation to Clinical Practice

Principal Investigator: MAJ Sean P. Murray, MC

Department: Radiology **Facility:** MAMC

Associate Investigator(s): CPT Gina J. Kim-Ahn, MC; MAJ Scott C. Williams, MC; MAJ Robert B. Gibbons, MC; LTC Bernard J. Roth, MC; MAJ Matthew P. Jones, MC; COL John M. Bauman, MC

Start Date:
03/20/1998

Est. Completion Date:
Apr 98

Periodic Review:
06/22/1999

Study Objective: To determine clinician attitudes regarding diagnosis and clinical decision making for pulmonary thromboembolic disease. Secondary objectives will be to determine the factors which affect work-up, and use data to educate referring clinicians.

Technical Approach: A self-administered and anonymous survey about pulmonary embolic disease will be mailed/distributed to each clinician. We will evaluate clinician's satisfaction with pulmonary embolism work-up, the performance of a complete (or incomplete) pulmonary embolism work-up, and the primary reason a pulmonary arteriogram is not ordered. These will be compared with demographic data such as years of clinical practice, referring service and number of such evaluations during past six months. The survey will also obtain descriptive data detailing diagnosis and management of these patients.

Progress: Only 54% of clinicians report performing a complete work-up of suspected pulmonary embolism (PE). There is no significant correlation between adherence of the work-up and years of clinical practice, frequency of performing a PE work-up, or referring services. In one-third of individual clinicians, the perceived risk of pulmonary arteriogram (PAG) is the primary reason for not ordering the procedure. The perceived risk of PAG is higher in obstetrics/gynecology (67%) and family practice (50%) compared with medicine (34%) surgery (27%) and emergency medicine (17%). No significant correlation is noted between perceived risk of PAG and years of practice. Most clinicians (56%) report only partial or no satisfaction with current diagnostic strategies. Those clinicians reporting the highest satisfaction of PE work-up have significantly more years of practice (p-value <0.05) compared to those who report the least satisfaction. Most clinicians (70%) never or almost never consider computed tomography angiography (CTA) as a tool for PE work-up. Other factors affecting the work-up and treatment of PE are described. **Conclusions:** Clinicians are marginally satisfied with the current PE work-up. Our survey demonstrates that only half reported consistently following current PE work-up algorithms. Radiologists need to educate clinicians of the true risks of PAG and the usefulness of CTA in work-up strategies for PE. Through understanding of clinician attitudes and education, radiologists may improve the efficiency and consistency of the PE work-up.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/106 | Status: Ongoing |
| Title: Peri-Hepatic Lymphadenopathy in Patients with Chronic Hepatitis | | |
| Principal Investigator: MAJ Sean P. Murray, MC | | |
| Department: Radiology | Facility: MAMC | |
| Associate Investigator(s): MAJ Daniel W. Walsh, MC; COL Amy M. Tsuchida, MC | | |
| Start Date: 09/15/1998 | Est. Completion Date: Sep 99 | Periodic Review: N/A |

Study Objective: Retrospective study evaluating abdominal computed tomography (CT) for abdominal lymphadenopathy in patients with either laboratory or histologic evidence of chronic hepatitis. Correlation will be made between radiology results and subtypes of hepatitis.

Technical Approach: Patients with histologic or laboratory evidence of hepatitis over the past four years will be identified through a computer search. The radiologic records of these patients will then be examined. Patients with both hepatitis and an abdominal CT scan within one year will be included in the study. Patients with known malignancy will be excluded. The abdominal CT scan will be evaluated for the presence of enlarged peri-hepatic lymphadenopathy. The incidence, location and size of the lymphadenopathy will be correlated to hepatitis subtypes.

Progress: Data on 89 subjects have been collected during FY99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/069 **Status:** Ongoing

Title: Percutaneous Image-Guided Biopsy Service: Improved Diagnostic Yield with Case-Specific Use of Computed-Tomography, Ultrasound, and Fluoroscopy

Principal Investigator: MAJ Sean P. Murray, MC

Department: Radiology **Facility:** MAMC

Associate Investigator(s): CPT Michael C. Royer, MC; CPT Paul J. Cunningham, MC; Troy H. Patience, B.S.

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 05/25/1999 | May 00 | N/A |

Study Objective: To determine success of comprehensive percutaneous biopsy service, with biopsy-imaging method designed to maximize tissue sampling and diagnostic accuracy.

Technical Approach: Percutaneous image-guided fine-needle aspiration of masses has become a common method of diagnosis of malignancy. The choice of image modality best suited for guiding the biopsy is not clear. Whether CT, US, or fluoroscopy is used traditionally depends on personal preference and experience of the radiologist. Each imaging method may have particular advantages or disadvantages related to specific masses or patients. The consolidation of image-guide biopsies within a single service and its resultant effect on efficacy and safety has not been previously evaluated. The purpose of this retrospective study is to determine the safety and efficacy of a comprehensive percutaneous biopsy service, with biopsy-imaging method designed to maximize tissue sampling and diagnostic accuracy.

Progress: Data on 111 subjects have been collected during FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/034

Status: Ongoing

Title: Computed Tomography Guided Percutaneous Placement of Injection Coils Ligated to Suture and Thoracoscopic Pulmonary Resection

Principal Investigator: CPT John P. Reinschmidt, MC

Department: Radiology

Facility: MAMC

Associate Investigator(s): MAJ Lawrence M. Casha, MC; MAJ Sean P. Murray, MC; MAJ David P. Tracy, MC; James H. Timmons, MD; MAJ Scott C. Williams, MC; LTC Maceo Braxton Jr, MC; CPT John P. Reinschmidt, MC

Start Date:
12/18/1997

Est. Completion Date:
Indef

Periodic Review:
03/23/1999

Study Objective: The primary objective is to reduce the number of displaced localization devices by the use of a Cook helical coil tied to a suture line as an alternative to the hookwire for VATS. A secondary objective is to reduce damage that occurs with displacement of wires.

Technical Approach: Twenty patients already slotted for needle localization with Hawkins III wires will have either coils attached to suture or hookwires placed. They will then be taken to the OR and thoracic surgery will remove the coils or hookwires with VATS. The degree of displacement and associated complications will be compared to our current 90% Hawkins III wire displacement rate.

Progress: 8 subjects have been entered in FY 99 for a total of 13 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/142 **Status:** Completed

Title: Radiologic Guided Aspiration of Intra-articular Ganglia in the Knee

Principal Investigator: CPT Nancy Shaffer, MC

Department: Radiology

Facility: MAMC

Associate Investigator(s): CPT Manish K. Varma, MC; LTC John D. Pitcher Jr., MC;
Rush A. Youngberg

Start Date:

07/19/1996

Est. Completion Date:

Mar 97

Periodic Review:

07/27/1999

Study Objective: To determine whether radiologic guided aspiration and subsequent injection of 1% Xylocaine of intra-articular ganglia in the knee is a feasible alternative to arthroscopic excision.

Technical Approach: Intra-articular ganglia in the knee are an uncommon cause of knee pain. Patients with intra-articular ganglia in the knee had good or excellent results with arthroscopic excision of the ganglia. However, 50% to 78% of these patients had no associated internal derangement. CT guided aspiration of intra-articular ganglia in the knee has been successful. Ultrasound guided aspiration of ganglion cysts is a potentially cost effective alternative to surgery. We propose to perform radiologic guided aspiration of 15 patients with intra-articular ganglia in the knee. These patients have knee pain and intra-articular ganglia in the knee demonstrated on MRI. All patients will be followed at 3 month and 6 month after the procedure. An MRI will be obtained immediately post-procedure and at 6 months follow up. Failures will be offered operative (arthroscopy) treatment. The standard treatment (arthroscopy) who do not opt for aspiration. We will determine whether the intra-articular ganglia in the knee is the cause of the patients' symptom. Also, we will show whether aspiration and injection of 1% Xylocaine will successfully remove the ganglion cysts.

Progress: 3 subjects have been entered in FY 99 for a total of 14 subjects enrolled. The needle was accurately placed in all the patients studied. In those patients whose cysts could not be satisfactorily localized by US, the cysts detected by MR examination were less than 1 cm in diameter, and could not be satisfactorily localized by CT. The procedure was performed in less than 25 minutes and patients were discharged after a one-hour observation. None of the patients required hospitalization or surgery. Patients were able to resume their daily activities the day following the procedure. All the patients had resolution of the symptoms within one week following the procedure. Follow up MRI revealed no recurrence. No long-term complications (9 months) occurred.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/099

Status: Ongoing

Title: Comparison of MRI with Bone Scintigraphy in the Evaluation of Suspected Hip Stress Fractures

Principal Investigator: CPT Paula J. Shepherd, MC

Department: Radiology

Facility: MAMC

Associate Investigator(s): Jerome Billingsley, M.D.; Rush A. Youngberg

Start Date:

9/28/1999

Est. Completion Date:

Dec 99

Periodic Review:

N/A

Study Objective: To determine whether MRI is at least as sensitive, and possibly more specific than bone scintigraphy in the detection of hip stress (fatigue) fractures.

Technical Approach: The first 50 consecutive patients who present for an initial bone scan or MRI to evaluate for hip stress (fatigue) fracture as ordered by their health care providers, will be consented for both studies (bone scan and MRI) if they agree to participate in the study and meet the URI screening criteria. Results are available to clinicians upon completion of the interpretation of each study. The standard consent form clearly states that patients can withdraw from the study at any time.

Patients will undergo the alternate study within 5 days of completion of the study for which the patient initially presented. Plain films are not required prior to either study, however are often already obtained before presenting for further imaging. If obtained, these films are available for review by both the nuclear medicine physicians and MRI radiologists interpreting the studies; however the diagnosticians are blinded to the results of the alternate study (bone scan or MRI).

The appropriate statistical test is the McNemar test, as the subjects are paired. There is no gold standard for diagnosing hip stress fractures.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/166 **Status:** Ongoing

Title: Cost Effectiveness of Early MRI in Traumatic Wrist Injury

Principal Investigator: Rush A. Youngberg

Department: Radiology

Facility: MAMC

Associate Investigator(s): MAJ Richard S. Makuch, MC; COL John M. Bauman, MC; CPT John D. Crocker, MC; S. P. Scheer, M.D.

Start Date:
08/18/1995

Est. Completion Date:
Feb 96

Periodic Review:
8/20/1998

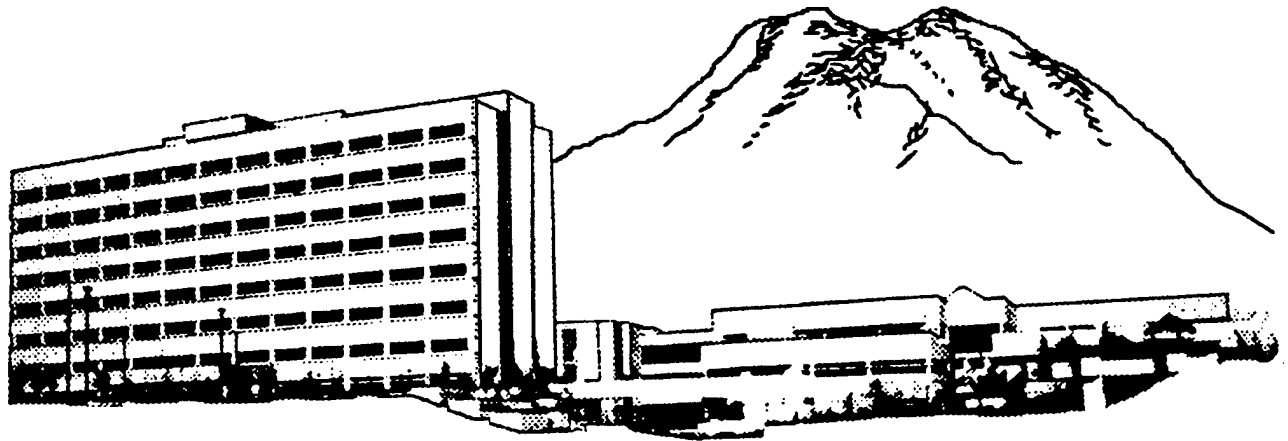
Study Objective: To determine the cost effectiveness and utility of scintigraphy in the management of patients with traumatic wrist injury whose initial radiographs are negative, yet who clinically are felt to have scaphoid fractures.

Technical Approach: This is a prospective blinded study to determine the cost effectiveness of a more accurate, slightly more expensive imaging modality in the management of patients with traumatic wrist injury. All patients over 18 years of age with a fall on the outstretched hand (a "FOOSH" injury) will be included. One hundred patients will be enrolled.

Those enrolled in the study will undergo a limited high resolution bone scan of each wrist (the uninjured wrist will serve as a comparison to the injured wrist) within 48-96 hours of the time of injury. When the clinician has determined that management is complete, the clinician will have access to the bone scan results, prior to the patients' discharge from care.

The radiographs will be reviewed by the chief of musculoskeletal radiology, the bone scans by a staff nuclear medicine physician, and the clinical evaluation and follow-up will be performed per usual orthopedic clinic practice at MAMC. Costs will be calculated based on the CHAMPUS allowable reimbursement for the services rendered as defined by the 1995 CPT codes of the American Medical Association. Data analysis will include determining if there is statistical significance between the costs of caring for clinically "false positive" fractures and the costs of early bone scintigraphy.

Progress: 8 subjects have been entered in FY 99 for a total of 26 subjects enrolled.



Detail Summary Sheets

Ft. Lewis Rangers

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/117 **Status:** Suspended

Title: Special Operations Medical NCO Sustainment Training Using the Goat Model
(Capra hircus)

Principal Investigator: CPT Charles Taylor, MC

Department: Ft. Lewis Rangers **Facility:** MAMC

Associate Investigator(s): 2LT David Nieman, PA-C, MS-SP; SFC Paul Linskens

Start Date:
07/18/1997

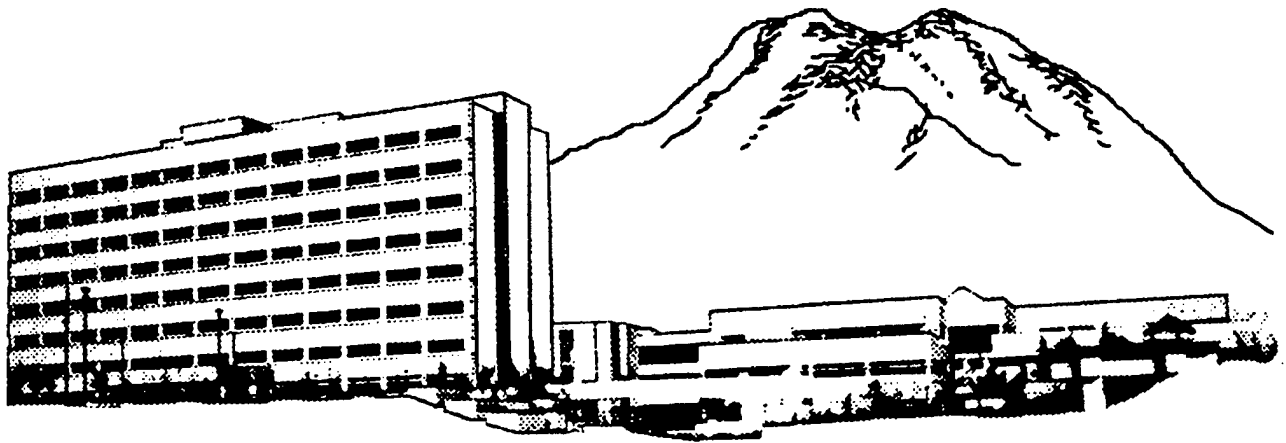
Est. Completion Date:
Jul 00

Periodic Review:
09/30/1998

Study Objective: Ranger medical personnel will be exposed, gain experience and demonstrate proficiency in the following invasive resuscitation procedures: cricothyroidotomy (needle and surgical), endotracheal intubation, needle thoracentesis, chest tube placement, pericardiocentesis, intravenous catheterization, venous cutdown and techniques of suture placement.

Technical Approach: Anesthetized adult goats will be used to train Ranger medical personnel basic surgical and emergency resuscitation skills they are expected to perform in combat. These tasks are identified by the American College of Surgeons in the Advanced Trauma Life Saving course. Ranger medical personnel must achieve a score of 70% on the written exam at the conclusion of the didactic instruction before proceeding to the hands on portions of the exercise. This protocol does not vary from previously accepted regimens for this purpose.

Progress: This protocol has been suspended since July 1998 because the PI was reassigned and DCI has been unable to get any definite commitments from the Special Operations Unit regarding who the new PI will be.



Detail Summary Sheets

**General Surgery Service,
Department of Surgery**

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/098

Status: Ongoing

Title: Gastrin Releasing Peptide Receptor: A Potential Novel Marker of Clinical Aggression in Human Neuroblastoma Cells

Principal Investigator: CPT Alec C. Beekley, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): Ann O'Connor, M.D.; Robert S. Sawin, M.D.; CPT James A. Sebesta, MC; Katherine H. Moore, Ph.D.; MAJ Kenneth S. Azarow, MC

Start Date:
08/20/1998

Est. Completion Date:
Jul 99

Periodic Review:
9/28/1999

Study Objective: To determine whether the expression of Gastrin Releasing Peptide Receptor by human Neuroblastoma cells correlates with increased malignancy.

Technical Approach: By using the fluorescent peptide technology described below, this study proposes to demonstrate that: 1) gastrin releasing peptide receptor is expressed by human neuroblastoma cells, and 2) expression of this receptor may correlate with advanced malignancy. The established cell lines will be grown to confluence at MAMC. After appropriate washes, cells will be incubated with Fluo-GRP which is expected to bind specifically to the GRP receptor on those cells which express it. Following incubation, cells will be fixed and studied under fluorescence microscopy to visualize cell surface binding and internalization of the labeled receptor. Future investigation will focus on analysis of fresh frozen sections of tumors from patients with neuroblastoma in the hopes that GRP receptor expression can be used both as a marker of advance disease, and as a potential target for specific anti-GRP receptor therapy.

Progress: This is a recent project which has not been started until other projects are completed.

Detail Summary Sheet

| | | |
|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 97/047 | Status: Completed |
| Title: Genetic Testing for Inherited Cancer | | |
| Principal Investigator: Preston L. Carter, M.D. | | |
| Department: Surgery/General Surgery | Facility: MAMC | |
| Associate Investigator(s): Jamilyn L. Daniels, M.S., C.G.C.; Charlene P. Holt, M.D. | | |
| Start Date: 02/21/1997 | Est. Completion Date: Sep 97 | Periodic Review: 02/23/1999 |

Study Objective: We propose to develop a model for genetic counseling and testing for patients at risk for breast cancer. Multiple phases of a program will be developed and tested in this pilot program at Madigan. Two breast cancer susceptibility genes will be studied, BRCA1 and BRCA2. A commercial laboratory will be used to perform the actual testing. Results and interpretation of each patient's test will be sent to Madigan, and each patient enrolled in appropriate counseling and medical care.

Technical Approach: Historical data indicate that 55 of 100 patients meeting the inclusion criteria may test positive for BRCA1 or BRCA2 genetic mutations. Thus we anticipate that approximately 23 patients from the group of 50 recruited at Madigan will have a positive test result and request additional care. Informed consent will be performed at two points in the project, first before patients complete a questionnaire, perform pre-test counseling and education, and second before providing a blood sample for genetic testing. The guidelines for follow-up of individuals testing positive for BRCA1 or BRCA2 genetic mutations have been presented by Dr. Wylie Burke to the National Cancer for Human Genome Research Advisory Council. Madigan patients will be instructed and counseled on their individual test results and choices of action for the follow-up surveillance.

Progress: 105 subjects were enrolled. Study to be published in Am J Hum Genet 65(4), p1182, A214, Oct 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/045 **Status:** Terminated

Title: The Effect of Low-Dose Dopamine on Splanchnic Blood Flow with Intra-abdominal Hypertension in Domestic Yorkshire Swine, *Sus scrofa*

Principal Investigator: CPT Mathew H. Chung, MC

Department: Surgery/General Surgery **Facility:** MAMC

Associate Investigator(s): LTC Patrick J. Offner, MC

Start Date:
01/19/1996

Est. Completion Date:
Jan 99

Periodic Review:
01/26/1999

Study Objective: To investigate the ability of low-dose dopamine to improve visceral blood flow and organ perfusion during induced intra-abdominal hypertension.

Technical Approach: We will use an established porcine model of elevated intra-abdominal pressure. The animals will be anesthetized, mechanically ventilated and instrumented. Femoral arterial and venous catheters will be placed and a Swan-Ganz pulmonary artery catheter will be placed via jugular vein. Laparotomy will be performed for the placement of Doppler flow probes and gastric and ileal tonometers. Two catheters will be placed in the abdominal cavity percutaneously and a urinary catheter will be placed through a cystotomy. Following instrumentation, animals will be randomly assigned to one of four experimental groups. Group I is the negative control with no further manipulations. Group II will have elevated intra-abdominal pressure by instillation of saline solution. Group III will have the same elevated (Group II) intra-abdominal pressure established plus low dose dopamine. Group IV will have low-dose dopamine alone. There will be six animals per group. Intra-abdominal pressures of 20 and 40 mm Hg will be studied.

Measurements will include the following every 20 minutes for two hours during the experiment: (1) renal, hepatic, and superior mesenteric arterial flow and portal vein flow, (2) hepatic and renal perfusion, (3) gastric and terminal ileum pH, (4) cardiac hemodynamics, and (5) laboratory values on ABG, mixed venous blood gas and lactate levels.

Progress: This protocol was terminated, 19 Jan 99, as it had passed the three year limit for approval. The study was never implemented.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/005 | Status: Ongoing |
| Title: Emergency Surgical Procedures Laboratory Training Using the Goat (<i>Capra hircus</i>) | | |
| Principal Investigator: COL William E. Eggebrotten, MC | | |
| Department: Surgery/General Surgery | Facility: MAMC | |
| Associate Investigator(s): MAJ Kenneth S. Azarow, MC | | |
| Start Date: 10/20/1998 | Est. Completion Date: Oct 01 | Periodic Review: N/A |

Study Objective: The objective of this training exercise is to teach physicians one safe method of performing six lifesaving procedures for trauma patients.

Technical Approach: This training protocol will instruct MAMC residents in the initial management of trauma patients. The students will practice the safe methods of performing the following lifesaving procedures in the order listed: venous cutdown, peritoneal lavage, chest tube placement, pericardiocentesis, thoracotomy and vessel cross clamp, cricothyroidotomy. The procedures will be performed after the animals are properly prepared and adequately anesthetized for surgery. The endpoint of this training will be completion of all procedures or evidence of excessive duress or anesthetic instability. Students will be evaluated by instructors on the basis of direct observation of psychomotor skills and verbalization of the indications, contraindications and potential complications of each procedure.

Progress: This protocol replaces ATLS protocol #95038. Four training sessions were held in FY 99, with approximately 68 residents/auditors in attendance.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/083 **Status:** Ongoing

Title: Porcine Iliac Artery Injury Model for Testing of Absorbable Vascular Templates

Principal Investigator: CPT Mohamad I. Haque, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT Scott R. Steele, MC; MAJ Kenneth S. Azarow, MC; COL David F. J. Tollefson, MC; LTC Stephen B. Olsen, MC; LTC William C. Williard, III, MC; MAJ David P. Tracy, MC; MAJ Sean P. Murray, MC; COL Charles A. Andersen, MC; CPT Alec C. Beekley, MC; MAJ Ronald E. Nielsen, VC

Start Date:
06/19/1998

Est. Completion Date:
Jun 01

Periodic Review:
8/24/1999

Study Objective: (1) To determine if pigs can serve as an adequate living tissue model for testing the in vivo absorption of polyphosphasene vascular templates and (2) if the absorbable vascular templates or stents will effectively treat deliberate, non-transecting iliac artery injuries in a porcine model in a reproducible fashion.

Technical Approach: An absorbable template will be unilaterally placed in each pig's normal iliac artery using manual and angiographic techniques via an arteriotomy in the opposite iliac artery. Impact of the stent will be assessed immediately through intraoperative arteriographic measurement of luminal diameters. Impact of the templates over time will be assessed by repeat angiography with subsequent sacrificing of the animals and tensile strength testing, routine histopathologic evaluation, and electron microscopic evaluation of the arterial segment containing the experimental stent at one, two, three, four, and five weeks after stent placement.

Bilateral, non-transecting iliac arteriotomies will be created in a standard fashion in each pig, placing an experimental absorbable vascular template across one lesion using manual, endovascular and/or angiographic techniques, and primarily repairing the opposite lesion with standard vascular suture techniques. Resulting artery and stent patency and integrity will be assessed by intraoperative arteriography. Impact over time will be assessed via repeat arteriography with subsequent sacrifice of the animals and tensile strength testing, routine histopathologic evaluation, and electron microscopic evaluation of the segments of artery containing the experimental stent at one, two, three, four, and five weeks following stent implantation. These results will be compared with the results of the same tests done on the arteriotomies that were repaired primarily with suture.

Progress: This protocol has not been implemented. The investigators are still awaiting the arrival of the absorbable stents.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/078

Status: Ongoing

Title: Inflammatory Response Related to Tracheobronchial Distention in Pigs (Sus scrofa) Using Absorbable Tracheal Stents

Principal Investigator: CPT Matthew J. Martin, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT Ronald A. Gagliano, MC; CPT Alec C. Beekley, MC; CPT Leroy J. Trombetta, MC; MAJ Andrew B. Silva; MAJ Kenneth S. Azarow, MC

Start Date:
05/22/1998

Est. Completion Date:
May 01

Periodic Review:
4/21/1999

Study Objective: To characterize the inflammatory reaction and granulation tissue formation following absorbable stent placement in the pig airway. To achieve this long term objective, our pilot should demonstrate any differences between in vivo and in vitro absorption of the stents.

Technical Approach: A total of 10 pigs will be utilized in this study, two pigs per group during a 5 week period of time. Group 1 will have stent insertion with sacrifice of the animals at day 7; Group 2 will be sacrificed at day 14; Group 3 will be sacrificed at day 21; Group 4 will be sacrificed at day 28 and Group 5 will be sacrificed at day 35. All animals will undergo histologic examination of their airways to include videoscopic recordings in order to more accurately measure airway lumen diameters and tissue condition and reactivity.

Progress: 10 pigs have been used in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/064 **Status:** Terminated

Title: Prognostic Significance of p53 Mutations in the Lymph Nodes of Dukes B Colon Cancer Patients

Principal Investigator: CPT Jerome M. McDonald, MC

Department: Surgery/General Surgery **Facility:** MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; CPT Wade K. Aldous, MS; LTC Jerome B. Myers, MC; LTC William C. Williard, III, MC; CPT Tommy A. Brown, MC

Start Date:
04/18/1997

Est. Completion Date:
Jun 97

Periodic Review:
04/27/1999

Study Objective: Our objective is to evaluate the relationship between p53 mutations in the lymph nodes and long term survival of patients with colon cancer.

Technical Approach: This is a retrospective pathology review and chart review. Slides of lymph nodes from 50 Dukes B colon cancer patients will be stained for p53 mutation using standard immunohistochemical stains. These results will be compared to long term tumor recurrence patterns.

Progress: No subjects have been entered in FY 99 for a total of approximately 30 subjects enrolled. Study terminated due to lack of evidence of p53 mutations.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/021 | Status: Ongoing |
| Title: Development of an In-vivo Model of Free Radical Production Utilizing Dihydroethidine in the Mouse (mus musculus) | | |
| Principal Investigator: CPT Jerome M. McDonald, MC | | |
| Department: Surgery/General Surgery | Facility: MAMC | |
| Associate Investigator(s): LTC David C. Elliott, MC; Katherine H. Moore, Ph.D.; MAJ Kenneth S. Azarow, MC | | |
| Start Date: 01/26/1999 | Est. Completion Date: Jan 02 | Periodic Review: N/A |

Study Objective: To generate an inexpensive and accurate model of in-vivo free radical production and quantification utilizing mice.

Technical Approach: Anesthetized animals will undergo a mid line laparotomy and the supra celiac aorta will be cross clamped for 30 minutes to generate ischemia. At 10 minutes post-clamping, 20umoles per liter estimated total body water of hydroethidine will be injected into the right iliac vein. At time 30 minutes, the clamp would be removed slowly and reperfusion for 15 minutes would commence. Following reperfusion, the aorta would be transected at the diaphragm and using a 14 gauge angiocatheter, would be flushed with normal saline to wash out residual hydroethidine and ethidium bromide. The liver, pancreas, small bowel, stomach and lungs would be rapidly removed and frozen in liquid isopentane utilizing OCT freezing medium. The specimen would then be sectioned on a cryostat at 12 um, placed on a slide, and evaluated under a standard rhodamine filter fluorescent microscope.

Photo documentation or fluorescence quantitation will then be performed. Ethidium bromide staining of the tissue after quantitation would allow for standardization of tissues in regard to total number of nuclei. Utilizing different time points in this model to maximize reactive oxygen species identification will be necessary. Utilization of nitrogen gas to minimize background may be necessary in preparation of the hydroethidine and in several stops of tissue processing.

Progress: Pending revisions needed by IACUC and approval of funding.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/004

Status: Ongoing

Title: Forward Surgical Team (FST) Sustainment Training Using the Goat Model
(Capra hircus)

Principal Investigator: LTC Craig M. Ono, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): LTC David C. Elliott, MC; MAJ Ann Everett, AN, CRNA;
CPT Michael S. Murphy, AN

Start Date:
10/20/1998

Est. Completion Date:
Oct 01

Periodic Review:
N/A

Study Objective: FST personnel will be exposed, gain experience and demonstrate proficiency in invasive resuscitation procedures.

Technical Approach: FST personnel must achieve a score of 70% on the written exam at the end of the didactic instruction before proceeding to the hands on portion of the exercise. Anesthetized adult goats will be used to train medical personnel basic surgical and emergency resuscitation skills they are expected to perform in combat. These tasks include: cricothyroidotomy (needle and surgical), endotracheal intubation, needle thoracentesis, chest tube placement, open thoracotomy, peritoneal lavage, exploratory laparotomies (FST surgeons), pericardiocentesis, intravenous catheterization, venous cutdown and techniques of suture placement (abdominal fascial closure). This protocol doesn't vary from previously accepted regimens for this purpose.

Progress: No training sessions were held in FY 99. LTC Craig Ono became the new PI for this protocol, 30 Aug 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/087

Status: Ongoing

Title: Madigan Army Medical Center Advanced Laparoscopic Training Using the Pig (Sus scrofa)

Principal Investigator: LTC Clifford A. Porter, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): COL William E. Eggebrotten, MC; LTC William C. Williard, III, MC; MAJ Kenneth S. Azarow, MC; LTC Alan L. Beitler, MC; LTC David C. Elliott, MC; LTC David M. Watts, MC; Preston L. Carter, M.D.

Start Date:
08/24/1999

Est. Completion Date:
Aug 02

Periodic Review:
N/A

Study Objective: To familiarize General Surgery residents, staff and invited surgeons from our community with techniques in the performance of advanced laparoscopic techniques. This training will include esophagus, stomach, biliary, small and large intestine, spleen, liver and retroperitoneal procedures. The training benefit will accrue to General Surgery residents, staff and invited surgeons by introducing these techniques or reinforcing earlier acquired skills in a controlled environment. Familiarity with these techniques will allow an increased margin of safety for patients decreased operative time, and minimizing of potential complications.

Technical Approach: Pigs will be maintained in an NPO status for 12 hours prior to the scheduled training procedures. An intramuscular tranquilizer will be used to aid in animal handling and preoperative management. General anesthesia will be induced with injectable agent and maintained by inhalational agent. Following anesthesia induction, pigs will be intubated endotracheally, will have an indwelling intravenous catheter placed in an ear vein for intraoperative fluid support, will have an orogastric tube inserted and connected to central suction for as-needed gastric decompression, and will be clipped and scrubbed as per aseptic surgery technique for the body regions of interest (e.g. abdomen, chest, etc.). Preoperative preparations will be conducted in the DCI animal surgery preparation and recovery room immediately adjacent to the DCI surgery. Following preoperative preparation, anesthetized animals will be transferred to either DCI surgery suite.

Five training sessions are scheduled for this training, they are: Advanced Laparoscopic Esophageal and Gastric Surgery, Advanced Laparoscopic Biliary Surgery, Advanced Laparoscopic Small and Large Intestinal and Rectal Surgery, Advanced Laparoscopic Splenectomy and Liver Surgery, and Advanced Laparoscopic Retroperitoneal Dissection and Lymph Node Dissection. Each session will be formalized into one day continuing medical education programs consisting of 1 hour of didactic lecture, 4 hours of hands-on procedural and/or instrumentation orientation using inanimate training models and non-living human or animal tissues, and 3 hours of live (anesthetized) animal laboratory for definitive procedural training. Each animal will be used for a single training session only, and will be euthanized at the end of the session without recovery from general anesthesia. Non-survival/training surgical procedures will be performed using clean (simulated aseptic) technique. Each training session will utilize up to four pigs.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/022 **Status:** Ongoing

Title: The Use of Autologous Fibrin Glue to Prevent Post-operative Seromas in Patients Undergoing modified Radical Mastectomy

Principal Investigator: CPT Christopher K. Sanborn, MC

Department: Surgery/General Surgery **Facility:** MAMC

Associate Investigator(s): LTC Patrick J. Offner, MC; CPT Daniel D. Mais, MC; CPT Bret R. Hansen, MC

Start Date:
11/18/1994

Est. Completion Date:
Dec 96

Periodic Review:
11/17/1998

Study Objective: To determine if the use of autologously donated fibrin glue can decrease the incidence of post-operative fluid collections in patients undergoing modified radical mastectomy.

Technical Approach: We plan to conduct a prospective, randomized study evaluating the effects of autologously donated fibrin glue on the flaps created during modified radical mastectomy in attempts to increase the adhesion of the flaps to the underlying tissue and prevent post-operative fluid collections. A total of 60 subjects will be recruited and randomized to a study group and a control group. All subjects will donate one unit of autologous blood pre-operatively. This blood will be used to provide the autologous fibrinogen for the study group. Surgeons will be given the fibrin preparation or saline to apply after mastectomy. The surgeons will be blinded as to whether they are applying fibrin glue or control saline. Drainage from the surgical area will be recorded by the subjects and a blinded evaluator will assess fluid accumulation at least weekly after drains are removed. Seroma fluids will be drained as necessary. Rates of seroma formation will be compared using chi-square analysis. The mean total amount of drain output and the mean length of time for the drains to be discontinued will also be analyzed using the Student's T-test or a non-parametric test should the distribution prove to be non-Gaussian.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/006 | Status: Completed |
| Title: Effects of Differentiation on Telomerase Activity in Neuroblastoma Cell Lines | | |
| Principal Investigator: CPT Christopher K. Sanborn, MC | | |
| Department: Surgery/General Surgery | | Facility: MAMC |
| Associate Investigator(s): MAJ Kenneth S. Azarow, MC; Ann O'Connor, M.D.; Robert S. Sawin, M.D.; M. J. DeHart, B.S.; Katherine H. Moore, Ph.D. | | |
| Start Date: 11/17/1998 | Est. Completion Date: Oct 99 | Periodic Review: N/A |

Study Objective: To determine the level of telomerase activity in human neuroblastoma cell lines via PCR-ELISA assays before and after induced differentiation by retinoic acid.

Technical Approach: TRAP assays will be performed on five neuroblastoma cell lines to establish baseline telomerase activity in those cell lines. Each of the cell lines will then be subjected to either normal culture medium or culture medium enhanced with retinoic acid. After completion of study period, TRAP assays will again be performed to detect any changes in telomerase activity. Morphological changes indicating differentiation will also be observed.

Progress: No statistical difference in telomerase activity was noted between control and treated groups.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/141

Status: Completed

Title: A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in ERCP Brushings for Detection of Pancreatic and Biliary Cancer

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; LTC William C. Williard, III, MC; CPT Wade K. Aldous, MS; COL Amy M. Tsuchida, MC; Maniscalco-Theberg M; LTC Jeffrey Kavolius, MC; LTC James North, MC; LTC Russell Martin, MC; LTC Steve Hetz, MC; CPT Michael C. Royer, MC; CPT Tommy A. Brown, MC

Start Date:
09/19/1997

Est. Completion Date:
Nov 98

Periodic Review:
11/17/1998

Study Objective: To evaluate telomerase activity as a screening modality for the detection of pancreatic and biliary tumors.

Technical Approach: This study is designed to evaluate the efficacy of measuring telomerase activity in endoscopic retrograde cholangiopancreatography (ERCP) brushings and bile samples as screening tool for pancreatic carcinoma and cholangiocarcinoma. The six Army medical centers involved include MAMC, WRAMC, TAMC, DDEAMC, WBAMC and BAMC. Patients with suspicious pancreatic or bile duct lesions will have lumen brushings of the lesions and bile collected and shipped to MAMC to determine if telomerase activity is present in the specimens. Additionally, after surgical excision of the suspicious lesions, a sample of the primary tumor will also be sent to MAMC for evaluation of telomerase activity. The results of these tests as well as patient clinical data will be analyzed to determine the sensitivity and predictive value of telomerase as a screening tool for pancreatic and bile duct malignancy. We estimate the total number of patients needed to complete the study to be 36 for each of the two groups utilizing a power analysis. The data will be collected and analyzed using statistical software to evaluate surgical correlation of telomerase activity in ERCP brushings and bile fluid. Major analysis being the correlation of the surgical results to the telomerase activity detected in FNAs, reporting sensitivity and specificity, along with positive and negative predictive value. The study will run for approximately 1 year. Consent is required for ERCP brushings for all patients.

Progress: Twenty-one subjects have been studied. Preliminary results were presented at the 1998 Gary Wratten Surgical Symposium and in process of analyzing data for submission of paper.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/143

Status: Ongoing

Title: A Prospective Multi-institutional Study to Determine the Sensitivity and Specificity of Telomerase in Thyroid FNAs for the Detection of Thyroid Cancer

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; LTC William C. Williard, III, MC; LTC Clifford A. Porter, MC; CPT Wade K. Aldous, MS; CPT Brenda K. Bell, MC; MAJ Raymond S. Lance, MC; MAJ Janice C. Stracener, MC; LTC Mary Maniscako-Thegerge, MC; LTC Jeffrey Kavolius, MC; LTC James North, MC; LTC Russell Martin, MC; LTC Steve Hetz, MC

Start Date:
09/19/1997

Est. Completion Date:
Nov 98

Periodic Review:
11/17/1998

Study Objective: Our objective is to evaluate telomerase activity in thyroid fine needle aspirations as a screening modality for the detection of thyroid cancer.

Technical Approach: This study is designed to evaluate the efficacy of measuring telomerase activity in fine needle aspirations of thyroid nodules as a screening tool for thyroid carcinoma. The six Army medical centers involved include MAMC, WRAMC, TAMC, DDEAMC, WBAMC and BAMC. Patients with suspicious thyroid nodules requiring fine needle aspiration (FNA) will have additional FNA samples taken at the time of surgery sent to MAMC to determine if telomerase activity is present in the specimens. Additionally, after surgical excision of the thyroid, a sample of the primary tumor will also be sent to MAMC for evaluation of telomerase activity. The results of these tests as well as patient clinical data will be analyzed to determine the sensitivity and predictive value of telomerase as a screening tool for thyroid malignancy. We estimate the total number of patients needed to complete the study to be 360 utilizing a power analysis. The total number of specimens analyzed will be approximately 1000. The data will be collected and analyzed using statistical software to evaluate surgical correlation to telomerase activity in FNAs. Major analysis being the correlation of the biopsy cytology to the telomerase activity detectability, reporting sensitivity and specificity, along with positive and negative predictive value. The study will run for approximately one year. Consent is required for additional FNA passes for all patients.

Progress: 44 out of 55 thyroid samples completed, extraction and telomerase assays pending.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/069

Status: Terminated

Title: Use of Alternative Medicine Therapies for Treatment of Cancer

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery

Facility: MAMC

Associate Investigator(s): CPT Aziz N. Qabar, MS; Katherine H. Moore, Ph.D.; Louis A. Matej, B.S.; CPT Wade K. Aldous, MS; ; M. J. DeHart, B.S.

Start Date:
05/22/1998

Est. Completion Date:
Nov 98

Periodic Review:
05/27/1999

Study Objective: To determine the effects of common therapies used in alternative medicine on cell viability and to determine the effects of the same therapies on telomerase activity.

Technical Approach: We intend to test a variety of "compounds" to determine their efficacy against cancer cells in vitro. We will subject the MCF cell line to a variety of the agents listed within the protocol in order to see if these agents have any effect on cell growth and telomerase activity. A Northern blot will be performed on cells treated with "promising" agents to determine if there is differential expression of any RNAs. We will measure the overall effects of the proposed reagents through TRAP assays (to measure telomerase activity) and total cell counts (to measure cell viability).

Progress: This protocol was terminated due to the PSC move of the original PI and lack of funding to continue working on this project. Minimal data had been collected up to the date of termination.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/096 **Status:** Ongoing

Title: Gastrin Releasing Peptide: A Potential Growth Factor Expressed in Human Neuroblastoma Tumors

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery

Facility: MAMC

Associate Investigator(s): Ann O'Connor, M.D.; Robert S. Sawin, M.D.; Jeff M. Bullock, M.S.; MAJ Kenneth S. Azarow, MC; Katherine H. Moore, Ph.D.; CPT Leroy J. Trombetta, MC; AL Young

Start Date:
08/20/1998

Est. Completion Date:
Dec 98

Periodic Review:
07/27/1999

Study Objective: To determine whether the Gastrin Releasing Peptide and Gastrin Releasing Peptide Receptor genes are expressed in human neuroblastoma tumors, and to determine whether expression of these genes is associated with more aggressive tumor histology.

Technical Approach: Once the sequentially numbered tumor samples are received, the total RNA will be harvested from each tumor (per standard protocols). The technique of reverse transcription polymerase chain reaction (RT-PCR) will be used to first synthesize GRP cDNA from the total RNA, and then amplify the GRP cDNA product (per standard protocols). The same technique will be used to synthesize and amplify GRP-R cDNA. Specific primers for these experiments have been obtained from the published GRP and GRP-R gene sequences, and have been used successfully in neuroblastoma cell culture models. The above result will be confirmed using Southern Blot analysis (per standard protocol) using digoxigenin labeled probes previously generated through PCR.

Progress: Tissue has been obtained and awaiting the repair of DNA sequencer before sequencing can be completed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/012

Status: Ongoing

Title: Comparison of the Harmonic Scalpel and the Standard Technique for Right Hepatic Lobectomy in Pigs (*Sus scrofa*)

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): LTC David C. Elliott, MC; CPT Ronald A. Gagliano, MC; A Gant

Start Date:
12/15/1998

Est. Completion Date:
Dec 01

Periodic Review:
N/A

Study Objective: To compare the time and ease of the standard fracture technique of liver resection to the heretofore undescribed method of using the harmonic Scalpel. Other factors evaluated will be blood and bile loss and the ability to complete the resection.

Technical Approach: Four pigs will be randomized into two groups. Group one will have the standard finger fracture technique right hepatic lobectomy. Group two will have the Harmonic Scalpel right hepatic lobectomy. Data collected will include noting the time of onset of hepatic dissection to the completion of the lobectomy, all bile and blood lost during the procedures will be collected and measured and all sponges and laparotomy pads will be weighed to estimate the fluid collected in them. A closed suction drain will be placed intraoperatively in the resection bed to measure the output for 24 hours. Irrigation will be avoided if possible, but if it is used, the amount will be recorded and subtracted from the total fluids collected. The resected portion of the liver will be submitted to pathology for evaluation of the extent of injury to the surrounding tissue.

Progress: This protocol has not been implemented due to funding issues.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/097

Status: Ongoing

Title: Gastrin Releasing Peptide's Effect on Telomerase Activity in Human Neuroblastoma Cell Lines

Principal Investigator: CPT James A. Sebesta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT Leroy J. Trombetta, MC; MAJ Kenneth S. Azarow, MC; Katherine H. Moore, Ph.D.; Robert S. Sawin, M.D.

Start Date:
8/24/1999

Est. Completion Date:
Jan 00

Periodic Review:
N/A

Study Objective: To determine the effect of Gastrin Releasing Peptide (GRP) on telomerase activity in neuroblastoma cell lines.

Technical Approach: Basic Culture Conditions:

Neuroblastoma (IMR32) and small cell lung carcinoma cell lines (H345) will be maintained in 5% fetal bovine serum and supplemented with 100 units of penicillin per ml, 100 ug of streptomycin per ml, 2.5 ug amphotericin B per ml at 370 C under 5% CO₂. Cultures will be grown in 25 cm² flasks and seeded with approximately 3.5E5 per inoculum.

Experiment One

Determination of basal production of Gastrin Releasing Peptide (GRP) from cultured cells. Previous work has shown that these cells express GRP mRNA. In order to know how much peptide and antibody to use in the following experiments, a measurement of the basal production of GRP from the cultured cells is essential. In addition, the basal activity of telomerase will be determined. Cells will be grown in culture for three days. Control flasks will be trypsinized for total cell counts and harvested for Telomerase activity. Initially, 1000 cells will be used for the Telomerase assay and then adjusted to provide the greatest sensitivity of the assay. Telomerase activity will be determined using the TRAP assay according to the manufacturers directions (Roche Molecular Biochemicals). RIA for GRP will be performed according to the manufacturer's instructions (Phoenix Pharmaceuticals). GRP will be separated for the growth media and other cellular products using a size exclusion filter that retains proteins larger than 10 kDa. GRP is 2859 Da, and will flow through the filter. Larger proteins that may interfere with the RIA will be retained behind the filter. Preliminary experiments will be performed to determine parallelism of the assay for GRP produced in cell culture, and to determine recovery.

Experiment Two

The cell lines will then be grown in the presence of the monoclonal antibody for GRP, 2A11. The monoclonal antibody 2A11 has been obtained from NCI, Navy Medical Oncology Branch, Bethesda, MD. The amount 2A11 used in the culture will be based on the baseline determination of GRP production of the cell lines. Cells will be grown in culture for 8 days, with cells harvested every two days. Cells will be counted to assess the effect of the antibody, and hypothesized neutralization of GRP on cell growth. Telomerase activity and free GRP assays will be repeated as described above. The GRP RIA will be done to ensure that GRP has been bound by the monoclonal antibody. As before, conditioned media from each data collection point (days 0, 2, 4, 6, and 8) will be collected, and processed with size exclusion spin filters. Any GRP bound to antibody will be retained by the 10 kDa filter, and only unbound GRP will be in the filtrate. The filtrate will be assayed in the RIA. This experiment will be repeated three times.

Experiment Three

The effect of additional GRP will be investigated. Three different types of GRP will be examined, the 27 amino acid full length GRP, and two peptide fragments, GRP 1-16, and GRP 14-27. Cell lines will be cultured in increasing concentrations of GRP (2x, 5x, 10x) added to the culture media. Cells will receive fresh GRP and media every two days, and cells harvested on days 0 (control), 2, 4, 6, and 8. GRP Telomerase assays will again be repeated as previously described. This experiment will be repeated three times.

Statistical Analysis

Repeated measured analysis of variance will be used to examine the effects of antibody 2A11 and GRP peptides on cell growth, telomerase activity and GRP concentrations. All data will be compared to the control day. In addition data will be analyzed within day to determine differences in effect of peptide concentrations on the above parameters.

Progress: Monoclonal antibodies have been obtained. Awaiting cell culture and RIAs on GRP.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/097

Status: Completed

Title: Telomerase Level in Neuroblastoma Tumors: Can This Be Used to Guide Prognosis and Management?

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT Tommy A. Brown, MC; MAJ Kenneth S. Azarow, MC; CPT Wade K. Aldous, MS; M. J. DeHart, B.S.; Robert S. Sawin, M.D.

Start Date:
08/20/1998

Est. Completion Date:
Sep 98

Periodic Review:
N/A

Study Objective: To evaluate telomerase activity in frozen neuroblastoma specimens, while being blinded to any and all data concerning the patients from which these specimens originated.

Technical Approach: Telomerase activity will be determined by the telomere amplification repeat protocol using the Telomerase PCR ELISA kit from Boehringer Mannheim according to manufacturers instructions. Positive and negative controls will be used from the kit. In addition, RT-PCR will be used to amplify the RNA component (HTR) from the same protein extracts used for telomerase assays. (-2 microglobulin, a common housekeeping gene, will be used as a quantitation control. PCR products will be run on 1% agarose gels, transferred to a nylon membrane and then probed for (-2 microglobulin and the RNA component. Densitometric analysis correcting for (-2 microglobulin content will determine the HTR.

Progress: Twenty-one telomerase specimens have been assayed via the TRAP-ELISA kit and RT-PCR gels have been run. Telomerase activity correlated with stage of tumor ($p < 0.007$). Age of patient did not correlate with telomerase activity independently.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/099

Status: Ongoing

Title: Postoperative Cisapride Therapy After Abdominal Surgery in the Pediatric Patient

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT Tommy A. Brown, MC; MAJ Kenneth S. Azarow, MC; COL James M. Noel, Jr., MC; LTC David Wiechmann, MC

Start Date:
08/20/1998

Est. Completion Date:
Jul 99

Periodic Review:
8/20/1999

Study Objective: To compare the effects of cisapride and erythromycin on return of bowel motility and length of hospital stay in pediatric post-surgical patients.

Technical Approach: Subjects will be randomized in one of two groups. Group A will receive erythromycin at 1-3 mg/kg orally TID and Group B will receive cisapride 0.2 mg/kg orally TID. The medications will be placed in a medication syringe labeled "Trombetta study med" to prevent identification by nursing and physician staff. Subjects will take the study medication until time of discharge. Information will be collected concerning length of hospital stay, onset of bowel movements, regular diet and intake and perioperative complications.

Progress: One subject completed the study last FY. All aspects of her enrollment in the study went very well.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/100 **Status:** Terminated

Title: Intra-abdominal Pressure in Elective Aortic Surgery Patients: A Prospective Series

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery **Facility:** MAMC

Associate Investigator(s): LTC Stephen B. Olsen, MC; COL David F. J. Tollefson, MC; COL Charles A. Andersen, MC; CPT Bret R. Hansen, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 08/20/1998 | Aug 00 | N/A |

Study Objective: To determine a range of normal values of intra-abdominal pressures (IAP) in patients undergoing elective surgery of the abdominal aorta.

Technical Approach: All subjects will have the IAP measured (1) immediately before surgery, after induction of anesthesia, before initial skin incision is made; (2) immediately post-operatively once the subject has been transferred to the intensive care unit, and all essential nursing tasks have been performed to ensure that the subject is stable; (3) four hours from reading number 2 above and (4) each morning on all subsequent post-operative days until the Foley catheter has been removed. Data recorded will include pre-operative weight, intra-operative fluid balance, length of surgery, hematocrit, pulmonary artery systolic and diastolic pressures, mean arterial pressure, overall fluid balance, peak airway pressure, serum creatinine level, use/non-use of pre-operative bowel preparation and type and use/non-use of evisceration to gain exposure at the time of surgery. Data will be recorded until subject is discharged from the hospital.

Progress: 5 subjects have been entered in FY 99 for a total of 9 subjects enrolled. This study has been terminated due to logistical problems in data acquisition and lack of patient enrollment.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/086 **Status:** Ongoing

Title: Telomerase Enzyme Activity in a Metastatic Neuroblastoma Nude Mouse Model

Principal Investigator: CPT Leroy J. Trombetta, MC

Department: Surgery/General Surgery

Facility: MAMC

Associate Investigator(s): CPT James A. Sebesta, MC; M. J. DeHart, B.S.; Robert S. Sawin, M.D.; CPT Jeffrey A. Vos, MC; Cynthia Pekow, Ph.D.; MAJ Kenneth S. Azarow, MC

Start Date:
9/28/1999

Est. Completion Date:
Apr 00

Periodic Review:
N/A

Study Objective: To evaluate telomerase activity in human neuroblastoma tumors grown in nude mice, with attention to the difference in telomerase activity between primary tumor and metastases.

Technical Approach: All foci of gross metastatic disease and the primary tumor will be assayed for telomerase activity via the TRAP-ELIZA technique described below:

Telomerase activity will be determined using the telomere repeat amplification protocol (TRAP assay). The commercially available kit from Boehringer Mannheim. First, a sample of each tumor is cut and weighed. The sample is then manually pulverized, and 200-400 ul of lysis reagent added, depending on the size of the sample. Samples are then placed on ice for 30 minutes to ensure maximum cell lysis. Samples are then centrifuged at 4 degrees centigrade and 15,300 rpm for 30 minutes, after which the supernant is removed and the precipitate discarded.

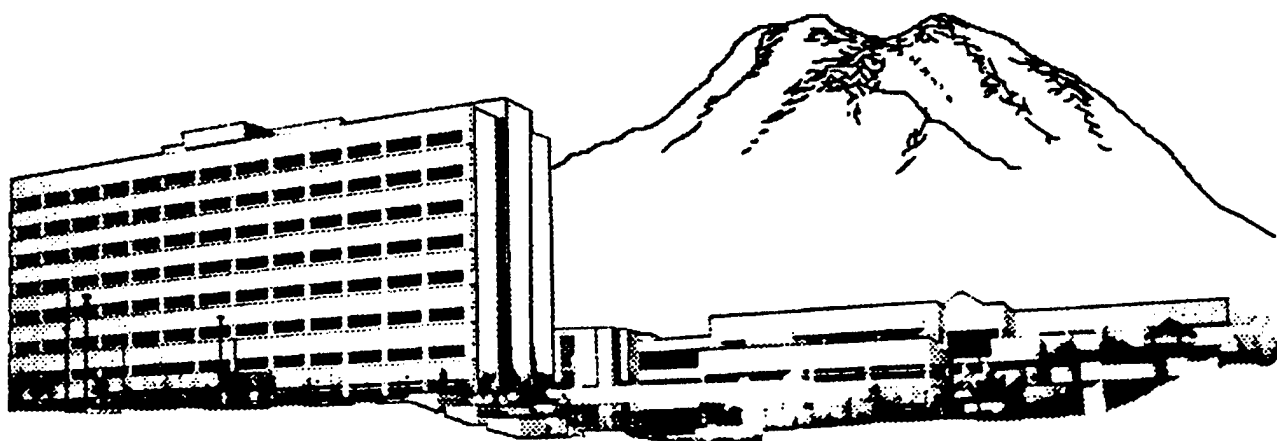
Protein content of each sample is determined using the Pierce BCA Protein Assay Reagent microliter plate protocol. Stock BSA protein solution is serially diluted and used as standards. Protein concentration of each sample is determined by plotting spectrophotometer absorbance against the standard controls using Microplate Manager software (Bio-Rad Laboratories).

The Telomerase Repeat Amplification Protocol (TRAP) is performed with the 21 samples. Serial dilutions of each sample using 6, 0.6, and 0.06 ug of protein are run simultaneously along with a positive and negative control at each dilution for a total of 69 samples. The positive control will be a thyroid carcinoma specimen proven to have telomerase activity. Sterile water is added to each sample to bring the total volume to 25 ul. Reaction Mixture, containing biotin-labeled primer, nucleotides, thermostable DNA polymerase, and telomerase substrate, is added to each sample according to kit instructions. This mixture is run through a PCR protocol. During this process, telomerase already present in the sample adds TTAGGG repeats to the biotin labeled primer. Then, the DNA polymerase amplifies the product. Thus, amount of product is dependent upon telomerase activity present in the sample.

ELISA is then done to quantify the amount of telomerase product in each sample according to kit instructions. Briefly, the DNA products is denatured and hybridized to a Digoxigenin labeled probe. Hybridized samples are then placed into a streptavidin impregnated microliter plate. The sample is immobilized to the microliter plate via a streptavidin-biotin bond. The microliter plate is incubated then washed with buffer solution. Anti-Digoxigenin antibody conjugated to a peroxidase (Anti-Dig-POD) is then added, and the solution incubated and rinsed. TME substrate is added, and the peroxidase reacts with the substrate resulting in a purple product. After incubation, a stop reagent is added, which results in a final product that is variable intensity of yellow. The microliter plate is read in a spectrophotometer at 450 nm with background of 655 nm. The resulting data is expressed as the absorbance at 450 nm against the absorbance at 655 nm. The absorbance value thus represents telomerase activity in the neuroblastoma specimen. Data to be

collected and analyzed includes: 1) Telomerase enzyme activity level represented by the absorbance values obtained from the TRAP-ELISA. Telomerase activity of the in vitro cell line, primary subcutaneous tumor, and metastatic foci will be compared; 2) Histologic analysis of neuroblastoma cell line, primary tumor and metastatic foci will be compared.

Progress: This protocol was recently approved and has not yet started recruiting subjects. Estimated start date is 1 Feb 2000.



Detail Summary Sheets

Ophthalmology Service,
Department of Surgery

Detail Summary Sheet

| | | |
|---|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 98/103 | Status: Completed |
| Title: Madigan Eye and Orbit Trauma Scale | | |
| Principal Investigator: MAJ Darryl J. Ainbinder, MC | | |
| Department: Surgery/Ophthalmology Surgery | Facility: MAMC | |
| Associate Investigator(s): CPT Earle G. Sanford, MC; LTC William R. Raymond IV, MC | | |
| Start Date: 09/15/1998 | Est. Completion Date: Aug 99 | Periodic Review: 9/28/1999 |

Study Objective: To remove a rapid, standardized triage trauma scale for the management of eye and orbital trauma.

Technical Approach: The Madigan Eye and Orbit Trauma Scale will provide a rapid, standardized triage guide for the management of eye and orbital trauma. Prompt identification of severe ocular injuries is a critical factor in reducing soldier morbidity and conserving fighting strength. The trauma scale will not replace current surgical standards. It will provide a useful training and triage tool for the evaluation and management of ocular and orbital trauma.

Progress: Data on 110 subjects have been collected. Publication is being prepared for AMEDD Journal and as a section of a chapter in The Textbook of Military Medicine.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/041 **Status:** Ongoing

Title: Refractive Changes Due to Hypoxia Following Cataract Surgery

Principal Investigator: CPT David M. Bushley, MC

Department: Surgery/Ophthalmology Surgery **Facility:** MAMC

Associate Investigator(s): COL Thomas H. Mader, MC; MAJ Mark L. Nelson, MC;
CPT Keith F. Dahlhauser, MC; Troy H. Patience, B.S.

Start Date:
02/23/1999

Est. Completion Date:
Jun 99

Periodic Review:
N/A

Study Objective: The purpose of this study is to observe and compare changes in corneal shape and visual acuity that may take place in subjects more than 1 month following cataract surgery using a clear corneal or sutureless scleral tunnel incision, when their corneas are exposed to a low oxygen tension environment.

Technical Approach: We will select three study groups for our experiment. Group 1 will consist of volunteers who have had sutureless scleral tunnel incision cataract surgery. We will study several ocular parameters on these individuals, both prior to corneal exposure to hypoxia and immediately after two hours of corneal exposure to pure nitrogen (0% O₂) gas via a goggle apparatus in one eye. The other eye will be exposed to compressed air (20% oxygen) as a control. These parameters include cycloplegic refraction, intraocular pressure, corneal video keratography, and central corneal thickness. Group 2 will consist of an equal number of subjects who have had clear corneal incision cataract surgery, in whom the same parameters will be monitored both pre and post corneal exposure to a hypoxic environment. Group 3 will consist of normal controls that have had no cataract surgery. The three groups will be age and gender matched.

Baseline evaluation of the subjects will include visual acuity, cycloplegic refraction 30 minutes after installation of one drop of 1% cyclopentolate, video keratography (corneal curvature mapping), central corneal pachymetry (thickness measurements), and intraocular pressure. One drop of proparacaine will be instilled into each eye prior to corneal pachymetry and measurement of the IOP. The same examiner using the same instruments will obtain all measurements.

The study will entail a one day process. On that day, baseline measurements will be obtained. Following baseline measurements, the subjects will be fitted with a pair of air-tight goggles. Compressed air will be released into one side of the goggles and 100% nitrogen will be released into the other after being bubbled through sterile water for humidification. Following two hours of exposure to these environments, the goggles will be removed and repeat measurements will be obtained immediately and again two hours post exposure. The examiner will be blinded to the type of gas to which each eye has been exposed.

The method of data analysis will be a multivariate analysis using repeated measures ANOVA. We will be comparing changes in corneal thickness (pachymetry), keratography, cycloplegic refraction, and visual acuity between baseline measurements and those obtained following corneal exposure to two humidified gas mixtures in Group 1, Group 2, and Group 3 patients, and between Group 1, 2, and 3 patients.

Progress: One subject was entered in FY 99, which comprised one study eye and one control eye. Results were inconclusive, however study recruitment will continue in FY 2000.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/086

Status: Completed

Title: A 6-Month, Randomized, Double-Masked Comparison of Fixed Combination of Latanoprost and Timolol with the Individual Components, Continuing into a 6-Month Open Label Safety Study of Fixed Combination in Patients with Glaucoma or Ocular Hypertension

Principal Investigator: COL Kevin J. Chismire, MC

Department: Surgery/Ophthalmology Surgery

Facility: MAMC

Associate Investigator(s): MAJ Roger K. George, MC; LTC Vernon C. Parmley, MC; LTC Robert A. Mazzoli, MC; LTC William R. Raymond IV, MC; MAJ Eugene F. May, MC; COL Anthony R. Truxal, MC; LTC Thaddeus J. Krolicki, MC; CPT Keith F. Dahlhauser, MC; COL Thomas H. Mader, MC; LTC Elizabeth A. Hansen, MC

Start Date:
04/18/1997

Est. Completion Date:
Jun 98

Periodic Review:
06/22/1999

Study Objective: To demonstrate that the fixed combination has a better IOP-reducing effect than the individual monotherapies. The differences from baseline diurnal IOP reduction after six months of treatment will be tested between the fixed combination and the monotherapy groups.

Technical Approach: This is a six month, randomized, double-masked, multicenter study with three parallel groups, continuing into a six month open label study with one treatment group. After a run-in period of two to four weeks on timolol 0.5% twice daily, the patients will be randomized at baseline into one of three treatment groups:

Group I - fixed combination of latanoprost 0.005% and timolol 0.5% in the morning and placebo in the evening.

Group II - Timolol 0.5% in the morning and evening.

Group III - Placebo in the morning and latanoprost 0.005% in the evening.

After six months of masked treatment, the patients will continue into a six month open treatment period when fixed combination is given in the morning to all patients. The patients shall be checked for eligibility within four weeks prior to baseline. A medical and ocular history as well as concomitant medications will be asked for and gonioscopy, perimetry, ophthalmoscopy, visual acuity and refraction, lid and slit lamp examination and IOP measurements will be performed. The masked treatment period comprises four visits at which visual acuity will be checked, lid and slit lamp examination performed, IOP measured, adverse events asked for and other ocular findings, as well as any changes in concomitant medications, will be recorded. Furthermore, at baseline, Week 26 and 52 heart rate and blood pressure measurements will be performed and the iris photographed. In addition, at Week 26 and 52 perimetry, refraction and ophthalmoscopy will be performed. During the open treatment period, patients will be examined at three visits. In addition, a follow-up contact will be performed two to four weeks after end of treatment

Progress: 5 subjects have been entered in FY 99 for a total of 10 subjects enrolled. This study was part of a multi-site study. Data has been submitted to Pharmacia-Upjohn for collation.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/060 **Status:** Completed

Title: Radial Keratotomy and Phototherapeutic Keratectomy: Comparison of Corneoscleral Integrity After Controlled Blunt Trauma to Post Mortem Eyes That Had Refractive Surgery

Principal Investigator: CPT Benjamin B. Chun, MC

Department: Surgery/Ophthalmology Surgery **Facility:** MAMC

Associate Investigator(s): MAJ Mark L. Nelson, MC; COL Thomas H. Mader, MC; LTC Vernon C. Parmley, MC; Larry Rich, M.D.; Larry White, M.D.

| | | |
|----------------------------------|--|---------------------------------------|
| Start Date: 03/21/1997 | Est. Completion Date: Jun 97 | Periodic Review: 04/27/1999 |
|----------------------------------|--|---------------------------------------|

Study Objective: The goal of this study is to examine and compare corneoscleral integrity, by means of controlled blunt trauma to the corneas of cadaver eyes obtained from the Lion's Human Eye Bank. The effects of phototherapeutic keratectomy (PTK) and radial keratotomy (RK) on postmortem corneas will be compared to controls.

Technical Approach: Three groups of eyes will be compared, two in each group. One group will have RK, done by an established Cornea Specialist, and the second group will have PTK, also done by an established Cornea Specialist who also specializes in the area of PTK. The third group will serve as control and will not have surgery. The intraocular pressure of each eye will be measured by Tonopen®. Intraocular BSS will be injected with a 27g needle until the IOP is 18.0m Hg in each eye. Each eye will be placed in a container measuring 35mm X 45mm X 40mm, closely approximating the human orbit. 30 cc's of orbital volume not replaced by the eye will be filled with surgical lubricant and 4 X 4 gauze pads. The eye will be held in place by tight packing with gauze. The specimen will then be placed on the Instron where a blunt 1 cm diameter probe will descend toward the cornea at speed of 10cm/min. The computer will dynamically measure by way of graph, the breaking elongation, breaking load, yield point load, work of rupture and elastic stiffness of the globe. The data from all three groups will then be studied and compared. Total of 6 eyes will be utilized.

Progress: Instron, a Servohydraulic Testing System, was used to measure the maximal load/failure point by applying a focal external force until globe rupture. RK eyes required 37% less force to rupture (at corneal incision site) than PTK or control eyes (near scleral equator).

Conclusions: Significantly less force is required to rupture RK corneas than PTK or normal corneas. The area most likely to rupture in PTK and normal eyes is near or anterior to the scleral equator.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/017 **Status:** Suspended

Title: Activated Protein C Resistance in Ophthalmologic Ischemic Syndromes

Principal Investigator: CPT Benjamin B. Chun, MC

Department: Surgery/Ophthalmology Surgery

Facility: MAMC

Associate Investigator(s): MAJ Mark L. Nelson, MC; MAJ Mary B. Grazko, MC; LTC Thaddeus J. Krolicki, MC; COL Anthony R. Truxal, MC

Start Date:

01/26/1999

Est. Completion Date:

Jul 99

Periodic Review:

N/A

Study Objective: To identify APC resistance in individuals that may have ophthalmologic ischemia associated with thrombosis, manifesting as Central Retinal Artery Occlusion and Pseudopapilledema.

Technical Approach: APCr will be examined in 80 consecutive subjects (40 subjects per group) who are diagnosed with CRAO and Pseudopapilledema in the Ophthalmology Department at Madigan. All subjects identified as have APCr will undergo a Factor V DNA mutation test as a confirmatory measure. If the Factor V DNA test confirms the APC resistance test, the subject will be referred to Hem/Onc services for further treatment. Data analysis will be mainly descriptive analysis along with chi-square to compare each group's incidence to the incidence in normal population.

Progress: This protocol was suspended, 12 Jul 99, due to the PCS of the PI. A new PI has not been assigned at this time.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/050

Status: Ongoing

Title: A Phase III Study of MDX-RA Compared with Placebo Administered in Patients Undergoing Phacoemulsification or Planned Extracapsular Extraction for Cataract

Principal Investigator: CPT Keith F. Dahlhauser, MC

Department: Surgery/Ophthalmology Surgery

Facility: MAMC

Associate Investigator(s): LTC Vernon C. Parmley, MC; COL Thomas H. Mader, MC; MAJ Mark F. Torres, MC; CPT Benjamin B. Chun, MC; MAJ Mark L. Nelson, MC; CPT Keith J. Wroblewski, MC; MAJ Roger K. George, MC; COL Kevin J. Chismire, MC; COL Dennis R. Beaudoin, MS

Start Date:
01/16/1998

Est. Completion Date:
Apr 99

Periodic Review:
02/23/1999

Study Objective: Describe and compare the safety of a single dose of the murine immunotoxin MDX-RA to placebo over a six-month period post-randomization, and to test the efficacy of MDX-RA by comparing the proportion of patients in the treated group to the proportion of patients in the placebo group who have had a visual acuity explainable YAG laser capsulotomy³ by 24 months of follow-up.

Technical Approach: In Phase I, subjects will undergo a pre-operative screening evaluation period prior to eye surgery for inclusion into the study; within four weeks for ophthalmic evaluations and within 2 weeks for physical evaluation. In Phase II, subjects will undergo phacoemulsification or planned extracapsular cataract surgery and receive 100 units of MDX-RA or placebo. In Phase III, during the 24 month follow-up period, ophthalmic examination, concomitant medication use, and occurrence of adverse experiences will assess safety. Subjects will be monitored for the need of visual acuity explainable YAG laser capsulotomies as the primary efficacy variable.

Progress: 1 subjects have been entered in FY 99 for a total of 7 subjects enrolled. The study is on hold as it has been for the majority of the year. We continue to monitor every 6 months patients that received the study medicine, but do not enroll any new patients. The study is on hold because of some retinal toxicity seen in patients in other institutions. None of our patients have had any problems.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/119

Status: Ongoing

Title: The Use of Photorefractive Keratectomy on Active Duty U.S. Army Personnel for the Correction of Myopia

Principal Investigator: COL Thomas H. Mader, MC

Department: Surgery/Ophthalmology Surgery

Facility: MAMC

Associate Investigator(s): LTC Vernon C. Parmley, MC; Troy H. Patience, B.S.

Start Date:
07/18/1997

Est. Completion Date:
Dec 99

Periodic Review:
07/17/1998

Study Objective: To determine if excimer laser photorefractive keratectomy (PRK) is a suitable procedure for use on active duty Army personnel for the correction of myopia.

Technical Approach: Refractive surgery of myopia with the excimer laser is of current command interest because of its potential to be performance enhancing in myopic active duty soldiers. Many active duty soldiers have an interest in this surgery and may elect to have it performed by civilian ophthalmologists at their own expense. There has been no prospective Army study to evaluate the effect of myopic excimer laser refractive surgery on active duty soldiers and how it affects the soldier's ability to perform his duties. This study proposes to 1) recruit a cohort of myopic active duty soldiers who voluntarily agree to participate, 2) prior to any treatment, evaluate their vision and its impact on certain basic military performance standards (such as qualifying with an M-16 rifle), 3) treat the myopia in both eyes by surface ablation of the cornea with an excimer laser, and finally 4) follow and re-evaluate vision and performance standards on these individuals for at least two years after treatment to examine the effect of the surgery on performance. One of the purposes of this study is to evaluate the potential of using this procedure to treat myopic soldiers thereby improving their ability to function in a combat environment and improve mission efficacy.

Progress: 90 subjects have been entered in FY 99 for a total of 90 subjects enrolled. All subjects experienced a significant decrease in their myopic refractive error. Eighty percent of all soldiers seen at one year after treatment had an uncorrected acuity (UCVA) of 20/20 or better. All of the subjects seen at one year after treatment had a visual acuity of 20/40 or better. One weakness of this study is the loss to follow-up over time. Of the 90 subjects originally treated, only 20 have one-year data.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/032 **Status:** Completed

Title: Study of Differential Swelling Using an ORB Scan (ORBTEK, Inc.) in Corneas Which Have Undergone Radial Keratotomy and are Exposed to Hypoxia with Resultant Corneal Edema

Principal Investigator: CPT Michael A. McMann, MC

Department: Surgery/Ophthalmology Surgery **Facility:** MAMC

Associate Investigator(s): COL Thomas H. Mader, MC; Larry White, M.D.; LTC Vernon C. Parmley, MC; CPT Earle G. Sanford, MC

Start Date:
12/18/1997

Est. Completion Date:
Feb 98

Periodic Review:
12/18/1998

Study Objective: To determine the amount and pattern of differential swelling in edematous corneas that have undergone radial keratotomy using an Orb scan (ORBTEK, Inc) along with central and peripheral pachymetry values.

Technical Approach: Seven subjects We will measure central and peripheral pachymetry in an effort to detect a 20 micron difference between the central and peripheral pachymetry values to the 0.05 level. With the normal cornea weakened by radial incisions, the hypoxic cornea may be able to expand in two

Progress: 20 subjects have been entered in FY 99 for a total of 20 subjects enrolled. Hypoxic hyperopic shifts in RK eyes occur secondary to flattening in anterior and posterior corneal curvature.

Detail Summary Sheet

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|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 97/121 | Status: Terminated |
|------------------------|-----------------------|---------------------------|

Title: Refractive Changes During Exposure to the Hyperbaric Environment Following Radial Keratotomy Surgery

Principal Investigator: MAJ Mark L. Nelson, MC

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| Department: Surgery/Ophthalmology Surgery | Facility: MAMC |
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Associate Investigator(s): Ted Edson, M.D.; GG Chun; COL Thomas H. Mader, MC; LTC Vernon C. Parmley, MC

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| Start Date: 07/18/1997 | Est. Completion Date: Nov 97 | Periodic Review: 06/22/1999 |
|----------------------------------|--|---------------------------------------|

Study Objective: Our objective is to verify significant changes in corneal shape, visual acuity, refraction and intraocular pressure that may take place in subjects within two years following radial keratotomy when these individuals are exposed to the hyperbaric environment.

Technical Approach: We will select three groups for our experiment. The first study group will consist of 13 U.S. Navy volunteers who have had bilateral radial keratotomies within two years prior to this study. (Currently RK's are disqualifying for flight status and entry into the military, but not disqualifying for retention in the military.) We will record and examine several ocular parameters, at sea level and immediately after exposure to depth equivalent to 50 feet of sea water: 1) cycloplegic refraction, 2) intraocular pressure, 3) corneal keratometry, and 4) central corneal thickness. Barometric pressure will also be recorded. Duration will be the maximum allowed at that depth for a no decompression dive (100 minutes). This depth was chosen because military divers carry out most of their missions at or above this depth, and this is an average depth for recreational diving. The second study group will also consist of 13 U.S. Navy volunteers who have had bilateral radial keratotomies within 2 years prior to the study. This group will be treated exactly the same as the first group except they will wear goggles with 100% oxygen infused into them at depth. The third study group will consist of 13 active duty volunteers with no previous ocular surgery. In these individuals, we will measure the above listed parameters at sea level and immediately after hyperbarics at 50 fsw. We will then compare data to see if a significant difference exists between the three groups. A power analysis was performed, assuming a 0.25 diopter intraobserver variability and a significant myopic shift of 0.50 diopters. The required sample size computed was 25 eyes. We will have 26 eyes in each study group.

Progress: This study was terminated due to non-availability of the hyperbaric chamber.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/101 **Status:** Completed

Title: Refractive Changes Due to Hypoxia Following LASIK Corneal Surgery

Principal Investigator: MAJ Mark L. Nelson, MC

Department: Surgery/Ophthalmology Surgery **Facility:** MAMC

Associate Investigator(s): COL Thomas H. Mader, MC; Larry White, M.D.; CPT Steven M. Brady, MC

Start Date:
08/20/1998

Est. Completion Date:
Jun 99

Periodic Review:
N/A

Study Objective: To observe changes in corneal shape and visual acuity that may take place in subjects more than 1 month following LASIK when their corneas are exposed to a low oxygen tension environment.

Technical Approach: Ten subjects who have undergone LASIK in both eyes and ten myopic controls are to be used for the study. Following baseline measurements, the subjects will be fitted with a pair of airtight goggles. Room air will be released into one side of the goggles and 100% nitrogen will be released into the other after being bubbled through sterile water for humidification. Following two hours of exposure to these environments, the goggles will be removed and repeat measurements will be obtained immediately and again two hours post exposure. The examiner will be blinded to the type of gas to which each eye has been exposed.

Progress: Using 20 normal controls and 20 patient that had LASIK, a myopic shift was found in the LASIK patients exposed to hypoxia. This study closed at MAMC, 30 Jun 99.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/052 | Status: Ongoing |
| Title: Correction of Low Myopia (-1.00 to -3.50 diopters) in Active Duty Personnel | | |
| Principal Investigator: LTC Vernon C. Parmley, MC | | |
| Department: Surgery/Ophthalmology Surgery | Facility: MAMC | |
| Associate Investigator(s): COL Thomas H. Mader, MC; CPT David M. Bushley, MC; CPT Michael A. McMann, MC | | |
| Start Date: 03/23/1999 | Est. Completion Date: Jun 02 | Periodic Review: N/A |

Study Objective: To determine the feasibility of correcting low myopia in active duty U.S. Army soldiers with the intrastromal corneal ring segment system (ICRS) developed by Keravision(r).

Technical Approach: We plan to recruit 100 patients into the study (200 eyes). Prior to performing the procedure, a baseline complete eye examination will be performed, including several tests of visual acuity. Pre and postoperative tests will also be conducted to determine the effect of the procedure on military performance. These tests will include M-16 weapons fire with and without protective mask, day and night navigation in good and inclement weather, and a subjective questionnaire on satisfaction with the procedure and symptoms associated with the procedure. The questionnaire will also address the effect on performance in the field after insertion of corneal rings.

The procedure involves inserting two small curved pieces of plastic into the stroma of the cornea, using a special trephine to create the stromal tunnel. The procedure can be done under topical anesthesia in the operating room (for sterility). The procedure takes approximately 15 to 20 minutes to perform. Evaluations will occur on postoperative day (POD) 1 and 6, and again at 1 month, 3 months, 6 months, and 1 year. If the patient consents, the second eye will be done 1 week following the first eye. The same postoperative follow-ups will occur for the second eye. Key data to be analyzed include: Post-operative visual acuity compared with pre-operative visual acuity; Post-operative refraction compared with pre-operative refraction, post-operative need for glasses; post-operative ability to perform specifically tested functions (weapons firing, ability to function in field without correction).

Progress: No subjects have been entered in FY 99. Protocol was submitted for funding to USAMRAA. The protocol has got a favorably reaction, decision on funding to be made in November 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/056 **Status:** Completed

Title: Congenital Esotropia Observational Study (CEOS)

Principal Investigator: LTC William R. Raymond IV, MC

Department: Surgery/Ophthalmology Surgery **Facility:** MAMC

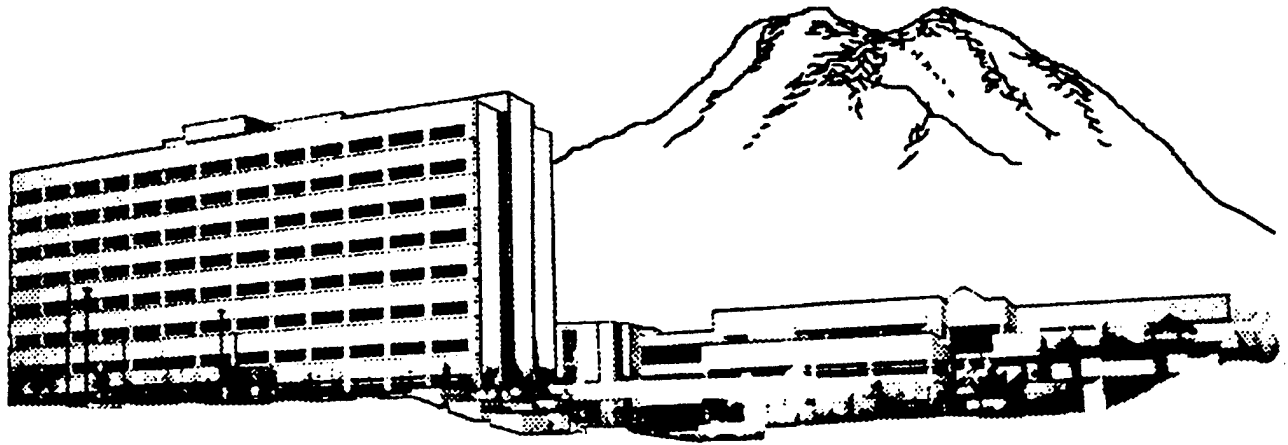
Associate Investigator(s): Avery Weiss, M.D.; CPT Benjamin B. Chun, MC

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| Start Date: 03/20/1998 | Est. Completion Date: Feb 99 | Periodic Review: 03/23/1999 |
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Study Objective: To observe the early course of congenital esotropia in order to determine the probability of spontaneous resolution and to try to correlate this finding with various aspects of the esotropia such as the size of the esotropia, variability and presence of hyperopia.

Technical Approach: Medical records of children identified as being early course congenital esotropia which meet eligibility criteria will be reviewed. Data will be collected from charts on their initial exam, 2 to 4 weeks (14-28 days) after the initial examination but no later than 19 weeks (133 days) of age, and between 28 and 32 weeks (196-224 days) of age. For each patient the change in the angle of the esotropia from the enrollment examination to the 28-32 week examination will be determined. The distribution of the change scores will be reported overall and also stratified by size of the esotropia at enrollment, age at enrollment, refractive error and treatment for amblyopia. In each stratum, the proportion of patents whose esotropia spontaneously resolved will be determined. A second approach will be to assess the patients whose esotropia resolved as a group to determine whether there are any common features that distinguish these cases from the ones that did not resolve.

Progress: Records from one patient at MAMC have been studied. Thirty-three patients have been entered nationwide. Results published in the Journal of AAPOS, Volume 2, p325-8, December 1998.



Detail Summary Sheets

Orthopedics Service,
Department of Surgery

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/098 **Status:** Completed

Title: Fixation of Salter Osteotomies with Bioabsorbable Pins

Principal Investigator: CPT Christopher P. Cannon, MC

Department: Surgery/Orthopedic Surgery **Facility:** MAMC

Associate Investigator(s): Kit M. Song, M.D.; MAJ Ronald E. Nielsen, VC; Alan F. Tencer, Ph.D.; Robert Welch, D.V.M., Ph.D.; MAJ Clyde T. Carpenter, MC

Start Date:
04/25/1997

Est. Completion Date:
Apr 00

Periodic Review:
04/27/1999

Study Objective: To review the feasibility of using bioabsorbable pins when doing pelvic osteotomies in children. We will do osteotomies on the pelvis of goats which are similar in size to a toddler.

Technical Approach: The first phase will involve an animal study. We have determined that the pelvis of a goat is near the size and orientation of a child's pelvis who might undergo a Salter pelvic osteotomy. We will perform a unilateral pelvic osteotomy, place bone graft, and insert pins to hold the pelvic osteotomy. The bone graft will be harvested from the ipsilateral iliac crest. The goat will be given antibiotics perioperatively. The second phase (which will involve another protocol and will be based on the goat studies) will be a multicenter prospective clinical trial of children undergoing Salter osteotomies for hip dysplasia. We will randomize the children on the basis of their institution so that all children treated at a given institution would be treated in a similar manner. Selection criteria would be children less than 3 years of age, neurologically and mentally normal, and requiring a Salter osteotomy for the treatment of congenital dislocation of the hip. We will seek to enroll 50 children (25 treated with Steinman pins and 25 children treated with bioabsorbable pins) in each group. We would endeavor to enroll 3 centers for each group for a total of 6 centers involved with each center treating approximately 8 children. We would use a fairly large human study because of the need for large enough numbers to address statistically the outcome.

Progress: Surgeries to harvest the pelvis from six goats have been completed. The investigators are in the process of sectioning and examining the specimens. Passing the Steinman pin proved initially to be quite difficult due to the extremely long, narrow pelvis of the goat. This was a known complication at the time of surgery. On the first surgery, one of the pins penetrated the medial wall of the pelvis resulting in death. Following this complication, the operative technique was modified and no further difficulties were experienced. Paper will be submitted for publication as soon as PI returns to MAMC in Jul/Aug 2000.

Detail Summary Sheet

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|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 98/085 | Status: Terminated |
| Title: Healing of Tibial Stress Fractures Using Pulsed Electromagnetic Fields (PEMF) | | |
| Principal Investigator: CPT Christopher P. Cannon, MC | | |
| Department: Surgery/Orthopedic Surgery | Facility: MAMC | |
| Associate Investigator(s): LTC (Ret) Richard A. Sherman, MS | | |
| Start Date: 06/19/1998 | Est. Completion Date: Dec 99 | Periodic Review: N/A |

Study Objective: To determine whether application of non-thermal, pulsed high peak power, high frequency, electromagnetic energy (PEMF) over a tibial stress fracture used in conjunction standard therapeutic approaches, reduces the amount of shin pain and increases endurance on the treadmill in relation to those receiving standard treatments with placebo PEMF.

Technical Approach: Subjects who are diagnosed by bone scan as having a stress fracture and experience pain during a treadmill test will be enrolled into this study. The first treadmill test will be done prior to initiation of PEMF. The subjects will grade their pain using the visual analog scale every 2 minutes to a max of 15 minutes. Subjects will then be randomized to either machine "a" or "b" by a computer generated sequence. They will then be exposed to PEMF on the involved lower extremity for one hour per day, five days per week for four weeks. The treadmill test will be repeated at the end of the four weeks of treatment and then followed clinically for 6 months to determine if and when they return to full duty and whether the problem returns.

Progress: This study was not implemented due to time commitments/rotations at UW by the PI.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/081 **Status:** Ongoing

Title: A Prospective Randomized, Blinded Study, Comparing Treatment of Fifth Metacarpal Neck Fractures

Principal Investigator: CPT Tad L. Gerlinger, MC

Department: Surgery/Orthopedic Surgery **Facility:** MAMC

Associate Investigator(s): LTC Frederic L. Johnstone, MC; Mary Miklos-Essenber

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 05/22/1998 | Jun 00 | 06/22/1999 |

Study Objective: To determine the effectiveness of treating fifth metacarpal neck fractures with closed reduction and casting with the metacarpal phalangeal joint in neutral and utilizing a three point mold.

Technical Approach: Patients with fifth metacarpal neck fractures will be randomized to undergo non-operative treatment, comparing closed reduction and casting with the metacarpal phalangeal joint in neutral and utilizing a three point mold, to closed reduction and casting with the metacarpal phalangeal joint approximating 90 degrees (the current standard technique). Outcome will be measured by the amount of residual angulation, grip strength compared to the contralateral hand, rotatory malalignment and range of motion at three weeks and again at three months after the injury.

Progress: 4 subjects have been entered in FY 99 for a total of 5 subjects enrolled.

Detail Summary Sheet

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|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 97/051 | Status: Terminated |
| Title: Comparison of Small Bone Cannulated Screw Systems | | |
| Principal Investigator: COL D. E. Casey Jones, MC | | |
| Department: Surgery/Orthopedic Surgery | Facility: MAMC | |
| Associate Investigator(s): CPT George K. Bal, MC | | |
| Start Date: 02/21/1997 | Est. Completion Date: Apr 97 | Periodic Review: 02/23/1999 |

Study Objective: To compare compression and pull-out strengths of three different small bone cannulated screw systems - the Accumed 'Accutrak' screw, the Herbert-Whipple screw, and the Synthes 3.0 mm cannulated screw.

Technical Approach: We will evaluate four different cannulated screws: an ASIF 3.5mm cannulated screw, Synthes 3.0mm cannulated screw/washer, Accumed's Accutrak screw, and Zimmer's Herbert-Whipple screw. The screws will be divided into three study groups designed to measure compression, pull-out strength, and compression holding. There will be ten screw of each type in each study group. We will use a synthetic cancellous bone material of uniform density, and a washer shaped strain gauge for collecting data. A servohydraulic testing machine will be used for measuring pull-out strength. The data will be evaluated by random-effects analysis of variance.

Progress: Implementation of this protocol never occurred because of a delay in acquiring appropriate materials and electronic pressure sensors to conduct the experiments. Protocol was terminated do to PCS of PI.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/087 **Status:** Suspended

Title: Duplex Sonographic Analysis of the Common Femoral Vein in Non-Weight Bearing: Age Difference in Men

Principal Investigator: CPT Bryant G. Marchant, MC

Department: Surgery/Orthopedic Surgery **Facility:** MAMC

Associate Investigator(s): LTC John D. Pitcher Jr., MC; COL David F. J. Tollefson, MC; CPT Kurtis L. Kowalski, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 07/17/1998 | Jun 98 | 07/27/1999 |

Study Objective: To define the venous dimensions during a variety of lower extremity cast applications, body positions, and ambulatory activities in various age groups of men.

Technical Approach: 15 subjects will be enrolled in this study; 5 patients about 18 years of age; 5 subjects about 50 years of age and 5 subjects about 70 years of age, all of similar size and weight and of the same sex. Baseline measurements of the common femoral vein will be made with the subject supine, erect, ambulatory full weightbearing, partial weightbearing, and non-weightbearing with B mode Duplex ultrasound. A treadmill will be used for the ambulatory readings. Next, an ace wrap, a knee brace, Ted Hose and a standard below the knee lower extremity cast will be applied to the subject's right leg. The order of device application will be randomized. The measurements will be repeated. Finally, an above the knee cast will be placed on the right leg and the measurements will be repeated.

Progress: This study has not been implemented due to PCS of the PI and no new PI assigned.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/088

Status: Suspended

Title: Blood Flow in the Common Femoral Vein in the Erect Patient with the Application of Compressive Devices

Principal Investigator: CPT Bryant G. Marchant, MC

Department: Surgery/Orthopedic Surgery

Facility: MAMC

Associate Investigator(s): LTC John D. Pitcher Jr., MC; COL David F. J. Tollefson, MC; CPT Kurtis L. Kowalski, MC

Start Date:
07/17/1998

Est. Completion Date:
Jun 98

Periodic Review:
07/27/1999

Study Objective: To study the changes in blood flow velocity in the erect patient with the use of compression devices.

Technical Approach: 10 subjects will be enrolled. Using a Doppler ultrasound, the blood velocity of the common femoral vein will be measured 1 cm proximal to the entry of the greater saphenous vein. The measurement will be made 5 times in the standing position during the expiration phase of the respiration cycle for each subject. A calf pneumatic intermittent compression device (PICD), a thigh high PICD, and a foot PICD will be placed on the patient and the velocity again measured during inflation and deflation of each SCD. Each measurement will be taken five times.

The order in which the devices are placed on the leg will be randomized.

Progress: This study has not been implemented due to the PCS of the PI and no new PI assigned.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/125 **Status:** Ongoing

Title: External Fixation of Displaced Clavicle Fractures

Principal Investigator: CPT Greer E. Noonburg, MC

Department: Surgery/Orthopedic Surgery **Facility:** MAMC

Associate Investigator(s): CG Turner; LTC Patrick St Pierre, MC

Start Date:
07/18/1997

Est. Completion Date:
Aug 99

Periodic Review:
07/27/1999

Study Objective: Determine the efficacy of external fixation in the treatment of clavicle fractures with greater than 100% displacement.

Technical Approach: Patients will be drawn from males and nonpregnant females over age 18, with acute traumatic clavicle fractures having greater than 100% displacement on radiographs. The study population will range from 10 to 20 subjects. After inclusion in the study, and a pre-operative examination, the subjects will be taken to the operating room for placement of threaded pins through four 1-cm incision sites over the clavicle. An Orthofix Pennig II External Fixator will be attached to the pins and the fracture reduced to as close as possible to anatomic alignment. After surgery, the patient will be given pain medications, instructed in pin site care, and sent home. The patient will be evaluated weekly by an orthopaedic surgeon (4-8 weeks) and usually will receive clavicle x-rays with each appointment. The external fixator will be removed in the clinic in four to eight weeks, depending upon healing of the fracture as evident on x-ray. Subsequent post-operative exams at 3, 6, and 12 months will be conducted. Outcome variables will be evaluated for functional outcomes (motor strength, range of motion, tenderness at the fracture site, residual displacement/deformity, time of healing, ability to perform occupation and activities of daily living).

Progress: 6 subjects have been entered in FY 99 for a total of 18 subjects enrolled.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/082 | Status: Completed |
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Title: A Dose-Ranging, Multicenter, Randomized, Subcutaneous, Low-Dose, Heparin-Controlled, Double-Blind Clinical Trial to Assess the Safety and Efficacy of Orally Administered Heparin With A Novel Carrier System (SNAC) in the Prevention of Major Venous Thromboembolic Events Following Elective Total Hip Arthroplasty

Principal Investigator: LTC John D. Pitcher Jr., MC

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| Department: Surgery/Orthopedic Surgery | Facility: MAMC |
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Associate Investigator(s): CPT John T. Steedman, MC

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| Start Date: 05/22/1998 | Est. Completion Date: Jun 99 | Periodic Review: N/A |
|----------------------------------|--|--------------------------------|

Study Objective: To assess and compare the safety and efficacy of postoperative 12 dose regimens of two different doses of oral SNAC/heparin combinations in preventing venous thromboembolism in patients who have undergone total hip arthroplasty, compared to low-dose heparin administered subcutaneously for 12 doses.

Technical Approach: Patients scheduled for total hip arthroplasty who sign informed consent will be randomized into one of three different treatment groups. Group A will take syrup with 1.5 gram SNAC and 60,000 units heparin, and an injection of saline; Group B will take syrup with 2.25 grams SNAC and 90,000 units heparin, and an injection of saline; and Group 3 will take SNAC syrup with no heparin, and an injection of saline. Treatment begins 10 hours after surgery, patients will receive a dose every 8 hours for a total of 12 doses. Examinations during the study period include blood and urine tests, echocardiogram, physical examinations and a bilateral venous ultrasonography of the legs to detect any blood clots that may be forming.

Progress: This study closed at MAMC, 28 Dec 98, per the sponsor as enrollment numbers had been met. Five patients were consented, with four patients completing the study. One patient wished to leave the hospital a day earlier than planned, preventing her from receiving the required number of doses of study medication. There were no adverse reactions reported.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/086 **Status:** Ongoing

Title: A Prospectively Randomized Trial of Rotator Cuff Repair to Cortical Bone versus A Cancellous Trough

Principal Investigator: LTC Patrick St Pierre, MC

Department: Surgery/Orthopedic Surgery **Facility:** MAMC

Associate Investigator(s): Hollis Potter, M.D.; CPT Roger W. Dougherty, SP

Start Date:
03/15/1996

Est. Completion Date:
Apr 99

Periodic Review:
04/27/1999

Study Objective: To determine if tendon repair to a cancellous trough is necessary for rotator cuff repair in humans.

Technical Approach: Forty patients with proven rotator cuff tears will be randomized to two surgical groups. Group A will have their rotator cuff tendon repaired to the greater tuberosity after a trough is made in the greater tuberosity of the humerus. Group B will have their rotator cuff repaired to the cortical bone of the greater tuberosity of the humerus without the creation of a trough. A thorough debridement of soft tissue to include bursa and scar will be performed in both groups. Postoperative treatment will be the same for each group. Clinical evaluations and physical exams to include range-of-motion, shoulder impingement signs and tenderness will be performed at one, six, twelve and twenty-four month follow-ups by the physical therapist department. The modified Hospital for Special Surgery (HSS) Score as well as an analog pain, function, and satisfaction score will be used for clinical evaluation. A significant difference in the assessment of strength scores would indicate superiority of one method over the other. MRI evaluations will be performed at six, twelve and twenty-four months. The MRI will be evaluated by an MRI radiologist at the HSS in New York City, New York, who will be blinded to the method of treatment for each patient. Criteria for success by MRI has been established by a recent study performed at the HSS by the radiologist and the principle investigator.

Progress: Seven subjects were entered in FY 99 for a total of 15 subjects enrolled. All patients have had satisfactory or better repair of rotator cuff. Protocol submitted for approval at the Hospital for Special Surgery, New York, NY.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 96/092 | Status: Ongoing |
| Title: A Prospectively Randomized Study on the Effectiveness of Post-Operative Knee Bracing for Anterior Cruciate Ligament Reconstruction | | |
| Principal Investigator: LTC Patrick St Pierre, MC | | |
| Department: Surgery/Orthopedic Surgery | Facility: MAMC | |
| Associate Investigator(s): CPT Michael E. Kirk, MC | | |
| Start Date: 04/19/1996 | Est. Completion Date: May 99 | Periodic Review: 06/22/1999 |

Study Objective: The objective of this study is to compare the effect of different post-operative brace patterns on the final outcome of an anterior cruciate ligament reconstruction. This will be performed by prospectively randomizing patients into two different bracing groups and comparing them with subjective and objective testing during their rehabilitation period.

Technical Approach: In summary, the present knowledge on post-operative bracing for ACL reconstruction is limited. This study is designed to determine if post-operative bracing has an effect on the outcome of an ACL reconstructed patient. A total of 80 patients will participate in the study. After arthroscopically assisted ACL reconstruction patients will be randomized to two study groups. Group A will wear a knee immobilizer for three weeks after surgery followed by no protective bracing for the remainder of their rehabilitation. Group B will wear a Don-Joy IROM brace locked at 0° for three weeks followed by three weeks in the brace with flexion set to 10° less than maximum flexion. At six weeks, the patient will wear a Don-Joy off-the-shelf functional knee brace daily for six months and for vigorous activities after that for at least the first year. Data collected at one, two, six, twelve, and 24 months will include range-of-motion, Lachman, anterior drawer and pivot shift tests, as well as thigh circumference measurements. In addition at the six, twelve and 24 month follow-up visits, KT-100, LIDO, Lysholm and IKDC tests will be administered. A significant difference in the stability or functional assessment scores would indicate superiority of one method over the other regardless of cost. If both treatment groups are found to be equivalent, the most cost effective treatment method would be without bracing.

Progress: No subjects were entered in FY 99. Total subject enrollment is 53. Patient enrollment is completed and patients are now in the two-year follow-up period. No significant differences noted except in patients whose knees hyperextend and they are reconstructed with hamstring tendons.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/095

Status: Ongoing

Title: Delayed versus Immediate Open Repair of Achilles Tendon Rupture; A Randomized Prospective Trial

Principal Investigator: CPT Robert V. Williamson, MC

Department: Surgery/Orthopedic Surgery

Facility: MAMC

Associate Investigator(s): CPT George K. Bal, MC; LTC John D. Pitcher Jr., MC; CPT John Glenden Devine, MC; LTC Frederic L. Johnstone, MC

Start Date:
05/16/1997

Est. Completion Date:
Jun 01

Periodic Review:
07/17/1998

Study Objective: To evaluate the differences in surgically repairing Achilles tendon ruptures immediately, or waiting 10-14 days to perform the repair.

Technical Approach: All patients identified with acute Achilles tendon ruptures, who are being considered for surgical repair, will be presented the option of enrolling in this study. The subjects will be randomized to one of two Groups: Group I - Immediate surgical repair (within 72 hours) of the Achilles tendon, or Group II - delayed (between 10 and 14 days) surgical repair of the tendon rupture. The patients will be randomized using a computer generated randomization table. We will initially randomize the first ten patients, and a subsequent power analysis will be performed at 6 month follow-up to insure that enough patients are enrolled to make our results significant. The next 20 patients will be randomized using a second computer generated table. The post-operative course for both Groups will be the same. The patients will be followed up at 2 week, 6 week, 9 week, 6 month, 12 month, and 24 month intervals. They will be evaluated for post-operative complications and functional outcome.

Progress: Five patients were enrolled in FY 99 for a total of 24 subjects. No adverse events have occurred. This study remains ongoing at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/099

Status: Ongoing

Title: Tendon-Healing to Cortical Bone After Tendon Reattachment Using Suture Anchors. A Biomechanical and Histological Evaluation in Goats

Principal Investigator: CPT Robert V. Williamson, MC

Department: Surgery/Orthopedic Surgery

Facility: MAMC

Associate Investigator(s): LTC Patrick St Pierre, MC; MAJ Ronald E. Nielsen, VC; CPT Jason L. Blaser, MS; CPT Tad L. Gerlinger, MC

Start Date:
04/25/1997

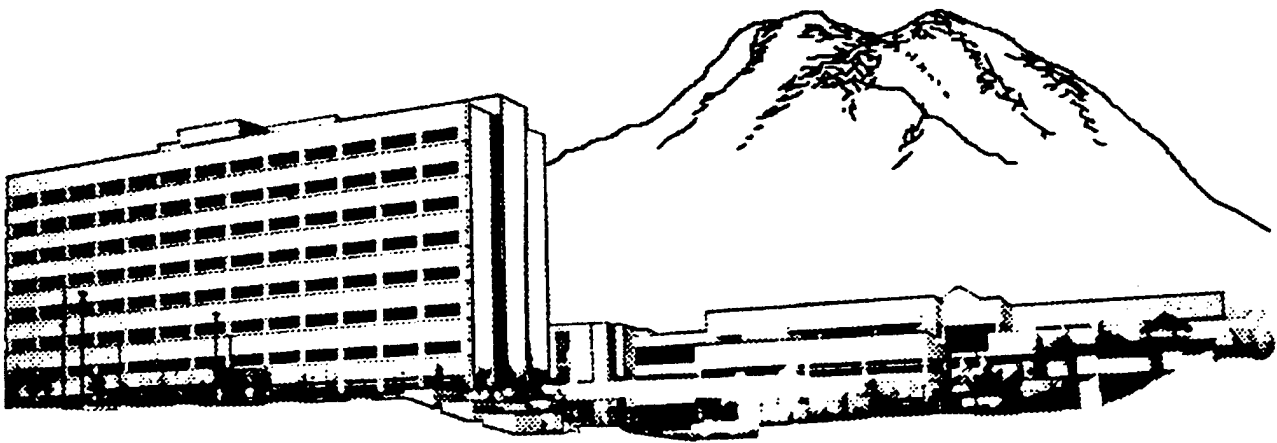
Est. Completion Date:
Apr 00

Periodic Review:
07/17/1998

Study Objective: To examine the biomechanical properties and histological appearance of the bone-tendon interface after rotator cuff tendon repair of the shoulder in goats. The tendon will be reattached directly to the outer surface of the bone (i.e. cortical bone) using four different types of commercially available suture anchors for fixation. This will test if the anchor properties have any effect on healing of tendon to bone after surgical repair.

Technical Approach: An experimental model using the infraspinatus tendon in goats for evaluation of tendon repair has been established. 36 adult (3-5 years old) goats, *Capra hircus*, will be treated with bilateral tenotomy and subsequent reattachment of the infraspinatus tendon. Each test goat will have different types of suture anchors used on contralateral shoulders. The study endpoint will be at six and twenty-six weeks following operative repair. A total of 40 animals will be assigned by randomized block design to the timing and sequence of the operative techniques, the types of fixation, and for biomechanical, histological or control testing. (e.g. The first animal may be randomized to have anchor #1 used in the left shoulder and anchor #4 used in the right. It may be randomized to the histological group. The second animal may be randomized to have anchor #2 used in the left shoulder and anchor #3 used in the right. It may be randomized to the biomechanical testing at 26 weeks). Thirty-six animals will be used for biomechanical testing and four for histological analysis. By performing bilateral procedures in the same animal, we will be able to use pairing to compare different methods of fixation. This increases the statistical power of the study and reduces the number of animals needed.

Progress: This project has not been initiated due to funding issues from the various anchor companies.



Detail Summary Sheets

Otolaryngology Service,
Department of Surgery

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/003

Status: Completed

Title: Modification and Control of Wound Healing in Tracheobronchial Injuries Using Minimally Invasive Surgical Techniques and Biological Growth Regulators

Principal Investigator: CPT George L. Coppit, III, MC

Department: Surgery/Otolaryngology

Facility: MAMC

Associate Investigator(s): MAJ Kenneth S. Azarow, MC; CPT Keith M. Ulnick, MC; MAJ Jonathan A. Perkins, MC; MAJ Larry K. O'Bryant, MC; MAJ Ronald E. Nielsen, VC

Start Date:
10/17/1997

Est. Completion Date:
Oct 00

Periodic Review:
12/15/1998

Study Objective: To test the hypothesis that the topical application of a fibroblastic inhibitor to an airway surgical site will enhance epithelialization, inhibit granulation tissue formation and fibrosis, in the pig (*Sus scrofa*) animal model undergoing airway injury and repair.

Technical Approach: The proposed research study will be in phases and center on external laryngotracheal reconstructive procedures in the pig airway.

Phase I: Wound healing in the airway with stenting alone; 28 pigs will undergo proximal tracheal stenting. Stents will be removed at 1 week, from animals in the 14 and 21 day groups. Evaluation of the healing process will consist of gross histologic examination and compared with a control pig euthanized at each of the same time periods.

Phase II: Wound Healing in the airway with augmentative reconstructive procedures using auricular cartilage; 18 pigs will undergo anterior tracheoplasty with auricular cartilage. Three pigs will be euthanized at 3 and 7 days to describe the healing process. The remaining pigs will be randomized into two groups; one will have no application of biologic modulators and the other will receive topical application of a fibrinoblast inhibitor. The harvested airways will then be assessed grossly and histologically for the degree of inflammation, healing and stenosis.

Phase III: Wound healing in the airway with augmentative reconstructive procedures using auricular perichondrium; 18 pigs will undergo anterior tracheoplasty with auricular perichondrium used for graft material. Three pigs will be euthanized at 3 and 7 days to describe the healing process. The remaining 12 animals will be randomized into two groups; one will have no application of biologic modulators and the other will receive topical application of a fibrinoblast inhibitor. The harvested airways will be assessed grossly and histologically for the degree of inflammation, healing and stenosis.

Progress: No pigs have been used in FY 99 for a total of 28 pigs. MTC seems to prevent the liquefactive necrosis of SS-LTP grafts, allowing improved graft incorporation. While the airway diameter was smaller in treated animals, this may reflect improved structural integrity seen with the better graft incorporation. Further studies are planned to assess the long-term effects of MTC on healing and stenosis following SS-LTP.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/068 **Status:** Ongoing

Title: Pharmacotherapy of Meniere's Disease. Project 1: Effects of General Anesthesia on the Vestibular System

Principal Investigator: CPT James V. Crawford, MC

Department: Surgery/Otolaryngology **Facility:** MAMC

Associate Investigator(s): LTC Vincent D. Eusterman, MC; George A. Gates, M.D.; JO Phillips

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| Start Date: 04/27/1999 | Est. Completion Date: Dec 00 | Periodic Review: N/A |
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Study Objective: Document and quantify the extent of vestibular suppression after general anesthesia.

Technical Approach: The subjects will have an otologic history and then undergo an abbreviated rotating chair test. This non-invasive procedure is a standard clinical test and can be completed in 20 minutes.

The rotating chair is done using the Neuro-Kinetics equipment. The subjects is seated on a chair that rotates gently from the left to the right and back again in a sinusoidal manner at frequencies of from 0.01 to 0.64 Hz at a velocity of 60 degrees/sec. For the purposes of this research the test procedure will be limited to the 0.4 and 0.8 Hz frequencies, where the test-retest results are best. The test is done in the dark with the subject's eyes open after calibrating the system with standard gaze shifts. The resultant eye movements are recorded by skin surface electrodes and digitized, filtered, and the slow phase eye velocity is computed and stored. The average gain, phase, and asymmetry of the vestibulo-ocular reflex eye movements are computed for each test frequency and compared against age normals. A change in gain of 0.5 standard deviations averaged across the 0.04-0.08 Hz frequencies will be the key outcome parameter. Finally, the vestibular time constant will be determined from the time it takes the VOR to stop after a step deceleration of the chair.

To obtain 103 evaluable subjects, we estimate 130 people will need to be test preoperatively, expecting 10% to have abnormal vestibular tests and anticipating that 15 % will not complete the postoperative testing. About 95 % of the subjects are expected to be tested at MAMC, leaving an estimated 5 % to be tested at UWMC. An additional 10 control subjects will be tested at MAMC to ensure the test-retest reliability of our facilities.

Progress: This protocol did not receive final IRB approval until 28 Sep 99; therefore, no patients were enrolled in FY 99.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/002 | Status: Completed |
| Title: The Effects of Functional Septoplasty on Facial Growth | | |
| Principal Investigator: CPT Timothy M. Cupero, MC | | |
| Department: Surgery/Otolaryngology | Facility: MAMC | |
| Associate Investigator(s): None. | | |
| Start Date: 10/20/1998 | Est. Completion Date: Oct 01 | Periodic Review: N/A |

Study Objective: (1) To assess the feasibility of performing this procedure on ferrets, (2) to become proficient in performing septoplasty on ferrets, (3) to assess whether this animal will tolerate the above procedure, and (4) to develop cephalometric analysis to measure facial growth.

Technical Approach: This will be a pilot study to evaluate facial growth in the ferret model following functional cartilage septoplasty (leaving nasal support structures), as compared to resection of portion of isolated bony septum. 10 ferrets, 8 weeks in age will be divided into 3 groups of 3, and all will have a cephalogram taken prior to surgery. One ferret will be sacrificed immediately in order to test for the technical feasibility of the procedure. The first group of three will be used as a control group and will have mucoperichondrial flaps raised only; the second group of three will have functional septal surgery on cartilage with preservation of the septal struts; and the third group of three will have resection of only bony portions of the septum. All groups will have preservation of the mucoperichondrium. The ferrets will then be allowed to grow until 16 weeks of age and then sacrificed. Lateral cephalograms will again be taken; facial growth of the septoplasty groups will be compared to the control group.

Progress: 10 ferrets have been entered in FY 99 for a total of 10 ferrets used. Awaiting completion of data analysis, then paper will be written and submitted.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/008 **Status:** Completed

Title: The Effect of Pre-operative Local Injection of a Steroid/Anesthetic Mixture on Postoperative Tonsillectomy Pain

Principal Investigator: CPT Timothy M. Cupero, MC

Department: Surgery/Otolaryngology **Facility:** MAMC

Associate Investigator(s): SY Kim; MAJ Andrew B. Silva

Start Date:
11/17/1998

Est. Completion Date:
Jan 00

Periodic Review:
N/A

Study Objective: To assess the postoperative benefits, if any, of the preoperative local injection of a steroid/anesthetic mixture into the tonsillar fossa.

Technical Approach: This is a prospective, single-blinded study with postoperative questionnaire consisting of a visual analog scale to assess tonsillar pain between the control and study side during the first 10 days following tonsillectomy. All subjects will undergo tonsillectomy by electrocautery dissection. The study mixture consisting of 1.5 cc of 40 mg/ml Kenalog (60 mg) and 1.5 cc of 0.25% plain bupivacaine (3.75 mg) will be placed in the same syringe and hand mixed. Subjects with SSNs ending with even digits will have the right side injected with the mixture just prior to the procedure; 1 cc superior pole, 1 cc inferior pole, and 1 cc between the tonsil and capsule. The contralateral side will be injected with a similar amount of normal saline in the same locations. Postoperative, subjects will be asked to complete a visual analog scale comparing the pain experienced on each side, 4 hours after surgery and 24 hours later for a total of 10 days. Subjects will be followed up in the ENT clinic for reevaluation and collection of the questionnaire. Data on ER visits for bleeding will be collected at that time.

Progress: 17 subjects have been entered in FY 99 for a total of 17 subjects enrolled. Analysis has shown that pain control is not better on the side injected with the study medications. Because no statistical trend exists there is little value in continuing this study.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/065 | Status: Ongoing |
| Title: AlloDerm Tympanoplasty of Chronic Tympanic Membrane Perforations: An Animal Model | | |
| Principal Investigator: CPT Timothy J. Downey, MC | | |
| Department: Surgery/Otolaryngology | Facility: MAMC | |
| Associate Investigator(s): MAJ Andrew B. Silva; CPT Anne L. Champeaux, MC; MAJ Larry K. O'Bryant, MC | | |
| Start Date: 04/27/1999 | Est. Completion Date: Mar 02 | Periodic Review: N/A |

Study Objective: To determine whether: 1) a chronic TM perforations can be created in chinchillas; 5) tympanoplasty success rates when using AlloDerm vs. fascia on chronic TM perforations in chinchillas; 6) histopathological integration of AlloDerm vs. fascia into the chinchilla TM after healed tympanoplasty of chronic TM perforations in chinchillas; 7) there are complications of AlloDerm vs. fascial graft tympanoplasty on chronic TM perforations in chinchillas.

Technical Approach: The proposed research project will involve 17 adult female chinchillas, weighing approximately 400-700 grams. At the outset, one chinchilla will undergo an ear exam under anesthesia, transcanal creation of bilateral chronic TM perforations, harvesting of temporalis fascia, and then post-auricular approach underlay type I tympanoplasty of AlloDerm in one ear and temporalis fascia in the other. This animal is our practice animal and since the TM perforations are acute, it will be euthanized at the end of these procedures.

Approximately one week later, the remaining 16 chinchillas will undergo surgical creation of chronic TM perforations in both ears.

Creation of chronic TM perforation: All animals will undergo all procedures under general anesthesia. The ear canal will be sterilized with a povidine iodine solution, then irrigated several times with saline. Through a transcanal approach, a thermal myringotomy loop will be used to create an inferior TM central perforation comprising approximately 50% of the pars tensa. The inner mucosal layer of the residual TM around the perforation will be abraded with a right-angle hook. Four radially oriented incisions will be made into the edge of the perforation with a myringotomy knife, thus creating four minute flaps. These microflaps will be infolded medially so that they coapt with the previously roughened mucosal layer of the TM. This procedure will be performed on both TM's. Perforations of this size cause approximately 20dB of conductive hearing loss in the lower frequencies. Any hearing loss that is less than 26dB is considered within normal limits of hearing. The animal's sensorineural hearing will be unaltered.

Postoperatively, the chinchillas will be followed for 6 weeks. Ear exam under anesthesia (EEUA) will be performed weekly. Any debris or inflammatory tissue will be removed. If signs of TM healing are found (i.e. granulation tissue), the microflap procedure will be repeated. At 6 weeks, the EEUA will be repeated on all chinchillas. Those animals with closure of both TM perforations will be removed from the study. One chinchilla with a chronic perforation will be euthanized at this time and the TM will be harvested for histologic analysis. The remaining chinchillas with chronic TM perforations will be randomized before undergoing the following tympanoplasties.

AlloDerm Tympanoplasty: A transcanal and postauricular approach to the TM will be done, creating an anterior-superior based tympanomeatal flap. The middle ear will be examined and packed with small pieces of gelfoam. The AlloDerm (0.3mm thick) will be cut to size and prepared with the instructions provided by the company. The graft will be placed, with the EMC facing

laterally, in the usual underlay Type I tympanoplasty fashion. The TM flap will be placed back into its normal position. The postauricular incision will be closed with 4-0 vicryl and mild chromic sutures, and the external ear canal packed with gelfoam.

Temporalis Fascia Tympanoplasty: The same approach will be utilized. The fascia will be harvested through the postauricular incision in the temporal area and prepared in the usual fashion. The rest of the procedure remains the same.

The chinchillas will be followed for 4 weeks. At this time, all will have an EEUA. Gelfoam will be suctioned from the external ear canals. One chinchilla from each group will be euthanized and their grafted TM's harvested for histologic analysis. At 8 weeks post-tympanoplasty (14 weeks post-perforation), all animals will be euthanized and then will undergo an EEUA with pertinent findings documented. Five animals from both tympanoplasty groups will have the grafted TM's harvested for histologic analysis. During each procedure, documentation will be done of any pertinent findings such as perforation size, granulation/inflammatory tissue, presence of infection, presence of cholesteatoma, graft breakdown, graft perforation, and surgical incision healing. Photodocumentation of the TM's will also be performed. One investigator will be blinded as to which graft material is present in each TM during EEUA. After resection the TM's will be marked for orientation and processed for paraffin embedding. Sections will be cut and stained with hematoxylin/eosin and trichrome. The tympanoplasty TM's will be examined for graft integration into the normal TM remnants and graft thickness. Documentation will be done of any inflammation, fibrosis, tympanosclerosis, epithelial hyperplasia, epithelial ingrowth, epithelial inclusion, or microperforations. The pathologists will also be blinded to the graft material in each TM specimen.

Progress: At 10-weeks after tympanoplasty, 9 of 9 fascia grafts and 9 of 10 AlloDerm grafts had successfully closed the chronic perforations. The tympanic membranes were submitted for histological analysis. Two of the AlloDerm grafted animals were found to have an uncomplicated serous otitis media only at necropsy. Histology results and statistical analysis are still pending.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 94/177 | Status: Completed |
| Title: ENT Surgical Simulator Project | | |
| Principal Investigator: CPT Glen J. Mesaros, MC | | |
| Department: Surgery/Otolaryngology | | Facility: MAMC |
| Associate Investigator(s): Dale Fawcett; Doug Sluis, Ph.D.; Suzanne Weghorst; Bill Winn, Ph.D.; Blake Hanaford, Ph.D.; Don Stredney; Roni Yagel, Ph.D.; Gregory J. Wiet, MD; Bill Bolger, MD; MAJ Charles V. Edmond Jr., MC | | |
| Start Date: 09/02/1994 | Est. Completion Date: Jun 96 | Periodic Review: 12/15/1998 |

Study Objective: To develop and evaluate a minimally invasive prototype surgical simulator to establish real time fidelity requirements for tactile feedback and computer image synthesis.

Technical Approach: This project is a two phase program with the goal of Phase I to construct a simulator prototype to serve as a platform for further enhancement and evaluation. This includes the development of the geometric and virtual database of the human sinus anatomy, the development of a system to track the surgical instruments, and the system software to implement sinuscope camera emulation and tissue dissection. The prototype will provide the novice with the ability to perform a limited sinus surgery procedure on a virtual patient using sinuscope and surgical tools similar to those used in the operating room. Visual recognition skills and psychomotor skills specific to the surgical context are improved through the experience of the simulated surgery.

In Phase II, development will continue by enhancing the simulator to include changes and enhancements suggested by surgeons in the Phase I evaluation. Additional features such as tactile feedback and tissue deformation will be integrated into the prototype as time and budget permit. During Phase II further analysis will determine the simulators training effectiveness in operation.

Progress: This study was completed Oct 98 with eight individuals run on the simulator in all three levels of difficulty and scores were tabulated. Video recordings of actual surgeries were obtained from all levels of training, including staff. These videos were then graded by the staff in a blinded fashion. The final report is still pending.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 96/044 **Status:** Terminated

Title: Pediatric Bronchoesophagology Laboratory Using Swine (*Sus scrofa*)

Principal Investigator: MAJ Andrew B. Silva

Department: Surgery/Otolaryngology **Facility:** MAMC

Associate Investigator(s): Andrew Inglis, M.D.; MAJ Jonathan A. Perkins, MC

Start Date:
01/19/1996

Est. Completion Date:
Jan 99

Periodic Review:
01/26/1999

Study Objective: To familiarize the junior Otolaryngology residents at MAMC and the UW and the Pediatric surgery fellow at CHMC, with endoscopic instrumentation and techniques required to evaluate and treat the tracheobronchial tree and esophagus in children.

Technical Approach: This is a 3-4 hour afternoon laboratory session. During this time, three pigs will be anesthetized under general anesthesia and rigid and flexible bronchoscopy and esophagoscopy will be performed by the course participants under the supervision of an attending endoscopist. Three separate stations will be used so a maximal number of procedures can be performed in the allotted time and the length of anesthesia is shortened. The first station will be for diagnostic flexible and rigid endoscopy. The second will be for tracheobronchial foreign body removal. The third will be for esophageal foreign body removal. A separate station will be used to teach endoscopic lasing techniques on prosected animal tracheal specimens. A morning lecture will be held on pediatric endoscopy prior to the laboratory and a quiz will be given over selected readings in pediatric endoscopy.

Progress: This protocol was terminated, 19 Jan 99, as it had passed the three year approval limit. No sessions were held in FY 99. Protocol #99050 was approved to replace this training protocol.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/050 | Status: Ongoing |
| Title: Pediatric Bronchoesophagology Laboratory Using Swine (<i>Sus scrofa</i>) | | |
| Principal Investigator: MAJ Andrew B. Silva | | |
| Department: Surgery/Otolaryngology | Facility: MAMC | |
| Associate Investigator(s): Andrew Inglis, M.D. | | |
| Start Date: 03/23/1999 | Est. Completion Date: Mar 02 | Periodic Review: N/A |

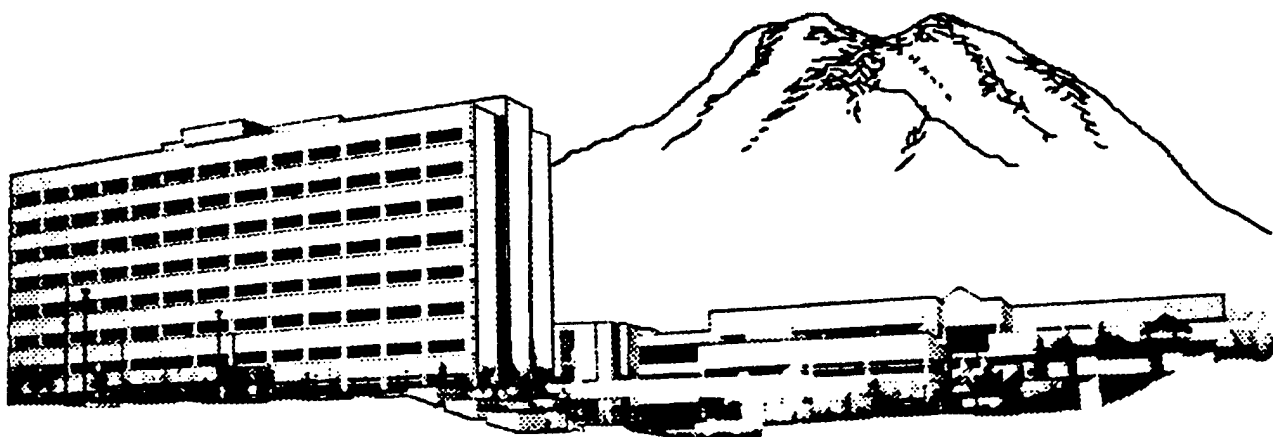
Study Objective: To familiarize the junior otolaryngology residents at MAMC and the UW and the Pediatric Surgery fellows at CHMC, with the endoscopic instrumentation and techniques required to evaluate and treat the tracheobronchial tree and esophagus in children. This would include familiarization with esophageal and tracheal foreign body removal, rigid and flexible endoscopic techniques and endobronchial laser use. Familiarity with these techniques would allow an increased margin of safety for children undergoing these procedures and better prepare the endoscopist to assist and then perform these procedures when necessary. Increased endoscopic training experiences will increase operative efficiency and minimize the potential operative risks involved in these procedures.

Technical Approach: This is a 4-hour afternoon laboratory session. The LARS, under the supervision of an attending veterinarian, will administer the anesthesia. During this time, 3 pigs will be anesthetized under general anesthesia using IM Rompun/ketamine (2.2mg/kg 20mg/kg). LARS will then obtain intravenous access. Once an adequate plan of anesthesia has been reached, the course participants will perform rigid and flexible bronchoscopy with extraction of a foreign body and esophagoscopy under the supervision of an attending endoscopist. In order to maximize the number of procedures that can be performed within the shortest amount of anesthetic exposure, three live animal stations will be used. The first and second station will be used to teach rigid endoscopy and foreign body removal. The third station will be used to teach flexible endoscopy and foreign body removal. There will also be two additional teaching stations. One will involve instrument set up and use, while the other will involve a teaching station for removal of a safety pin.

Approximately 20 endoscopic procedures will be performed on each animal. Foreign bodies will be used that reproduce those encountered in clinical practices (peanuts, beans, Lego). The foreign bodies will be endoscopically placed and extracted from the bronchus and trachea, under direct vision of the participants and instructors. At the end of the laboratory session, the pigs will be euthanized while they are still under general anesthesia in accordance with the IAW LARS SOP for euthanasia.

All course participants will perform bronchoscopies and foreign body removal on models prior to operating on the swine. The course participants will also participate in a half-day didactic component prior to the laboratory session and will be required to undergo a post course quiz. Completion of the training will be determined by the participant's ability to successfully, and atraumatically perform a bronchoscopy and esophagoscopy with airway foreign body removal.

Progress: 25 physicians were trained in FY 99 in the art of using both flexible and rigid diagnostic and therapeutic bronchoscopy and esophagoscopy. Evaluations from the course showed that the participants felt the training was very useful.



Detail Summary Sheets

**Urology Service,
Department of Surgery**

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/158

Status: Ongoing

Title: Multi-center Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicor Inflatable Penile Prosthesis

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; CPT Douglas W. Soderdahl, MC; MAJ John B. Ellsworth, MC; MAJ Henry E. Ruiz, MC; MAJ Raymond S. Lance, MC

Start Date:
08/16/1996

Est. Completion Date:
Oct 02

Periodic Review:
09/15/1998

Study Objective: The primary effectiveness objective is to evaluate the ability of the AMS Ambicor inflatable penile prosthesis to provide an erection suitable for sexual intercourse (device function) as determined by physical examination and patient self-report. Secondary effectiveness objectives include estimating the effects of the prosthesis on patient sexual function and satisfaction, self-esteem, quality of life, and psychological well-being. The study will also evaluate levels of patient satisfaction with various aspects of the prosthesis including rigidity, length, girth and flaccidity. Safety will be evaluated by measuring rates of post implant complications (including device malfunction) and the occurrence of medical conditions.

Technical Approach: This is a multi-center, prospective, cohort study with the pre-implant experience of patients serving as the comparison for the evaluation of effectiveness and safety. The study sample will be derived from patients who present to the clinic with the diagnosis of erectile dysfunction. After an eligible patient makes an informed decision to be implanted with an AMS Ambicor penile prosthesis and signs the surgical consent he will be asked to participate in the study. A total of 250 patients will be recruited nationwide (12-20 being from MAMC) and will be implanted with the Ambicor inflatable penile prosthesis. The primary measure of effectiveness (sexual function, self-esteem, and psychological well-being), will be monitored for 2 years with visits at 6 weeks post-surgery, 6 months, 1 year, 18 months and 2 years. Follow-up for complications, associated medical conditions and other adverse device effects will be followed for 5 years with phone contact at 3 and 4 years, and a visit at 5 years.

Progress: Six patients were entered in FY 99 for a total of 25 subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/023 **Status:** Terminated

Title: Quality of Life of Female Patients After Anti-incontinence Surgery

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; LTC Leland D. Ronningen, MC; COL John C. Norbeck, MC; COL Gary D. Davis, MC; Kerry Meyers, Ph.D.; MAJ Henry E. Ruiz, MC; CPT Jerome L. Buller, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; MAJ Raymond S. Lance, MC

Start Date:
12/18/1997

Est. Completion Date:
Aug 01

Periodic Review:
12/15/1998

Study Objective: To determine if the quality of life of female patients suffering from stress urinary incontinence is improved after anti-incontinent surgery and which of the two most commonly performed procedures, Raz Urethropexy or sling procedures, has the greatest improvement in quality of life of female patients with stress urinary incontinence.

Technical Approach: Patients will be divided into 2 groups. Group 1 will be those patients having sling procedures. Group 2 will be those patients having the Raz Urethropexy. All patients will be evaluated pre-operatively. The questionnaire will be administered pre-operatively and post-operatively at 1, 3, 6, and 12 months and yearly for a total of four years. Two questions will be added to the post-operative questionnaire.

Progress: Standard of care at MAMC for female incontinence is the sling procedure; therefore this no patients were enrolled and this study was terminated.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/031

Status: Completed

Title: Dose Escalation Study with Tolterodine in Patients with Overactive Bladder. A Single-Blind Study in Patients with Symptoms of Overactive Bladder Including Urinary Urgency and Frequency With or Without Urge Incontinence

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; COL John C. Norbeck, MC; LTC Leland D. Ronningen, MC; CPT Keith J. O'Reilly, MC; MAJ John B. Ellsworth, MC; MAJ Henry E. Ruiz, MC; MAJ Bryon D. Joyner, MC; CPT Karen C. Evans, MC; MAJ Raymond S. Lance, MC

Start Date:
12/18/1997

Est. Completion Date:
Feb 99

Periodic Review:
04/27/1999

Study Objective: 1) Ascertain in a 16 week study the percentage of patients with overactive bladder who will require a dose reduction or escalation of tolterodine dose when the initial treatment dose will be 1 mg bid; 2) investigate the incremental clinical improvement in efficacy in those patients who increase tolterodine dose to 2 mg bid; 3) identify factors which predict response to tolterodine without urodynamic evidence of detrusor instability.

Technical Approach: A wash out and run in period of 10 days (visit 1) will precede the start of tolterodine treatment. Treatment with tolterodine will start at visit 2. After two weeks of treatment, the patient will be called to report on compliance and possible adverse events. At week 4, the patient will come to the office (visit 3) where the dose of tolterodine may be adjusted according to the investigator's evaluation of effectiveness and tolerance. The next visit will be after 4 weeks of treatment to evaluate the response to the drug and safety. The patient will continue on the chosen dose another 8 weeks. At that time, information about drug efficacy, compliance, and any adverse events will be collected. If a patient cannot tolerate 1 mg bid, he/she will off study.

Patients opting for the open-label segment (Part B) will undergo a two week follow-up/washout period prior to visit 6.

Progress: Seventeen patients were entered in this study with no adverse events reported at MAMC. The study has been closed to enrollment; however patients will continue on treatment for several months.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/044 **Status:** Terminated

Title: A Phase II, Double-Blind, Randomized, Placebo-Controlled, Crossover Study of the Safety and Efficacy of Dapoxetine HCl in the Treatment of Premature Ejaculation

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; MAJ Raymond S. Lance, MC; MAJ Bryon D. Joyner, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC

Start Date:
02/23/1999

Est. Completion Date:
May 99

Periodic Review:
N/A

Study Objective: a) To determine safety of dapoxetine (20, 40, and 60 mg prn) in subjects with premature ejaculation. b) To determine the efficacy of dapoxetine in managing the signs and symptoms of premature ejaculation. c) To determine whether there is a dose-response relationship (20, 40, and 60 mg prn) as a basis for selecting the optimal dose for managing symptoms of premature ejaculation.

Technical Approach: This study uses a double-blind, randomized, placebo-controlled four period crossover design, conducted at 14-16 sites, to assess the safety and efficacy of dapoxetine in the treatment of premature ejaculation in adult heterosexual males. Screening and a lead-in period will precede randomization. Approximately 200 Subjects will be screened. Those Subjects who meet the eligibility criteria will receive a notice of enrollment within 2 weeks of the screening visit. After the Subject confirms his enrollment by telephone, he will be considered to have enrolled in the lead-in period. It is expected that approximately 150 Subjects will be enrolled in the lead-in period of the study. No study medication will be administered during the lead-in period. Those Subjects who have made at least four attempts at intercourse during the lead-in period and who meet all other entry criteria will be randomized to one of four treatment sequences comprising placebo, 20 mg, 40 mg, or 60 mg dapoxetine. These study treatments will be administered during a series of four periods, each study period having a maximum duration of 4 weeks. For each period, Subjects will be encouraged to attempt intercourse 4-6 times. A bottle containing six doses (12 capsules) of the first dosage of randomized study medication will be distributed at Visit 2. During the study periods Subjects will take a dose of study medication (two capsules) within 1-3 hours prior to anticipated sexual activity. Study medication is not to be taken more than one time per day. Administration of each dose of study medication will be recorded in the event log. At the end of each period, the Subject will return to the study site to complete the efficacy and safety assessments. Any unused study medication from the preceding period will be collected at this visit. A bottle containing six doses (12 capsules) of a new dosage of randomized study medication will be distributed for use in the following treatment period at Visits 3, 4, and 5. An interim analysis will be conducted and an integrated clinical and statistical report will be generated after the first period using statistical techniques for a parallel trial with four treatment groups. However, trial continuation is not contingent on the interim analysis results. For the final analysis, statistical tests will be performed with adjustment of the criterion probability value to preserve an overall ($\alpha=0.05$). It is expected that approximately 100 Subjects will complete Period 1. Over the four treatment periods, each Subject will have received placebo, 20 mg, 40 mg, and 60 mg dapoxetine. There will be no washout period between the treatment periods. On the basis of the combined data from all four periods, the efficacy will be evaluated using a repeated measures analysis of variance appropriate to the crossover design. Further, the dose response relationship will be estimated using the same statistical model. It is expected that approximately 80 Subjects will complete all four treatment periods. The efficacy of dapoxetine will be assessed primarily by comparing

ejaculatory latencies recorded with a stopwatch by the Partner and entered in the event log (See Appendix B). Secondary variables that will be used in the evaluation of success during intercourse will include the incidence of ejaculation during foreplay, Subject and Partner Premature Ejaculation Questionnaires (PEQs), and Subject and Partner global satisfaction scores. Safety will be assessed by clinical laboratory analyses, vital signs, ECGs and physical examination data obtained at each visit as well as adverse experience reports collected throughout the study.

Progress: This protocol was terminated by the study sponsor one day following final IRB approval at MAMC. No patients were enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/048

Status: Completed

Title: Screening Protocol for Identification of Patients with Erectile Dysfunction for Participation in Schering Study P00186 (Twelve-Week Double-Blind Treatment of Oral Phentolamine, Oral Sildenafil Citrate vs Placebo)

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ Raymond S. Lance, MC; MAJ Bryon D. Joyner, MC; CPT Karen C. Evans, MC; LTC Robert C. Allen, Jr., MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Andrew C. Peterson, MC

Start Date:
03/23/1999

Est. Completion Date:
Aug 99

Periodic Review:
N/A

Study Objective: The objective of this study is to identify patients with mild to moderate erectile dysfunction who will qualify for participation in a twelve-week treatment efficacy and safety study of oral phentolamine and oral sildenafil citrate compared to placebo.

Technical Approach: This is a multicenter (30 US sites) screening study that consists of a four-week treatment free screening period. Subjects (patients) will be screened to determine eligibility for participation in Schering Study P00186. Following the initial screening at Visit 1, eligible subjects will be given practice diaries (sexual encounter profile log and Time to Erection Questionnaire) to complete after each sexual attempt during the four-week treatment free run-in period. After the four-week run-in, subjects will return to study site. If eligible for participation in Study P00186, in treatment study, they will be randomized to double-blind treatment in Schering Study P00186. If ineligible for study participation in Schering Study P00186, they will end participation and undergo a 30-day follow-up period to assess general health status.

During the treatment free run-in period, the subjects will be required to attempt sexual intercourse (vaginal) at least four times during a four-week interval. Attempts must occur on separate days. Subjects should be instructed to refrain from drinking more than two drinks of alcohol within two hours of sexual attempt. Sexual stimulation is required prior to each attempt. Safety will be assessed by adverse event monitoring.

Progress: This study closed to patient accrual 31 Aug 99, per sponsor request as enrollment numbers had been met. 14 patients were consented at MAMC. Of these 14, 6 were screening failures and 2 were withdrawn by the sponsor as it was felt these patients did not meet inclusion criteria. 6 patients completed this screening protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/054

Status: Completed

Title: A Double-Blind, Twelve-Week Comparative Efficacy and Safety Study of Oral Phentolamine Mesylate, Oral Sildenafil Citrate Vs. Placebo in Patients with Erectile Dysfunction

Principal Investigator: MAJ Sunil K. Ahuja, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ Raymond S. Lance, MC; MAJ Bryon D. Joyner, MC; CPT Karen C. Evans, MC; LTC Robert C. Allen, Jr., MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; CPT Andrew C. Peterson, MC

Start Date:
03/23/1999

Est. Completion Date:
Aug 99

Periodic Review:
N/A

Study Objective: The objective of this study is to determine the efficacy and safety of oral phentolamine mesylate (40 mg, 80 mg), sildenafil citrate (50 mg, 100 mg) each compared to placebo using the same evaluation methods in patients with mild to moderate erectile dysfunction.

Technical Approach: This is a multicenter (30 US sites), randomized, double blind, placebo-controlled, parallel group, titration study. The entire study consists of four study periods: screening, a four-week treatment free run-in, 12-week double-blind treatment and 30-day post treatment follow-up. Subjects (patients) will be screened to determine eligibility for randomization. After the four-week run-in, subjects will return for Visit 2. If eligible for randomization, they will be randomized to Dose Level 1 double blind treatment. After four weeks of double blind treatment, subjects will titrate to Dose Level 2 medication for titration for an additional eight weeks, if subject reports an inadequate treatment response to Dose Level 1 medication as determined by protocol titration criteria. For those who have an adequate treatment response and treatment is tolerable, treatment will continue as Dose Level 1 for an additional eight weeks.

During the treatment free run-in and double blind treatment periods, the subjects will be required to attempt sexual intercourse (vaginal) four times per four-week interval. Attempts must occur on separate days. Efficacy will be assessed using a global efficacy question (GEO), the International Index of Erectile Function (IIEF), and a sexual encounter event log diaries (SEP). Safety will be assessed by adverse event monitoring. The double-blind treatment period will be followed by a 30-day follow-up period. A telephone contact will be made to assess the patient's general health status.

Progress: Data on 6 subjects have been collected during FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/080

Status: Ongoing

Title: Phase III Randomized Study of a Single Adjunctive Instillation of Intravesical AD-32 (N-Trifluoroacetyladiamycin-14-Valerate) versus No Adjunctive Therapy Immediately Following Transurethral Resection in Patients with Multiple Superficial (Ta/T1) Bladder Tumors

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; MAJ Sunil K. Ahuja, MC; MAJ Bryon D. Joyner, MC; MAJ Raymond S. Lance, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC

Start Date:
07/27/1999

Est. Completion Date:
Dec 00

Periodic Review:
N/A

Study Objective: To assess the efficacy of a single 800 mg dose of intravesical AD-32 administered adjunctively, i.e., within two to twenty-four hours following a complete transurethral resection of presumed stage Ta or T1 bladder tumors, in 1) extending the time to recurrence in patients with Ta tumors; 2) reducing the rate of disease recurrence during the first 12 months following treatment in this patient population; 3) reducing the rate of and/or delaying the time to disease progression in patients with T1 tumors; 4) improving the outcome of patients diagnosed with stage T1 tumors and/or concurrent Tis [carcinoma in situ (Cis or stage Tis tumor)] treated subsequently with intravesical BCG therapy. Also, the toxicity of AD-32 treatment in this setting, including its effect on subsequent BCG immunotherapy, will be evaluated.

Technical Approach: This is an open-label, randomized, multicenter clinical study comparing adjunctive intravesical therapy with AD 32 immediately following a complete transurethral resection of bladder tumors (TURB) to TURB alone. Approximately 300 adult patients at 65 sites will be enrolled. Patients presenting with newly diagnosed or recurrent multifocal superficial transitional cell carcinoma of the bladder (> or = two presumed stage Ta or T1 tumors) will be treated with complete TURB. Then, immediately prior to catheter removal, patients will be randomized to receive either a single adjunctive intravesical instillation of 800 mg AD 32 within 2 to 24 hours of resection, or no peri-surgical therapy. Patients will be observed for two hours after TURB whether or not they receive AD 32. Patients with T1 tumor(s) or concurrent Tis based on pathological analysis of biopsies performed at the time of surgery will receive immunotherapy with intravesical BCG starting > or = 7 days but no later than 21 days after TURB (treatment schedule: six weekly instillations, a six week "rest period", and three additional weekly instillations). All patients will be followed at 3 month intervals until disease recurrence or progression, or for two years following treatment. Laboratory and diagnostic studies will be performed including medical history, CBC, serum chemistry, vital signs, physical examination and clinical observations for bladder symptoms, toxicities and adverse effects. Samples from all resected tumors and random biopsies will be analyzed locally to determine the pathological stage and histological grade of tumors; samples will also be reviewed by a central reference laboratory. All patients will undergo cystoscopy and cytology at each visit for 104 weeks (2 years) or until recurrence; in addition, patients determined to have Tis in post-surgical pathology analysis will undergo complete bladder mapping at the Week 13 evaluation and urine cytology analysis every 13 weeks for 104 weeks following TURB.

Progress: Approved late Aug 99. Awaiting drug shipment.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/089

Status: Ongoing

Title: Phase III Randomized, Double-Blind Study of DFMO vs. Placebo in Low Grade Superficial Bladder Cancer

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; MAJ Bryon D. Joyner, MC; MAJ Sunil K. Ahuja, MC; MAJ Raymond S. Lance, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC

Start Date:
08/24/1999

Est. Completion Date:
Mar 03

Periodic Review:
N/A

Study Objective: To compare DFMO to placebo in patients with low grade superficial bladder cancers according to a) time to first recurrence of tumor, and b) toxicities.

Technical Approach: This will be a phase III randomized, double blind study of DFMO (an inhibitor of ornithine decarboxylase) versus placebo in low-grade superficial bladder cancers. Patients who meet the eligibility criteria will be stratified according to 1) history of newly diagnosed vs. recurrent; 2) stage Ta vs. T1; 3) grade 1 vs. grade 2; and 4) multifocal vs unifocal tumors. Then patients will be centrally randomized to receive either DFMO 1 gm/day or placebo, orally for 12 months in a double-blind fashion. Treatment will be discontinued in the presence of biopsy-proven recurrent disease, unacceptable toxicity, or patient refusal; however, every effort will be made to continue follow-up on these patients until the end of study. Patients will be followed with cystoscopy every three months for 2 years (every 6 months the 3rd year and annually for the 4th year). Based on 1.5 year enrollment and 3 year follow-up, study duration will be 5.5 years. CBC, including platelet count will be required within 12 weeks of randomization and at 6 months. An audiogram will be required at baseline and when indicated during the study. An independent pathologist will centrally review tumor specimens.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/090

Status: Ongoing

Title: A Randomized Double-Blind Placebo-Controlled Phase III Trial Evaluating Zoledronate Plus Standard Therapy versus Placebo Plus Standard Therapy in Patients with Recurrent Carcinoma of the Prostate Who Are Asymptomatic with Castrate Levels of Testosterone and Have Rising PSA Levels Without Radiologically-evident Metastatic Disease

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ Bryon D. Joyner, MC; MAJ Raymond S. Lance, MC; MAJ Sunil K. Ahuja, MC; LTC Robert C. Allen, Jr., MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC; MAJ Henry E. Ruiz, MC; MAJ David E. McCune, MC

Start Date:
08/24/1999

Est. Completion Date:
Oct 05

Periodic Review:
N/A

Study Objective: To determine if intravenous infusions with 8mg zoledronate is superior to placebo in the prevention of bone metastases.

Technical Approach: This is a prospective, stratified, randomized, double blind, placebo-controlled multicenter study in parallel groups. Five hundred prostate cancer patients with castrate levels of testosterone who are progressing biochemically by PSA only and have no radiologically evident metastases will be enrolled. Patients will be stratified according to the prior local treatment and the time interval between surgical castration or initiation of LHRH agonist and trial entry. Patients will receive double-blind study treatment until the development of bone metastases. After the development of bone metastases, all patients will receive open-label 8 mg zoledronate until the end of the study. Both the double-blind treatment phase and the open-label treatment phase have a fixed assessment schedule that must be followed. Once patients have completed the 48th month of the fixed assessment schedule, all patients will be followed for survival until LPLV (Last Patient Last Visit). LPLV for this study is defined as the time when the last patient completes the 4th month of study visit or has died. Assuming a placebo bone metastases-free survival rate of 20% at 2 years, this study is powered to determine if sequential infusion with 8 mg zoledronate administered every 4 weeks is superior to placebo in increasing the bone metastases- survival rate at 2 years to 32% (reduction of the hazard rate of bone metastatic disease in patients with prostate cancer by 29%). It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis. The Biostatistics department of Novartis will analyze the data from this study.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/091

Status: Ongoing

Title: A National Phase II Trial of Intron Interferon (Alpha 2b) Plus BCG for Treatment of Superficial Bladder Cancer

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; MAJ Raymond S. Lance, MC; MAJ Bryon D. Joyner, MC; MAJ Sunil K. Ahuja, MC; CPT Keith J. O'Reilly, MC; CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC

Start Date:
08/24/1999

Est. Completion Date:
Jul 03

Periodic Review:
N/A

Study Objective: 1) To determine the clinical efficacy of combination BCG plus interferon-alpha 2b (IFN-alpha) immunology among various clinical subgroups with superficial bladder cancer including those that have failed prior therapy. 2) To determine the relative local and systemic toxicities of BCG plus IFN-alpha intravesical therapy and the effect on quality of life. 3) To determine the effect of BCG dose reduction during therapy on symptom tolerance and ability to maintain an extended treatment plan.

Technical Approach: The purpose of this study is to evaluate combination therapy for efficacy and toxicity in divergent groups of patients with superficial bladder cancer including those that have failed other forms of intravesical therapy. Depending on past history of BCG treatment and tolerance, patients will be enrolled into one of 3 arms for 6 weekly induction treatments: Arm 1 - full dose BCG for previously BCG untreated patients; Arm 2 - 1/3 dose BCG for prior BCG failures without intolerance; and Arm 3 - 1/10 dose BCG for BCG intolerant patients or those undergoing re-induction after prior BCG/IFN-alpha failure. The IFN- alpha (intron A) dose will be 50 million units (50 MU) in the first 2 arms and IOOMU in Arm 3. A maintenance program adapted from SWOG's successful 3 weekly mini-series regimen will involve 3 cycles given 3, 9, and 15 months after the end of the induction cycle.

Toxicity and treatment tolerance will be determined based on patient symptom scores, a previously validated quality of life instrument, and clinician assessment. The use of BCG dose adjustment and/or delay or initiation of specific treatment will follow specific recommendations and results captured. Additional BCG dose adjustment may be permitted in special circumstances after approval from the National Principal Investigator. Premature termination of induction treatments will require study termination but abandonment of any or all maintenance treatments will not. Any tumor recurrence during the maintenance phase or any cancer progression will likewise require study termination. Patients with tumor recurrence after initial induction but before initiation of maintenance therapy may be re-treated in Arm 3. Treatment response will be assessed using standard of care bladder cancer monitoring every 3-4 months for 2 years with cystoscopy, urinary cytology, and biopsies when clinically indicated.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/095 **Status:** Ongoing

Title: The Evaluation of Seminal Leucocytes and Cytokine Function of Infertile Males

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): None.

Start Date:
8/24/1999

Est. Completion Date:
Sep 01

Periodic Review:
N/A

Study Objective: To evaluate leucocyte function in infertile males and fertile controls.

Technical Approach: Patients seen in infertility clinic have a semen analysis as part of their routine evaluation. An aliquot of this semen analysis (approximately 10 microliters) will be cryopreserved in liquid nitrogen for immunohistochemical and microscopic (H&E) analysis for leucocyte, cytokine and germ cell composition and cataloging. Cell types will be counted on a hemocytometer to determine leucocyte composition after preferential staining with immunoreagents. Measurement of ROS by luminol florescence will be performed on fresh aliquots of semen specimens. Semen aliquots will also be obtained from patients undergoing vasectomy and vasectomy reversal. These aliquots will serve as controls (healthy, fertile males) and changes in leucocyte/cytokine composition before and after sterilization/reversal can also be documented. Semen analysis from vasectomy patients (known fertile controls) will be analyzed before and after vasectomy to establish mean populations of seminal leucocytes in healthy "normal" males. By measuring these populations before and after vasectomy, the testicular WBC contribution will be established. These "norms" of seminal WBC population can then be compared to infertility patients to evaluate any deviation in seminal leucocyte population. Immunoassays will be performed to measure levels of Interferon alpha, beta, gamma, as well as IL-2, IL-6 and TNFalpha. Additional cytokines may be measured as immunoassays are developed. Total seminal leucocyte count and differential seminal leucocyte count will be compared in infertile males and fertile male controls using the Student's two-sample t test to evaluate statistical significance. Seminal cytokine levels in fertile and subfertile males will also be analyzed using the Student's two-sample t test.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 99/096 | Status: Ongoing |
| Title: Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens | | |
| Principal Investigator: LTC Raymond A. Costabile, MC | | |
| Department: Surgery/Urology | | Facility: MAMC |
| Associate Investigator(s): None. | | |
| Start Date: 8/24/1999 | Est. Completion Date: Sep 01 | Periodic Review: N/A |

Study Objective: 1) Describe the gross and microscopic blood supply to the vas deferens. 2) Assess the variability of the arterial and venous structures. 3) Assess collateral blood supply to the vas deferens. 4) Utilize the new understanding of the vascular supply to improve operations on the spermatic cord, scrotal adnexa and vas deferens.

Technical Approach: Gross dissection of the, deferential blood supply: a) Gross dissection of cadaveric and specimens; b) Dissection of en bloc spermatic cord specimens from fresh and frozen cadavers; c) Microdissections on cadaveric specimens and autopsy specimens and recording of findings using photos and drawings. Microscopic description of deferential blood supply: a) Injection studies will be performed using India ink injections of the deferential artery, internal iliac artery and internal spermatic artery; b) Histologic sections will be performed using a dissecting microscope in the straight and convoluted portions of the vas deferens sagittally and transversely. These sections will be recorded using photomicrographs and drawings from medical illustrators.

The microscopic penetration of blood supply to human tissue does not lend itself to variability. The means by which arteries penetrate the wall of the vas deferens will likewise have minimal variability in normal vas deferens and deferential arteries. For this reason microdissection of 10 cadavers will give 20 examples of the method of penetration, providing more than 'adequate numbers for our purposes. The cadavers will be supplied from the Anatomical Teaching Lab at USUHS. They will either be fresh or frozen cadavers. A total of 10 cadavers will be required for this study.

Documentation of the blood supply to the vas deferens will be performed using photographs. Please see attached data collection sheet. Medical illustrations will be required since this is an anatomical study, picture will be needed to present and/or publish data from this study. Medical illustrations will be done at the Graphics Department at USUHS or through the Graphics Department at HMJF.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/101

Status: Ongoing

Title: A Six-Month, Two-Part, Sequential, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Endocrine Efficacy of Monthly Doses of LA-2500 in Patients with Advanced Prostate Cancer

Principal Investigator: LTC Raymond A. Costabile, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; Donna Ruttkay, BS, CCRC; Caryn Goolsby, RNC

Start Date:
9/28/1999

Est. Completion Date:
Oct 00

Periodic Review:
N/A

Study Objective: To evaluate the safety, tolerance, pharmacokinetics, and endocrine efficacy of monthly doses of a novel SC depot formulation of 7.5 mg leuprolide acetate (LA-2500) in patients with advanced prostate cancer.

Technical Approach: This is a multicenter, two-part, sequential, open-label, fixed-dose investigation of six monthly doses of LA-2500 administered to patients with Jewett Stage C1, C2, DI, or D2 adenocarcinoma of the prostate. A total of approximately 120 patients (30 patients in Part I and 90 patients in Part II) will receive a single, SC injection of LA-2500 every month (28 days) for six months. The study will be divided into two sections, Part I and Part II. During Part I, approximately 30 patients will be enrolled, given LA-2500, and evaluated. Twenty of the patients in Part I (denoted Group A) will have serum leuprolide acetate levels measured during the study for pharmacokinetic analysis. Once the 30 patients in Part I have completed through Day 42 (two injections of LA-2500), serum leuprolide acetate, T, LH, PSA, fractionated alkaline phosphatase, and safety data (including adverse experiences and safety labs) will be collated and summarized. While this analysis and summarization is being performed and reviewed, Part I patients will continue to be treated monthly with LA-2500 (provided that testosterone suppression is acceptable) and followed per the protocol. All Part I patients must complete through Day 42 (two injections) before Part II of the study can begin and the additional 90 patients enrolled. Both Part I and Part II patients will be followed for six months.

Descriptive pharmacokinetic parameters, including the maximum serum leuprolide concentration (C_{max}), time of maximum serum concentration (T_{max}), and area under the serum leuprolide concentration versus time curve for various time periods (0-28 days, 28-56 days, 56-84 days, and potentially other time intervals), will be determined. Observed values will be used for C_{max} and T_{max}. Area under the serum concentration versus time curve will be calculated using linear trapezoidal integration over the respective time limits. Plots of serum leuprolide concentrations versus time will be constructed for individual patients and for the mean values of all patients. The time scale for the plots will be selected to best present the observed data. Concentrations of serum leuprolide are expected to increase and vary somewhat within an initial equilibration phase, then approach a plateau. The time required to reach the plateau phase will be estimated from observed data. In addition the duration of measurable concentrations of serum leuprolide will be defined as the time of the last measurable serum leuprolide concentration. The steady-state average concentration during the plateau phase will be calculated as the area under the curve (AUC) for the plateau time interval divided by the duration of the plateau phase. Additional parameters or modifications of the stated parameters or analysis methods may be necessary to best describe the results.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 98/077 | Status: Completed |
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Title: Depo-Provera Therapy for Hot Flushes Associated with Hormonal Treatment of Advanced Carcinoma of the Prostate

Principal Investigator: MAJ John B. Ellsworth, MC

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|------------------------------------|-----------------------|
| Department: Surgery/Urology | Facility: MAMC |
|------------------------------------|-----------------------|

Associate Investigator(s): CPT Keith J. O'Reilly, MC; LTC Leland D. Ronningen, MC; MAJ J. Brantley Thrasher, MC

| | | |
|----------------------------------|--|---------------------------------------|
| Start Date: 06/19/1998 | Est. Completion Date: Apr 98 | Periodic Review: 07/27/1999 |
|----------------------------------|--|---------------------------------------|

Study Objective: To determine response rates to Depo-provera for the treatment of hot flushes in hormonally treated males with advanced carcinoma of the prostate and compare these rates to published rates of alternative monotherapy regimens.

Technical Approach: The depo-provera treatment is not part of this research study. The only difference from standard treatment is patients will be contacted during regularly scheduled clinic visits, or by phone at 1, 3, 6 and 12 months after treatment has been initiated to assess frequency and severity of hot flushes. Retrospective information on frequency and severity of hot flushes prior to therapy initiation will be pulled from patient chart review.

Progress: Retrospective review revealed that there is nothing available (unless DES comes back, but it has greater adverse effects) as effective as Depo-provera for the treatment of hot flushes. DES is roughly equivalent but carries high risk of stroke, DVT and MI. A question was raised, since DPV is an androgen, is there any increase of disease progression due to prostate cancer androgen receptor binding? Though few in number, many patients, followed for 18 months, showed no acceleration of disease progression on DPV. Another point made was that many patients can stop DPV after 3-6 months and still have ablation of hot flushes. This was seen in this study and planned to be looked at in a future prospective study. Due to PCS of the PI, only the retrospective portion of this study was completed. The study was closed 24 Jun 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 94/051 **Status:** Ongoing

Title: Immunohistochemical Localization of Insulin-Like Growth Factor (IGF) Binding Proteins in Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): Stephen R. Plymate, M.D.; MAJ Richard R. Gomez, MC; CPT Michael D. Bagg, MC; CPT Patrick A. Twomey, MC; MAJ J. Brantley Thrasher, MC

Start Date:
04/01/1994

Est. Completion Date:
Jan 95

Periodic Review:
06/22/1999

Study Objective: The purpose of this study is to localize IGFBP's -2,-3,-4, and -6 in regions of histologically proven prostate cancer. Additionally, these same techniques will be used to identify these binding proteins in areas of prostatic intraepithelial neoplasia (PIN) and benign prostatic hyperplasia (BPH). The information gleaned from this study will help better understand IGFBP expression in both malignant, premalignant, and benign prostatic tissue.

Technical Approach: Radical prostatectomy specimens will be obtained by the Urology Service and taken to Pathology for histologic sectioning. Prostate adenocarcinoma will be identified in sections (as well as areas of PIN or BPH) with an adjacent section taken for immunohistochemical staining. Immunohistochemical staining will be performed for identification of IGFBP's -4, -2, -3, and -6 in regions of associated neoplasms, PIN or BPH. Approximately 10 patients will be studied with comparisons to be made between neoplastic premalignant, and benign prostatic tissue.

Progress: 10 subjects have been entered in FY 99 for a total of 168 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/104 **Status:** Ongoing

Title: Telomere Length and Telomerase Activity in Human Testicular Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): CPT Wade K. Aldous, MS; MAJ J. Brantley Thrasher, MC; MAJ Kenneth W. Westphal, MC; CPT Keith J. O'Reilly, MC; Troy H. Patience, B.S.; Lisa M. Pierce, D.Sc.

Start Date:
06/16/1995

Est. Completion Date:
Jul 97

Periodic Review:
06/22/1999

Study Objective: This study encompasses four objectives. To determine the presence or absence of telomerase activity in tumorous testicular tissue and normal tissue. To observe the average telomeric length of both tissue types to compare differences in length, hypothesizing that tumor tissue would have shorter telomeres. To quantify telomerase activity in tissues with an active enzyme. To determine the relationship, if any, between activity of telomerase and the stage and grade of testicular cancer.

Technical Approach: Tissue samples will be taken from 40 male patients undergoing surgical resection for testicular cancer. All malignant and benign tumor types resected during surgery will be investigated. Tissue from the tumor and from surrounding histologically normal areas will be transferred from the Dept. of Pathology to the Dept. of Clinical Investigation. Genomic DNA will be extracted from the tissues and subjected to Rsa1 and Hinf1 restriction digestion. The fragments will then be separated by agarose gel electrophoresis, Southern blotted, and detected by chemiluminescence using a digoxigenin-labeled telomere probe. These will be visualized by x-ray film exposure and will provide the composite lengths of all telomeres in a cell population. Actual telomerase activity in tumorous and normal tissue will also be measured by extracting the enzyme from tissues and assaying for activity. The positive control is an immortalized cell line. Activity is measured by the successful incorporation of radio-labeled dGTP nucleotide into the telomere repeats on a known DNA primer. These will be separated on a polyacrylamide gel and quantified by densitography. The differences in telomere length will be tested by a non-parametric T-test. Chi-square analysis will be used to test for telomerase activity assuming normal tissue has inactive enzyme and tumor tissue has active enzyme. The paired T-test will be used to quantify telomerase activity compared to positive controls and a non-parametric ANOVA will be used to determine the correlation between the amount of activity and the stages and grades of tumors.

Progress: 1 subjects have been entered in FY 99 for a total of 4 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/134 **Status:** Completed

Title: Comparative Study of the Clinical Efficacy of Two Dosing Regimens of Eulexin:
250 mg Q8h vs 500 mg QD

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): LTC Kurt L. Hansberry, MC; COL John N. Wettlaufer, MC;
CPT Douglas W. Soderdahl, MC; MAJ Henry E. Ruiz, MC; COL John C. Norbeck, MC;
MAJ J. Brantley Thrasher, MC

Start Date:
05/19/1995

Est. Completion Date:
Jul 96

Periodic Review:
05/25/1999

Study Objective: To compare the clinical effectiveness of a new dosing regimen (500mg QD) for administering flutamide (FLT) to the currently indicated dosing regimen of 250 mg QD according to (1) the percent of patients normalizing PSA and (2) quality of life differences between the two regimens.

Technical Approach: This phase IV, multi-center, open label, prospective randomization study will include 400 patients (10 from MAMC), ages 40 to 85, with clinically proven and histologically confirmed adenocarcinoma of the prostate gland. The subjects will be randomized to one of two treatment groups, Flutamide 250mg QD or Flutimade 500 mg QD, at Time 0. Time 0 is the day of surgical or medical castration. The study treatments will be continued for three months. The two variables to be evaluated are normalized PSA values as determined by standard laboratory PSA test, and quality of life as determined by questionnaire. Laboratory tests will be taken at clinic visits at Time 0, and weeks 4, 8, and 12. PSA normalization will be performed on 12 weeks data after the last patient accrued has reached the 12 week point. In order to achieve the conventional 80% power for showing equivalence, 200 patients per arm will be required based on a threshold criterion of 15%. Evaluation of the Quality of Life modules will involve multivariate analysis of variance for repeated measures for HQL domains and symptoms. Treatment by time interaction effect will be assessed under the repeated measures model to identify HQL domains that are significantly different between the two treatment arms using a two-sided 5% level test.

Progress: 8 subjects have been entered in FY 99 for a total of 60 subjects enrolled. 500 mg of FLT when combined with castration appears to be equally effective in lowering serum PSA and is not significantly more toxic than conventional FLT dosing. The use of 500 mg QD instead of the standard 250 mg q8h would result in a cost savings of 30%.

Detail Summary Sheet

| | | |
|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 97/097 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: Telomerase Activity in Voided Urine and Bladder Washings As A Diagnostic and Surveillance Marker for Transitional Cell Carcinoma

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; CPT Wade K. Aldous, MS; CPT Jason L. Blaser, MS; Nan W. Kim; Judd W. Moul, M.D.; MAJ Steven Lynch, MC; LTC James P. Foley, CH; LCDR Christopher Kane, MC

Start Date:
05/16/1997

Est. Completion Date:
May 97

Periodic Review:
05/25/1999

Study Objective: The objective of this study is to determine the sensitivity and specificity of telomerase activity in the voided urine and bladder washings of patients with bladder cancer as a diagnostic and surveillance marker. This will be compared to traditional cystoscopic examination.

Technical Approach: Bladder cancer remains a significant cause of cancer among both men and women in this country. Diagnosis and surveillance require invasive and often painful testing. Telomerase activity in the voided urine appears to be a promising non-invasive marker of bladder cancer. We seek to determine telomerase activity or its absence in the voided urine of 100 patients with newly diagnosed bladder cancer as well as approximately 200 patients at high risk for recurrence. We will compare these results to the telomerase activity in voided urine from 100 age matched, mixed gender subjects undergoing cystoscopy and found not to have bladder cancer. Data collected will include percentage of telomerase positive urine in the newly diagnosed bladder cancer group compared to the non-cancer control group. Furthermore the number of telomerase positive urine in patients with recurrent TCC in the group of patients at high risk for recurrent bladder cancer. Data will be analyzed to determine sensitivity, specificity, and positive predictive values.

Progress: Twenty-three controls, 73 patients with new cancer, and 125 patients with recurrence have been entered. The first part of the study showed a problem with the specimen processing methods. No telomerase activity was detected with accuracy in the urine. The processing methods have been revised and the protocol has been restarted. 57 subjects have been entered in FY 99 for a total of 57 subjects enrolled. Specimen processing does not allow for cell viability making telomerase activity a poor indicator in urine.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/120 **Status:** Completed

Title: A Randomized, Double-Blind Study (With Open-Label Treatment Extension) to Evaluate the Efficacy and Safety of VIAGRA (Sildenafil) in Erectile Dysfunction

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): COL John C. Norbeck, MC; LTC Leland D. Ronningen, MC; MAJ Henry E. Ruiz, MC; CPT Douglas W. Soderdahl, MC; MAJ J. Brantley Thrasher, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC; MAJ Bryon D. Joyner, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 07/18/1997 | Feb 97 | 07/17/1998 |

Study Objective: To assess the efficacy, safety, quality of life, and patient and partner satisfaction over a 3 month period of oral administration of VIAGRA™(Sildenafil), as required, approximately one hour prior to sexual activity in male outpatients with erectile dysfunction.

Technical Approach: The study population will be male outpatients, 18 years of age and older, with well-documented history (>6 months) of erectile dysfunction of broad-spectrum etiology. The study design is a randomized, double-blind, placebo-controlled, parallel group, multicenter, flexible dose study. Patients will be randomized equally into either a placebo treatment group or a VIAGRA™ treatment group. All patients will commence at a dose of 50 mg of VIAGRA™(or corresponding placebo) and depending on efficacy, safety, and toleration, the dose may be increased to 100 mg or decrease to 25 mg, if necessary. Doses will be taken as required (not more than once daily) approximately 1 hour prior to anticipated sexual activity. The study will last 16 weeks for each patient (4 week run-in period and 12 weeks double-blind treatment). Patients who complete the 16 week study protocol will be eligible to receive open label supplies of VIAGRA™ for 48 weeks or until the time that VIAGRA™ becomes commercially available, whichever comes first.

Progress: This study was completed at MAMC, 10 Dec 98. Thirteen patients were entered. The last two patients completed the follow-up stage in December 1998. One patient had a fainting episode, which was felt to be related to his underlying heart problem. He recovered without incident.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/147

Status: Ongoing

Title: Comparison of Quality of Life (QOL) Differences Between Radical Retropubic (RRP) and Radical Perineal Prostatectomy (RPP) for Clinically Localized Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC

Start Date:
10/17/1997

Est. Completion Date:
Sep 99

Periodic Review:
01/26/1999

Study Objective: To determine QOL differences between patients undergoing RRP and those undergoing RPP for clinically localized prostate cancer.

Technical Approach: This study will prospectively evaluate and compare the QOL of male patients 30-80 years of age who undergo RRP and RPP for clinically localized carcinoma of the prostate. The study will utilize a validated questionnaire, the UCLA-RAND Prostate Cancer Index, administered to the patients (alone and without interruption) at least one week prior to the procedure and then at 1 month, 3 months, 6 months and 1 year postoperatively. This instrument will allow us to compare the effects of the 2 procedures on the patients' health-related QOL and eventually aid the urologist in choosing the appropriate approach for each patient.

Progress: 27 subjects have been entered in FY 99 for a total of 54 subjects enrolled at MAMC. A total of 147 subjects enrolled from all participating sites. MAJ J. Brantley Thrasher was the original principal investigator for this study.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/092 **Status:** Ongoing

Title: Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcomes, and Prognostic Analysis

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC

Start Date:
07/17/1998

Est. Completion Date:
Jan 13

Periodic Review:
07/27/1999

Study Objective: Comprehensive longitudinal collection, maintenance and analysis of prostate cancer-specific and demographic standardized information from a large cohort of military health care beneficiaries from multiple geographically diverse health care centers.

Technical Approach: Standardized data collection instruments will be used at ten military medical centers by clinical research personnel and physicians to collect comprehensive prospective and retrospective information from men with prostate cancer. Patients will be followed proactively at a minimum of every twelve months until death. Data will be entered and maintained securely at USUHS in a relational database designed exclusively for this purpose. Standard statistical analysis will include survival analysis and univariate and multivariate analysis for prognostic factors.

Progress: 335 subjects have been entered in FY 99 for a total of 335 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/114

Status: Ongoing

Title: A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemiological, Detection, Natural history, and New Management Strategies for Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Stephen C. Groo, MC

Start Date:
09/15/1998

Est. Completion Date:
Jun 03

Periodic Review:
9/28/1999

Study Objective: To establish a prostate cancer serum and tissue repository that will focus on the pathology and contain supportive clinical data for the study of the etiology of prostate cancer and will incorporate a demonstration project to illustrate the utility of the repository by examining interracial differences among men with prostate cancer.

Technical Approach: Subjects will be asked to allow the intraoperative collection of a blood sample, tissue biopsies of the excised organ and use of these specimens, as well as the retrieval and use of their original archival biopsy tissue. The sera and tissue will be tested for new markers in later studies to be conducted by both military and civilian prostate cancer researchers. Some of serum and tissue may be supplied to other research centers in the future.

Progress: No subjects have been entered at MAMC. Funding has only recently been secured.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/003 **Status:** Ongoing

Title: A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEX) 150 mg Monotherapy Versus Placebo in Patients with a Rising PSA After Radical Prostatectomy for Prostate Cancer

Principal Investigator: MAJ Raymond S. Lance, MC

Department: Surgery/Urology **Facility:** MAMC

Associate Investigator(s): None.

Start Date:
10/20/1998

Est. Completion Date:
Jan 01

Periodic Review:
N/A

Study Objective: (1) To compare bicalutamide 150 mg with placebo for time to treatment failure; (2) Quality of Life

Technical Approach: Subjects will be randomized to receive either bicalutamide 150 mg daily or placebo until treatment failure, which is defined as an adverse event leading to withdrawal of randomized therapy, objective disease progression, death, initiation of systemic treatment or radiotherapy, or withdrawal from study therapy for any reason. Quality of Life data includes a PSA anxiety questionnaire (MAX-PC) and the FACT-P instrument, time to objective disease progression, PSA response, and time to PSA progression.

Progress: 12 subjects have been entered in FY 99 for a total of 12 subjects enrolled. One patient expired due to cardiac complications unrelated to the study.

Detail Summary Sheet

| | | |
|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/109 | Status: Ongoing |
| Title: Limits of Serum Detection of Circulating Prostate and Bladder Cancer Cells using Telomerase Reverse Transcriptase (H-TERT) mRNA Detection by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) | | |
| Principal Investigator: MAJ Raymond S. Lance, MC | | |
| Department: Surgery/Urology | Facility: MAMC | |
| Associate Investigator(s): Lisa M. Pierce, D.Sc.; LTC Raymond A. Costabile, MC; ; M. J. DeHart, B.S. | | |
| Start Date: 9/28/1999 | Est. Completion Date: Apr 00 | Periodic Review: N/A |

Study Objective: To determine the methods necessary to detect circulating prostate and bladder cancer cells in human blood using highly sensitive techniques in preparation of testing in human prostate and bladder cancer patients.

Technical Approach: The human prostate cancer cell lines LNCAP and M12 and the human bladder cancer cell line T24 (all epithelial-derived cell lines) will be used for analysis in this study. Serial dilutions in phosphate buffered saline (PBS; 10, 20, 50, and 100 cells per 10 ml PBS) will initially be tested for telomerase activity using the telomere repeat amplification protocol (TRAP) assay (telomerase PCR ELISA kit, Boehringer Mannheim) and for H-TERT mRNA expression using RT-PCR (Perkin Elmer) including the appropriate positive and negative controls for these assays supplied in the assay kits. The cells will be prepared to a single cell suspension with 10 MM EDTA treatment instead of trypsin as trypsin removes the cell surface antigen necessary for the epithelial-specific BerEP4 antibody. RT-PCR to detect H-TERT mRNA expression will be performed using the primers and cycling conditions previously described by Ulaner et al. (1998). Telomerase activity will be measured according to the manufacturer's protocol.

In addition, serial dilutions of each of these cell lines will be spiked into 10 ml of volunteer whole blood (10, 20, 50, and 100 cells per 10 ml whole blood) prior to analysis for telomerase activity and H-TERT mRNA expression. Blood will be collected in 10 ml EDTA tubes to prevent coagulation. Heparin tubes will not be used because residual heparin may interfere with downstream RT-PCR applications. Fresh spiked whole blood (10 ml) will be layered over 10 ml Histopaque-1077 (Sigma) in 50 ml tubes and centrifuged at 400 x g for 30 min at room temperature to separate the mononuclear cells (MNCs) from the red cells and plasma. These MNCs will be processed according to the manufacturer's instructions and resuspended in 1 ml PBS/2% fetal bovine serum. The epithelial cells (spiked cancer cells and any normal epithelial cells from the volunteer blood) will be harvested from these MNCs using 10E7 immunomagnetic beads coated with the epithelial-specific monoclonal antibody BerEP4 (Dyna) according to the manufacturer's protocol using a magnetic field. Harvested epithelial cells (BECS) will be stored at -80°C prior to RT-PCR and TRAP analyses.

A subset of H-TERT RT-PCR assays performed on the HECs will utilize the Dynabeads mRNA DIRECT Micro kit (Dyna) for RT-PCR application. These oligo(dT)25 immunomagnetic beads are designed to rapidly isolate pure, intact polyadenylated mRNA ready for RT-PCR. The sensitivity of this mRNA isolation method will be compared to traditional total RNA isolation (Purescript RNA Isolation kit, Genta Systems) by examining the quality of the H-TERT RT-PCR results obtained by both methods.

Four vials of human volunteer blood will be collected per dilution of cells per cell line. For example, for the T24 cell line (as well as for the M12 and LNCAP cells), 4 vials (10 ml each) will be

collected and spiked with 10 cells, 4 vials spiked with 20 cells, 4 vials spiked with 50 cells, and 4 vials spiked with 100 cells. Following the separation of the MNCs from all vials of whole blood, 2 of the 4 vials will be processed with immunobeads and 2 will not. H-TERT and TRAP ways (1 assay per vial of spiked 10 ml whole blood) will be performed on HECs recovered using the epithelial-specific immunobeads as well as on the MNCs not processed with immunobeads. However, some "background" telomerase activity and H-TERT mRNA levels may be seen in the unprocessed MNCs due to the contaminating lymphocytes and stem cells which may possess low levels of telomerase activity and H-TERT mRNA. The number of specimens equals 3 cell lines (LNCAP, M12, T24) x 4 dilutions each (10, 20, 50, 100 cells) x 4 vials of blood per dilution (2 processed with immunobeads and 2 without immunobeads, 1 vial per TRAP assay and 1 vial per H-TERT assay) which is 48. In addition, several 10 nil vials of control, unspiked blood will be processed with and without epithelial-specific immunobeads and used in all experiments performed. An additional 4 vials will be collected and spiked with either 20 cells (2 vials) or 50 cells (2 vials) per 10 ml whole blood (only 1 cell line in this mini-experiment) to compare the immunomagnetic mRNA isolation and total RNA isolation methods prior to RT-PCR.

Progress: This protocol was recently approved and has not yet started recruiting subjects.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/129

Status: Completed

Title: The Correlation Between Free and Total PSA, Prostate Specific Membrane Antigen and Sex Hormone Binding Globulin Across the Spectrum of Prostate Disease

Principal Investigator: CPT Keith J. O'Reilly, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): MAJ Raymond S. Lance, MC; MAJ J. Brantley Thrasher, MC; Gerald P. Murphy, M.D.; Katherine H. Moore, Ph.D.

Start Date:
09/19/1997

Est. Completion Date:
Jul 98

Periodic Review:
12/15/1998

Study Objective: To examine across the spectrum of prostate disease (normal to prostate cancer) whether there is a statistically significant correlation between the serum levels of the free and bound fractions of Prostate Specific Antigen (PSA), sex hormone binding globulin (SHBG), Prostate Specific Membrane Antigen (PSMA) and serum androgens.

Technical Approach: This study will evaluate men aged 45-80 and examine the serum levels of free and bound Prostate-specific antigen (PSA), sex hormone binding globulin (SHBG), Prostate-specific membrane antigen and serum androgens. The subjects will be divided into one of two arms: those with no evidence of prostate cancer and those with histologically proven adenocarcinoma of the prostate. All subjects will be patients who present to the urology clinic for urologic evaluation and will have one extra vial of serum drawn. The levels of these proteins will be examined for statistically significant correlation. By proving or disproving a relationship among these proteins and its variation across the spectrum of prostate disease a greater knowledge of the biochemistry of the prostate will be apparent and hopefully improve current diagnostic methods for detecting the presence or absence of prostate cancer.

Progress: No subjects have been entered in FY 99 for a total of 200 subjects enrolled. Data analysis is just about complete.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/043

Status: Ongoing

Title: Liposomal Amikacin (MiKasome) in Complicated Urinary Tract Infections:
Randomized, Double, Blind, Dose-Ranging Study

Principal Investigator: MAJ Henry E. Ruiz, MC

Department: Surgery/Urology

Facility: MAMC

Associate Investigator(s): LTC Robert C. Allen, Jr., MC; MAJ Sunil K. Ahuja, MC;
MAJ Bryon D. Joyner, MC; MAJ John B. Ellsworth, MC; CPT Keith J. O'Reilly, MC;
CPT Karen C. Evans, MC; CPT Andrew C. Peterson, MC; MAJ Henry E. Ruiz, MC; LTC
Raymond A. Costabile, MC; MAJ Raymond S. Lance, MC

Start Date:
02/23/1999

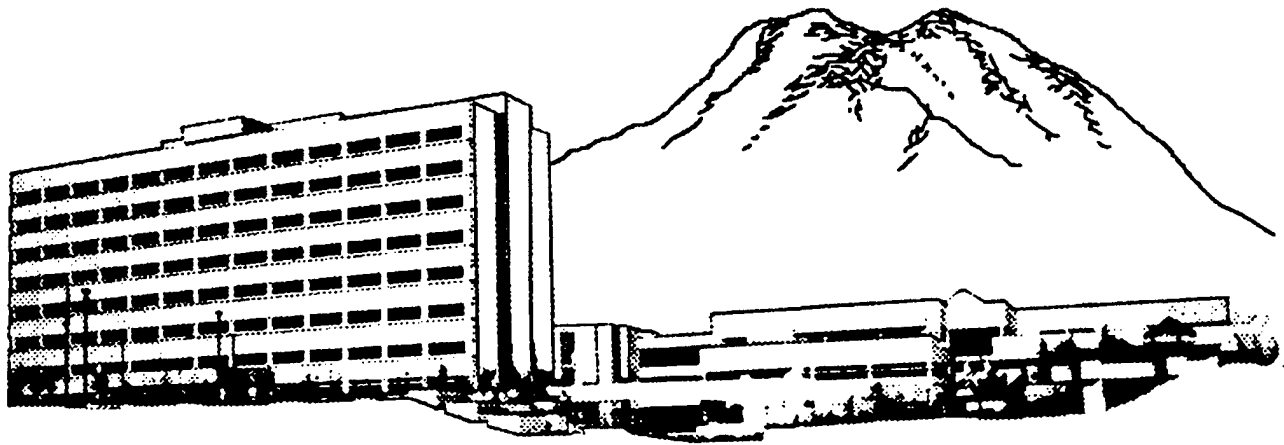
Est. Completion Date:
Feb 00

Periodic Review:
N/A

Study Objective: To evaluate the safety and efficacy of three different doses of liposomal amikacin in the treatment of complicated urinary tract infections or acute uncomplicated pyelonephritis.

Technical Approach: A multicenter, double blind study of intravenous liposomal amikacin randomized between three fixed, single dose regimens. 165 evaluable patients will be enrolled and complete the study (55 evaluable patients per dose group). A maximum of 300 patients will be enrolled to obtain these 165 evaluable patients. Patients of either sex aged 18 years or older, with complicated urinary tract infections or acute uncomplicated pyelonephritis. The presence of at least one uropathogen at > 10 , CFU/mL will be required and patients with urinary catheters must be able to have these removed no more than 5 days after the start of therapy. Patients will be evaluated at Day 6, Day 14 (Test-of-Cure visit), Day 21, and Day 36 (Late Post-Treatment visit) after initiation of therapy. Efficacy endpoints will be microbiologic eradication and clinical cure assessed on each evaluation day. Safety assessments will include an evaluation of all adverse events spontaneously reported, elicited, or observed by the investigators including clinically significant laboratory test abnormalities.

Progress: Data on 6 subjects have been collected during FY 99. One subject was lost to follow-up.



Detail Summary Sheets

Vascular Surgery,
Department of Surgery

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/163

Status: Ongoing

Title: Clinical Evaluation of the Handling and Performance of the HEMASHIELD Knitted Double Velour Fabric and Polytetrafluoroethylene (PTFE) Patched for Carotid Endarterectomy Patch Procedures in Patients

Principal Investigator: COL Charles A. Andersen, MC

Department: Surgery/Vascular Surgery

Facility: MAMC

Associate Investigator(s): COL David F. J. Tollefson, MC; LTC Stephen B. Olsen, MC; Edmund A. Kanar; George J. Collins, Jr.

Start Date:
09/20/1996

Est. Completion Date:
Nov 98

Periodic Review:
9/28/1999

Study Objective: The objective of this randomized, parallel group, multi-center study is to evaluate the performance of the test product, the HEMASHIELD® Knitted Double Velour patch in comparison to the control product, the Gore-Tex patch, for use as a carotid artery patch following carotid endarterectomy in patients.

Technical Approach: This is a prospectively randomized, multi-center clinical trial in which a maximum of 40 patients will be enrolled, with approximately equal numbers of patients in each of the 2 treatment groups, Hemashield patch vs. the Gore-Tex patch. Anticipated MAMC enrollment is approximately 20 patients. Patients included in this study will be evaluated preoperatively, intraoperatively, at discharge from the hospital, and at 3 months, 6 months, 12 months and up to a total of 24 months postoperatively. Follow-up evaluations will include a medical history and physical exam at 3, 6, 12 and 24 months and duplex ultrasound testing at 6 and 12 months (with optional duplex scan at 24 months) for assessment of patch repair. Completion of follow-up assessment and final report is anticipated about one and one half years after the first patient enrollment.

Progress: 18 subjects were entered in FY 99 with no serious adverse events. A total of 39 patients have entered the study with no serious adverse events.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/097 **Status:** Ongoing

Title: Abdominal Aortic Aneurysm (AAA) and Chronic Obstructive Pulmonary Disease (COPD); Is There a Relationship

Principal Investigator: CPT Chatt A. Johnson

Department: Surgery/Vascular Surgery

Facility: MAMC

Associate Investigator(s): CPT Peter J. Armstrong, MC; LTC William H. Cragun, MC; COL Charles A. Andersen, MC; COL Thomas A. Dillard, MC; LTC Stephen B. Olsen, MC; COL David F. J. Tollefson, MC; CPT Eric A. Shry, MC

Start Date:
04/21/1995

Est. Completion Date:
Mar 96

Periodic Review:
9/28/1999

Study Objective: To determine the association, if any, of AAA and COPD as well as potential pathophysiologic explanation.

Technical Approach: A comparison will be made between patients with and without COPD and the incidence of AAA. Patients 50 years and older will be selected from those followed in the pulmonary, family practice or adult primary care clinics who have been determined to have COPD by screening history, spirometry and carbon monoxide diffusing capacity (DLCO). Controls will be age/sex matched without COPD. Selected participants will be evaluated by pulmonary function tests (spirometry, DLCO), serum alpha 1 anti-trypsin levels, serum elastase levels, serum cholesterol levels, ankle-brachial indices and abdominal aortic duplex. The incidence in the control and study groups will be compared through Chi-squared analysis and individual variables will be determined through student T-test. A $p < 0.05$ will be determined to be statistically significant. Patients and primary care physicians will be notified of the presence or absence of AAA, abnormal ankle-brachial indices, COPD, or hypercholesterolemia.

Progress: 4 subjects have been entered in FY 99 for a total of 20 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/081

Status: Ongoing

Title: A Double-Blind, Randomized, Parallel Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of NM-702 in Subjects with Intermittent Claudication

Principal Investigator: LTC Stephen B. Olsen, MC

Department: Surgery/Vascular Surgery

Facility: MAMC

Associate Investigator(s): COL David F. J. Tollefson, MC; COL Charles A. Andersen, MC; CPT Chatt A. Johnson

Start Date:
07/27/1999

Est. Completion Date:
Aug 00

Periodic Review:
N/A

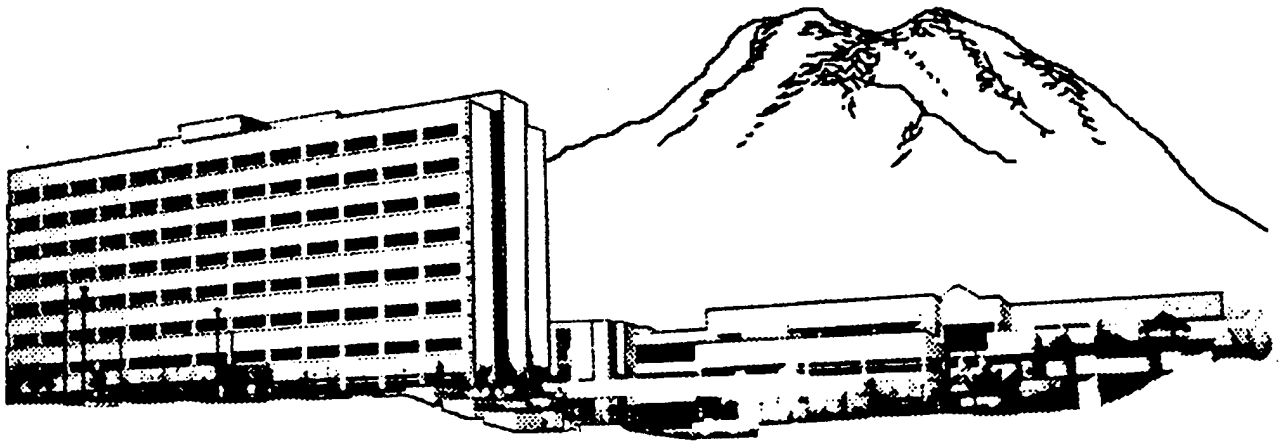
Study Objective: 1. Demonstrate the efficacy of NM-702 at three different doses compared to placebo in the treatment of patients with intermittent claudication. The following assessments will be used to determine efficacy: improvement in peak walking time, improvement in claudication onset time, and change in functional status as measured by the Health Status Survey Questionnaire and Walking Impairment Questionnaire.

2. Assess the safety of NM-702 treatment in subject population as determined by physical examination, blood and urine analysis, Holter monitoring, 12-lead. ECG, blood pressure measurements and by evaluation of adverse events and concomitant medication usage.

Technical Approach: This will be a double-blind, parallel-group, dose- response study in which subjects will be randomized to receive either 1, 2, or 4 mg of NM-702, or placebo, twice a day for 12 consecutive weeks. A total of 200 evaluable subjects (50 per group) will be studied. A minimum of 10 study sites will participate in this trial. Total study time per subject, including follow-up, is one year.

Subjects will be seen in clinic 2-3 times during the screening period to obtain two consecutive treadmill results (peak walking time) that are within 25% of each other on separate days. Also, all baseline information will be collected on the first screen attempt. Upon enrollment into the study, subjects will be required to walk on the treadmill until claudication onset, administered two assessment questionnaires and given drug. Subjects will return to clinic for three visits over the ensuing 12 week treatment period. At that time, EKGS, treadmill test for claudication onset time, and assessment questionnaires will be performed. Subjects will be seen twice in clinic during follow-up period. Adverse events, including significant laboratory abnormalities, will be recorded on the Case Report Forms.

Progress: 8 subjects have been entered in FY 99 for a total of 8 subjects enrolled.



Detail Summary Sheets

Weed Army Community Hospital

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/084

Status: Ongoing

Title: Confirmation of Endotracheal Tube Placement by Special Operations Combat Corpsmen and Medics

Principal Investigator: MAJ Charles Price, AN

Department: WACH

Facility: MAMC

Associate Investigator(s): MAJ Mark D. Calkins, MC

Start Date:
06/19/1998

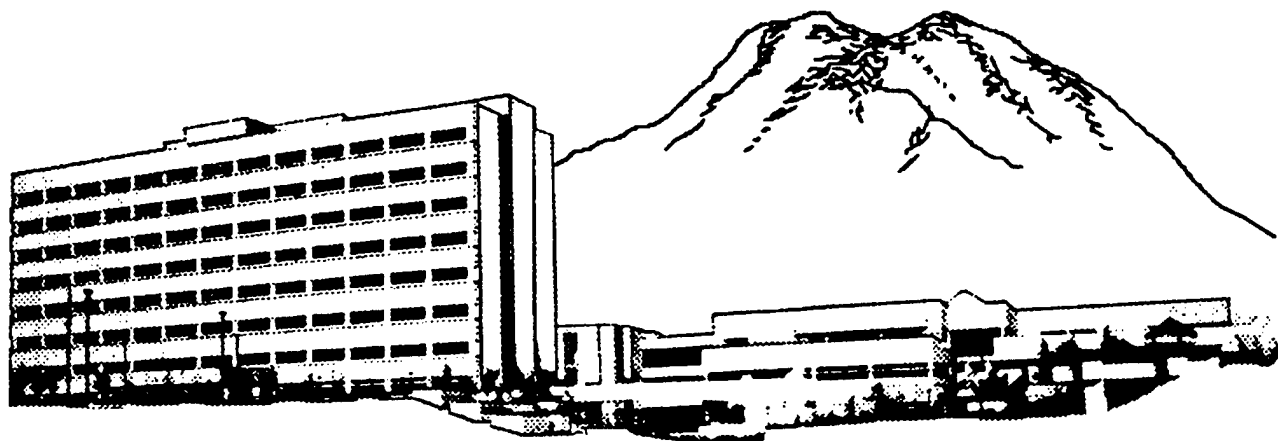
Est. Completion Date:
Jul 99

Periodic Review:
07/27/1999

Study Objective: To evaluate the effectiveness of several techniques in determining endotracheal tube placement when used by combat corpsmen and medics.

Technical Approach: The trachea and esophagus will be intubated with an identical tube. Randomization will determine which ETT will be checked (either the tracheally or esophageally placed ETT) and the order which each technique will be used to determine whether the ETT is in the esophagus or trachea. Techniques used will include observation only with ventilation of randomized ETT, stethoscope, esophageal detector device, colorimetric end-tidal CO2 detector, stethoscope and EDD and stethoscope and ETCO2. The medic will be allowed up to 6 breaths via an adult ambu bag and not to exceed 30 seconds to assess proper ETT placement. They will then leave the operating room and report their findings on an assessment form. Three evaluations per patient are likely, but dependent on the clinical/surgical situation.

Progress: 7 subjects have been entered in FY 99 for a total of 160 subjects enrolled.



Detail Summary Sheets

Department of Clinical Investigation

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/104

Status: Ongoing

Title: Expression of Angiostatin and TSP1 in Human Microvascular Endothelial Cells and Breast Cancer Cells: In Vitro Study of a Potentially Superior Antiangiogenic Activity

Principal Investigator: Jeff M. Bullock, M.S.

Department: Clinical Investigation

Facility: MAMC

Associate Investigator(s): Katherine H. Moore, Ph.D.; CPT Aziz N. Qabar, MS; James R. Wright, M.T.

Start Date:
09/15/1998

Est. Completion Date:
Aug 99

Periodic Review:
7/27/1999

Study Objective: (1) To establish the profile of Plasminogen and TSP1 expression in quiescent and proliferating human microvascular endothelial cells and two breast cancer cell lines, MCF-7 and MDA-431 and (2) to compare the antiangiogenic phenotype of Angiostatin, TSP1, and type I repeat truncations on the proliferation of human microvascular endothelial cells (HMVEC) in vitro.

Technical Approach: This study is designed to examine the possibility of a combinatorial antiangiogenic activity in vitro, where the effectiveness of two or more antiangiogenic molecules against proliferating human microvascular endothelial cells (HMVEC) is evaluated. The expression of an angiostatin, a proteolytic fragment of Plasmino (gen), in the non-invasive breast cancer cell lines MCF-7, the invasive breast cancer cells line MDA-431, and HMVEC is evaluated using Western blots, Northern blots, and polymerase chain reaction (PCR). A profile of TSP1 and angiostatin expression in these cells will be established, as a function of time in culture and following bFGF-induced proliferation. Moreover, the inhibitory effect of truncated forms of TSP1 on HMVEC angiogenesis will be determined and compared to that of both TSP1 and angiostatin separately. Finally, a combination of two or more of the antiangiogenic molecules will be tested to determine the most potent inhibitory activity.

Progress: Preliminary results using reverse transcriptase polymerase chain reaction indicate that none of the three breast cancer cell lines tested (MCF-7, ZR-75, and MDA-431) express K1-3 message. Angiostatin K1-3 inhibited human microvascular endothelial cell proliferation in a dose-dependent manner, but reached a plateau at 150 ng/ml. There was an angiostatin K1-3/TSP1 additive antiproliferative effect on human microvascular endothelial cell proliferation that was significant only at higher concentrations of more than 150 ng/ml.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/128 **Status:** Ongoing

Title: Enhancing the Effectiveness of Tamoxifen Therapy in Breast Cancer

Principal Investigator: COL Roderick F. Hume Jr., MC

Department: Clinical Investigation

Facility: MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; Maryls J.M. Nessel, Ph.D.; Katherine H. Moore, Ph.D.

Start Date:
08/15/1997

Est. Completion Date:
Oct 00

Periodic Review:
08/20/1998

Study Objective: 1) Investigate the mechanism by which SHBG and tamoxifen mediate a reduction in cell number in MCF-7 breast cancer cells in-vitro by measuring their effect on both G1 cell cycle arrest and apoptosis, as well as level of expression of factors which mediate apoptosis such as Bcl-2 and Bax; 2) study the regulation of production of endogenous SHBG by estrogen and tamoxifen, as well as agents reported to affect SHBG levels on other systems, such as insulin, prolactin, androgen, and cAMP; and 3) determine the effect of simultaneous treatment of MCF-7 cells with exogenous SHBG and tamoxifen on cell growth and apoptosis.

Technical Approach: We will be exploring the novel idea that interaction occurs between two effectors of steroid response in breast cancer cells, tamoxifen and sex hormone binding globulin (SHBG), resulting in a reduction of the rate of cell growth and increasing the rate of cell death. This study may provide the foundation to developing more effective treatment of breast cancer. The inhibitory effect of tamoxifen, a partial antagonist of estrogen action, on cell growth has been well documented. Evidence for an effect of tamoxifen on programmed cell death (apoptosis) has been reported recently. In preliminary studies in our laboratory, tamoxifen decreases the level of the anti-apoptosis factor Bcl-2, and this effect appears to depend on the level of estrogen to which cells are exposed prior to treatment. An inhibitory effect of cAMP on cell growth in response to estrogen has been recently shown by others and confirmed in our laboratory. Additionally, treatment with exogenous SHBG has been shown to increase cAMP levels and inhibit response to estrogen. Our group has demonstrated that SHBG is produced endogenously by MCF-7 breast cancer cells. Interestingly, recent data suggest that serum SHBG levels increase in patients treated with estrogen antagonists, suggesting that antiestrogen agents may regulate SHBG production. A potentially important aspect of this study would be the discovery of a means to increase the inhibitory effect of antiestrogens on breast cancer cell growth and/or cell death by modulation of SHBG levels as addressed in objective 2. If one of these agents is found to modulate SHBG levels, and if SHBG is shown to modulate the inhibitory effect of tamoxifen, a potential means of biologically increasing the effectiveness of breast cancer treatment with antiestrogens could be identified.

Progress: 150 subjects have been entered in FY 99 for a total of 200 subjects enrolled.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/025 **Status:** Suspended

Title: The Department of Clinical Investigation's Molecular Biology Short Course for Physicians

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility:** MAMC

Associate Investigator(s): MAJ Rodger K. Martin, MS; CPT Wade K. Aldous, MS; CPT Aziz N. Qabar, MS

Start Date:
01/20/1995

Est. Completion Date:
Jun 96

Periodic Review:
02/23/1999

Study Objective: To familiarize MAMC residents, fellows, and staff physicians with the research capabilities and resources of the Department of Clinical Investigation. To support MAMC Graduate Medical Education through instruction and research. To foster an appreciation of molecular biology concepts in residents, fellows, and staff physicians and to augment their understanding of the scientific literature. To encourage residents, fellows and staff physicians to develop research protocols incorporating these technologies.

Technical Approach: This course is designed to familiarize physicians with the most commonly encountered molecular approaches in the scientific and clinical literature. It is hoped that this will foster more critical reading of the literature as well as encouraging the development of research protocols employing these technologies. Although six weeks in duration, students will be required to attend two hours of lecture per week in addition to approximately seven hours of laboratory exercises. Topics addressed and used in the course range from DNA isolation to cloning and sequencing of PCR products.

Progress: No courses were held this year due to PCS of investigators. Protocol is suspended pending appointment of new PI.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/138 **Status:** Terminated

Title: The Effect of Tamoxifen and Ionizing Radiation on Expression of Bcl-2, Bcl-x, and p53 in Breast Cancer Cells In Vitro

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility:** MAMC

Associate Investigator(s): LTC Robert B. Ellis, MC; MAJ Nyun C. Han, MC; MAJ Mark D. Brissette, MC; MAJ Richard F. Williams, MC

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|----------------------------------|--|---------------------------------------|
| Start Date: 06/16/1995 | Est. Completion Date: Mar 96 | Periodic Review: 07/17/1998 |
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Study Objective: The objective of this study is to define the molecular mechanism by which antitumor agents such as estrogen receptor antagonists and ionizing radiation initiate programmed cell death (apoptosis) in cultured breast cancer cells. Specific objectives are to examine the treated breast cancer culture cells for morphologic and biochemical evidence of apoptosis and to determine the time course for apoptotic death as well as that for changes in the level of bcl2 and p53 in the cells. Thereby, we will determine if changes in the level of these factors precede the onset of apoptotic death and provide evidence for the importance of modulation of the expression of these proteins as antitumor effects of these agents. Also, changes in other bcl2-related factors such as bax and bcl-x will be examined.

Technical Approach: Three breast cancer cell lines will be used MCF-7, MDA-MB-231, and ZR-75. Cells from each of these lines will be grown in the presence of estrogen for 24 hours, after which the medium will be treated with either tamoxifen or 4-hydroxytamoxifen, at 0.1 and 1.0 micromolar for six days. For the effects of radiation, cell will be grown in estrogen for 24 hours and then irradiated. At 24 hour intervals, cells from each experimental condition will be harvested and examine for apoptosis and for the level of expression of bcl2, bcl-x and p53. Morphologic and biochemical evidence for apoptosis in these cultures will be obtained by light microscopy and DNA agarose gel electrophoresis. Flow cytometry will be used to determine the fraction of apoptotic cells. Expression of the protein products of the three oncogenes will be determined by quantitative Western blot electrophoresis. The mean and standard deviations for three separate cultures with each treatment at each time point will be determined. Statistical analysis will be performed using two way analysis of variance methods.

Progress: The principal investigator was changed from MAJ Richard Williams (who resigned from the Army) to Katherine Moore, Ph.D., in Jul 98. The protocol has been suspended while discussions are taking place as to whether it will be possible for Dr. Williams and Dr. Moore to continue working on this protocol to determine if further information can be obtained to elucidate the findings of the protocol thus far. Dr. Moore has left MAMC so protocol is terminated.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/033 **Status:** Terminated

Title: Is BRCA1 Loss of Expression Found in Tumors Others Than Breast and Ovarian Cancer?

Principal Investigator: Katherine H. Moore, Ph.D.

Department: Clinical Investigation **Facility:** MAMC

Associate Investigator(s): MAJ Richard F. Williams, MC; CPT Jerome M. McDonald, MC; MAJ Thomas P. Baker, MC; CPT Sandra L. Carter, MC; James R. Wright, M.T.

Start Date:
02/21/1997

Est. Completion Date:
Nov 97

Periodic Review:
03/23/1999

Study Objective: 1) To determine the prevalence of loss of expression of BRCA1 protein in tumors. We will examine tumors that are linked to increased risk of breast cancer (prostate, breast, ovarian and endometrial cancers) in families as well as tumors that are not associated with an increased risk (lung and kidney). We also will examine colon cancer samples, as this tumor may also be linked to BRCA1 associated cancer. 2) Through the use of two antibodies against BRCA1, we can determine if normal protein is being expressed in the tumors and surrounding normal tissue, or if a truncated protein that may be a product of a mutant BRCA1 allele is being expressed.

Technical Approach: This study will lead to an increased understanding of the role of BRCA1 protein in tumorigenesis. BRCA1 is associated with familial breast and ovarian cancer. The gene was identified by loss of heterozygosity studies in families with a high incidence of breast and ovarian cancer. In these families, it has been found that members with a mutant allele for BRCA1 have a much greater risk for developing cancer than the unaffected population. The presumed mechanism of action of BRCA1 in the development of cancer involves the loss of the normal allele which was producing a normal, functional protein. The mutant alleles contain a mutation in the BRCA1 gene, of which 85% produce a truncated protein. It is assumed that the truncated protein is not functional. It also is presumed that the function of BRCA1 is as a DNA binding protein. The basis of this assumption is the presence of a zinc ring domain near the amino terminal end of the protein. The zinc ring domain was identified through amino acid sequence homology and molecular modeling. The zinc ring is a common component of DNA binding proteins. This structure in BRCA1 may be functionally important, as a common mutation that is associated with increased risk, 185delAG, deletes two nucleotides in this region.

The presence of an inherited BRCA1 mutation, which may lead to the production of non-functional protein, is becoming a well accepted risk factor for the development of familial breast and ovarian cancer. However, the role of BRCA1 in tumors other than breast and ovarian is not well understood. We will determine if the loss of BRCA1 protein expression occurs in tumors other than breast and ovarian. If BRCA1 loss can be documented in a variety of tumors, this will add to the importance of BRCA1 loss in the progression of a normal cell to a cancerous one.

Progress: PI PCS'd and project was not underway long enough to warrant continuation.

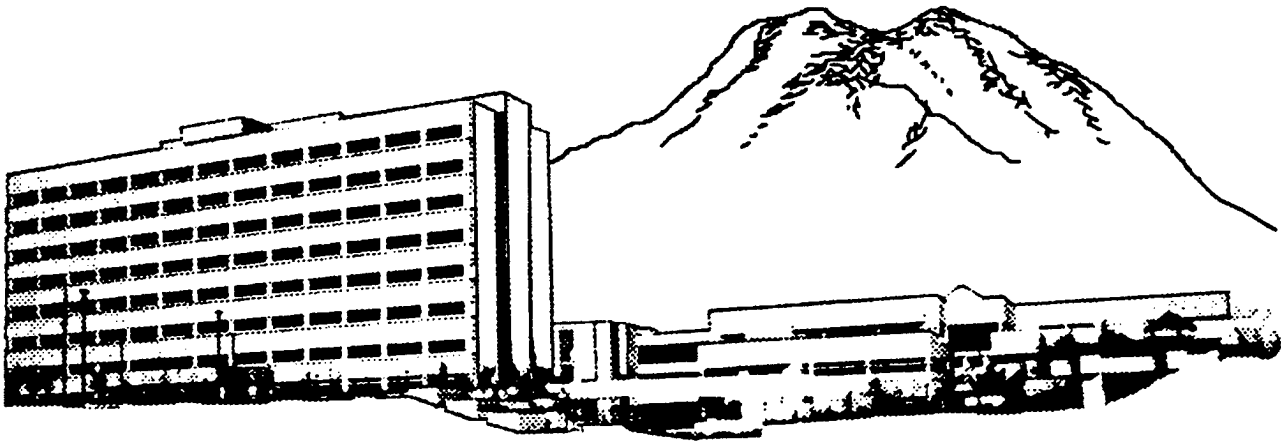
Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 97/013 | Status: Completed |
| Title: The Role of Thrombospondin in Macrophage-Mediated Wound Healing. A Structural/Functional Dissection of Thrombospondin | | |
| Principal Investigator: CPT Aziz N. Qabar, MS | | |
| Department: Clinical Investigation | Facility: MAMC | |
| Associate Investigator(s): None. | | |
| Start Date: 11/15/1996 | Est. Completion Date: Oct 98 | Periodic Review: 11/17/1998 |

Study Objective: To delineate the role of macrophage thrombospondin in the process of wound healing; to determine the mechanism(s) by which angiogenesis, associated with wound healing is controlled; and to analyze the functional and structural domain of thrombospondin.

Technical Approach: This study will examine the role of macrophages in wound healing. The profile of thrombospondin 1 and 3 secreted by activated macrophages will be tested in an in vitro system consisting of circulating monocytes (human monocytic cell lines, THP-1 and HL-60) which are activated with a phorbol ester or retinoic acid. Assays will consist of Western blots, metabolic labeling and immunoprecipitation, and Northern blots. The level of expression of each molecule will be determined quantitatively from developed autoradiographs. The level of regulation will be determined from the corresponding Northern blot, by comparing the profiles of the protein expression with that of its mRNA expression. A human TSP1/murine TSP3 chimera will be constructed using recombinant DNA techniques and PCR technology, resulting in a cDNA encoding the NH₂-terminal of murine TSP3 and the COOH-terminal of human TSP1. A mutant form of the chimera will also be constructed, such that the two cysteine residues involved in S_S bridging in mTSP3 (Cys245 and Cys248) will be mutated into serine residues. The two chimeric proteins will be expressed in mammalian cells and their role on cell growth and differentiation will be investigated.

Progress: We looked at thrombospondin 1(TSP1) expression profile in the human monocytic leukemia cell line, THP-1. Northern and Western blot analysis showed overexpressed TSP1 mRNA and protein within 24 hours of activation with peak expression on day 3. We then looked at the effect of media conditioned with THP-1 cells on the sprouting of human microvascular endothelial cells (HMVEC) plated on collagen matrix (angiogenesis in vitro). The percentage of sprouting cells decreased when media from day 1 and day 5 were included in the assay. However, the most dramatic reduction in cell sprouting occurred when day 3 media was added. A TSP1-specific monoclonal antibody was able to partially reverse this inhibition. The effect of TSP 1 trimeric structure on its anti-angiogenic activity was also investigated. Using PCR and mutagenic primers, we constructed and subcloned recombinant truncated, mutated, or full length TSP1 and/or TSP3 cDNAs in two eukaryotic expression plasmid vectors, pCEP4 (hygromycin B resistance), and pcDNA3 (G-418 resistance). Furthermore, two chimeric molecules were constructed either by replacing the trimer-forming amino terminus heparin-binding domain (HBD) of human TSP1 with the pentamer-forming amino terminus domain of murine TSP3 (TSP1/TSP3 chimera), or by fusing the trimer-forming HBD and Type 1 repeats of TSP1 with the dimer-forming Fc portion of human immunoglobulin G (TSP1-Ig chimera). We found that overexpressed recombinant trimeric TSP1 or its trimeric Type 1 repeats but not mutant monomeric Type 1 repeats were the only constructs that were capable of inhibiting angiogenesis of endothelial cells in vitro. Taken together, these results indicate that the three-dimensional structure of the Type 1 repeats of TSP 1 is crucial for its anti-angiogenic activity.



Detail Summary Sheets
Gynecology Oncology Group

Detail Summary Sheet

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|---|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 81/035 | Status: Ongoing |
| Title: GOG 0041: Surgical Staging of Ovarian Carcinoma | | |
| Principal Investigator: COL Mark E. Potter, MC | | |
| Department: GOG | Facility: MAMC | |
| Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC | | |
| Start Date: 01/16/1981 | Est. Completion Date: Jan 86 | Periodic Review: 10/5/1999 |

Study Objective: To determine the spread of ovarian carcinoma to intraperitoneal structures and retroperitoneal lymph nodes by direct examination, cytologic sampling, and biopsy; to establish a surgical protocol for patients entered into GOG ovarian cancer treatments protocols; to determine the complication rate of the procedures.

Technical Approach: This protocol is being performed as a statistical protocol on patients who have surgery as standard treatment. Eligible patients will be those who have Stages I, II, or III ovarian carcinoma. Patients undergoing total abdominal hysterectomy, bilateral or unilateral salpingo-oophorectomy, bivalving of the ovary, selective pelvic and para-aortic lymphadenectomy, omental biopsy, or peritoneal cytology sampling will be studied. They will not be given any preoperative treatment, but will be subjected to a completed and thorough evaluation before surgery. All patients will be explored and the steps for surgery will be as standard surgery dictates. Specific observations will be made as to the findings. If fluid is not present, washings will be taken from the inside of the abdomen to study cells. A thorough examination of all structures from the diaphragm to the pelvic floor will be carried out. After surgical staging, patients will be transferred to the appropriate treatment protocol or to standard treatment if no protocol is available.

Progress: This study was closed to patient entry, 12 Feb 87. Thirteen patients were enrolled. Eight patients are currently being followed who remain disease free at least 11 years after therapy.

Detail Summary Sheet

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|---|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 84/033 | Status: Ongoing |
| Title: GOG 0072: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and a Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease | | |
| Principal Investigator: COL Mark E. Potter, MC | | |
| Department: GOG | Facility: MAMC | |
| Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC | | |
| Start Date: 02/17/1984 | Est. Completion Date: Dec 88 | Periodic Review: 10/5/1999 |

Study Objective: To evaluate the biologic behavior of ovarian tumors of low malignant potential; to evaluate the effectiveness of chemotherapy against this disease (initially, a Phase II study of melphalan); and to evaluate the response rate to cisplatin in melphalan failures.

Technical Approach: Patients without prior chemotherapy or radiotherapy who have had adequate surgical staging will be eligible. Patients with no grossly visible residual disease will receive no treatment and be followed for five years if there is no subsequent disease. If there is no grossly visible clinically apparent residual for 12 months, the patients will have second look surgery and then proceed to melphalan treatment (5 days every four weeks) or follow-up (complete response). With progression after melphalan, patients will proceed to third look and cisplatin treatment (once every three weeks for eight weeks) or follow-up. If there is no evidence of response after three courses of cisplatin, the treatment will be discontinued. Patients who have progression during the first 12 months will be treated as above except they will proceed directly to melphalan treatment without second look surgery. Follow-up will be for a minimum of five years with clinical examination every three months for the first two years, then every six months thereafter.

Progress: This study was closed to patient entry 25 Feb 92. Ten patients were enrolled; of these, 6 patients are being followed, three have been lost to follow-up, and one has died.

Detail Summary Sheet

Date: 30 Sep 99

Number: 84/074

Status: Ongoing

Title: GOG 0078: Evaluation of Adjuvant VP-16, Bleomycin, and Cisplatin (BEP) Therapy in Totally Resected Choriocarcinoma, Endodermal Sinus Tumor, Embryonal Carcinoma and Grade 3 Immature Teratoma of the Ovary, Pure and Mixed with Other Elements

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:
08/17/1984

Est. Completion Date:
Jul 89

Periodic Review:
10/5/1999

Study Objective: To evaluate the effect of adjuvant vinblastine, bleomycin, and cisplatin (VBP) chemotherapy in patients with endodermal sinus tumor and choriocarcinoma of the ovary (pure and mixed) after removal of all gross tumor; to evaluate the role of serum markers, especially alpha fetoprotein and HCG, in predicting recurrence; to evaluate the role of reassessment laparotomy in determining response, detecting early relapse, and planning further therapy; and to compare the biologic behavior of pure endodermal sinus tumors with mixed germ cell tumors containing endodermal sinus elements. Per addendum of Jan. 87: to evaluate the acute and chronic toxicity of this chemotherapy on gonadal and reproductive function.

Technical Approach: Patients with totally resected Stage I choriocarcinoma, endodermal sinus tumor, or embryonal carcinoma of the ovary with negative peritoneal washings, normal (or falling at a rate that does not suggest residual disease) serum AFP and beta-HCG levels, and adequate bone marrow, renal, and hepatic function will be studied. Stages II and III will also be eligible if all gross tumor is resected. After recovery from surgery, patients will receive 3 cycles of VBP therapy. Patients who show evidence of progression while on VBP therapy will be candidates for GOG Protocol 26. Patients completing three cycles of treatment clinically free of disease will undergo reassessment laparotomy. Patients with recurrent disease at reassessment laparotomy will be candidates for GOG Protocol 26. To be eligible a patient will receive at least one week of chemotherapy and live another two weeks. Each patient will remain on study until adverse effects prohibit further therapy or until evidence of progression is noted. Per addendum of Jan. 86: the title has been changed as shown above; vinblastine has been replaced by VP-16; Grade 3 immature teratoma has been added for entry and evaluation.

Progress: This study was closed to patient entry, 10 Feb 92. One patient is being followed and remains disease-free after 6 years off-therapy.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 86/089 | Status: Ongoing |
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Title: GOG 0085: A Randomized Comparison of Hydroxyurea versus 5-FU Infusion and Bolus Cisplatin as an Adjuvant to Radiation Therapy in Patients with Stages II-B, III, and IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): COL William L. Benson, MC; COL Roger B. Lee, MC; LTC Gordon O. Downey, MC

Start Date:
08/15/1986

Est. Completion Date:
Feb 94

Periodic Review:
10/5/1999

Study Objective: To determine whether hydroxyurea or the combination of 5-FU and cisplatin is superior as a potentiator of radiation therapy in advanced cervical carcinoma and to determine the relative toxicities of hydroxyurea versus the combination of 5-FU and cisplatin when given concurrently with radiation therapy.

Technical Approach: Patients with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix, Stages II-B, III, and IV-A, who meet the eligibility requirements as listed in the protocol, will undergo clinical staging as permitted by FIGO rules. All patients will undergo surgical staging to include extraperitoneal sampling of the para-aortic lymph nodes, peritoneal cytology, and intraperitoneal exploration. Patients with cancer confined to the pelvis will receive pelvic irradiation and will be randomly assigned to receive either concomitant 5-FU and cisplatin or hydroxyurea. Patients with disease outside the pelvis are not eligible for this protocol. The study will continue as long as treatment protocols remain activated. The patients will be followed for two years and then every six months for three additional years.

Progress: This study was closed to patient entry, 3 Dec 90. Two patients, disease free ten years after completion of therapy, are being followed at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 87/104

Status: Ongoing

Title: GOG 0092: Treatment of Selected Patients with Stage 1B Carcinoma of the Cervix After Radical Hysterectomy and Pelvic Lymphadenectomy: Pelvic Radiation Therapy versus No Further Therapy

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC; COL Donald H. Kull, MC

Start Date:
08/21/1987

Est. Completion Date:
Indef

Periodic Review:
10/5/1999

Study Objective: To determine the value of adjunctive pelvic radiation in the treatment of Stage 1B carcinoma of the cervix but with selected high-risk factors; to determine the recurrence-free interval, survival and patterns of failure in those patients; and to determine the morbidity of adjunctive pelvic radiation following radical hysterectomy.

Technical Approach: All patients with Stage 1B cancer of the cervix who have been treated by radical hysterectomy and pelvic node dissection and found to have cancer confined to the cervix and who have a large tumor and/or lymph or blood vessel invasion in the cervix will be eligible to enter the study. Patients will be randomized to one of two groups. One group will receive external radiation therapy to the pelvis and the other group will receive no further therapy. Patients assigned to receive the radiation therapy will receive the therapy daily for 4 to 6 weeks. Both groups of patients will be required to have check-ups every three months for three years and then every six months for two more years.

Progress: This study was closed to patient entry, 18 Dec 95. One patient, enrolled in FY 88, remains disease free.

Detail Summary Sheet

Date: 30 Sep 99

Number: 87/028

Status: Ongoing

Title: GOG 0095: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected IAi and IBi and IAii and IBii Ovarian Cancer, Phase III

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:
11/21/1986

Est. Completion Date:
Indef

Periodic Review:
10/5/1999

Study Objective: In definitively staged patients who have tumor involving one or both ovaries with pelvic extension and/or malignant ascites and/or positive peritoneal washings and in those Stage IAi and IBi patients with poorly differentiated tumors and stage IAii and IBii (all grades) to: compare the progression-free interval and overall survival of the two treatment regimens; determine the patterns of relapse for each form of therapy; and define the relative toxicities of the two treatment approaches.

Technical Approach: The study design will be a randomized comparison between the standard adjuvant treatment (P32) and an experimental arm of short term intensive adjuvant combination chemotherapy with cyclophosphamide/cisplatin in patients with ovarian cancer. One to two weeks following surgery, P32 therapy will be started. Fifteen millicuries of chromic phosphate suspension mixed in 500 cc of normal saline will be infused into the peritoneal cavity via the peritoneal dialysis catheter after a technetium scan or abdominal x-rays with contrast material has demonstrated adequate distribution. In order to facilitate distribution of the P32, the patient will be turned every 15 minutes to the left side, onto the back, in Trendelenburg and reverse Trendelenburg positions, onto the right side and so on for two hours following the infusion. Chemotherapy will consist of cyclophosphamide, 1 mg/m² I.V., on day 1 plus cisplatin, 100 mg/m² IV, on day 1 administered one hour after cyclophosphamide. Cycles of combination chemotherapy will be repeated every three weeks depending upon the time to recovery of the blood counts to pretreatment level. Cycles of chemotherapy will be repeated for a total of three cycles. Patient follow-up will continue until death, loss of follow-up, or termination of the study. Patients will remain on study until disease progression or adverse effects dictate otherwise. An adequate trial is defined as receipt of at least one course of therapy and one follow-up visit.

Progress: This study was closed to patient entry, 14 Mar 94. Five patients were enrolled. One patient, who remains disease free, is currently being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 87/091

Status: Ongoing

Title: GOG 0099: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): COL Roger B. Lee, MC; COL William L. Benson, MC

Start Date:
06/19/1987

Est. Completion Date:
Indef

Periodic Review:
10/5/1999

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

Technical Approach: Patients with primary histologically confirmed Grade 2 or 3 endometrial adenocarcinoma (endometrioid, villoglandular, mucinous and adenosquamous) and clear cell carcinoma will be eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic node sampling, pelvic washings and found to be surgical Stage 1 with myometrial invasion. Following surgery, patients will be randomized to no additional treatment of pelvic radiation therapy to begin no later than eight weeks after surgery. Those randomized to radiation therapy will be treated with AP and PA parallel ports with each port being treated each day. A daily tumor dose of 180 cGy will be given to a total dose of 5040 cGy in approximately six weeks. Each patient will be followed with regular visits occurring every three months for the first two years, every six months for the third, fourth and fifth years, and yearly thereafter.

Progress: This study was closed to patient entry, 3 Jul 95. Three patients were enrolled. All are currently clinically disease free.

Detail Summary Sheet

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|---|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 91/086 | Status: Ongoing |
| Title: GOG 0109 (SWOG 8797): 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 I-A2, I-B, and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection | | |
| Principal Investigator: COL Mark E. Potter, MC | | |
| Department: GOG | | Facility: MAMC |
| Associate Investigator(s): None. | | |
| Start Date: 08/02/1991 | Est. Completion Date: Sep 94 | Periodic Review: 10/5/1999 |

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 I-A2, I-B, and II-A carcinoma of the cervix and to determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

Technical Approach: Patients must have primary, histologically confirmed, invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, clinical stages I-A2, I-B, or II-A and must have had a radical hysterectomy with total pelvic lymphadenectomy and para-aortic sampling. Patients must have, at surgical evaluation, either histologically confirmed positive pelvic lymph nodes, positive parametrial involvement, or positive surgical margins. Patients with confirmed positive para-aortic lymph nodes are not eligible. Patients must not have received prior chemotherapy, immunotherapy (including biologics), hormonal therapy, or pelvic irradiation. Patients will be randomly assigned to receive either 5-FU and cisplatin plus pelvic irradiation or pelvic irradiation alone. Patients with positive high common iliac lymph nodes will receive extended field para-aortic irradiation. Irradiation and chemotherapy will begin simultaneously within six weeks after surgery. Chemotherapy will be given once a week every three weeks for four cycles. Radiation therapy will be given for six weeks. After completion of therapy, patients will be followed every 3 months for two years and every 6 months thereafter. Formal analysis of progression-free and overall survival will be performed at 2 1/2 years after the start of patient accrual to determine if consideration should be given to early termination of either treatment arm.

Progress: This study was closed to patient entry, 20 May 94. One patient, enrolled in 1991, remains without evidence of recurrence of disease.

Detail Summary Sheet

Date: 30 Sep 99

Number: 91/074

Status: Ongoing

Title: GOG 0115: Bleomycin (NSC #125066), Etoposide (NSC #141540) and Cisplatin (NSC #119875) (BEP) as First-Line Therapy of Malignant Tumors of the Ovarian Stroma (Granulosa Cell, Sertoli-Leydig Tumor, and Unclassified Sex Cord Stromal Tumor)

Principal Investigator: COL Mark E. Potter, MC

Department: GOG

Facility: MAMC

Associate Investigator(s): None.

Start Date:
07/12/1991

Est. Completion Date:
Indef

Periodic Review:
10/5/1999

Study Objective: To assess the efficacy of bleomycin, etoposide (VP-16), and cisplatin (BEP) chemotherapy in patients with malignant tumors of the ovarian stroma as a first-line regimen.

Technical Approach: Eligible patients will be those with histologically confirmed primary Stages II, III, or IV with incompletely resected disease, recurrent or persistent tumor of the ovarian stroma (granulosa cell tumor, granulosa-theca cell tumor, Sertoli-Leydig cell tumor, androblastoma, gynandroblastoma, unclassified sex cord stromal tumor, or sex cord tumor with annular tubules). Patients will undergo, where appropriate, a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Omentectomy, cytologic washings, and other surgical staging such as pelvic and peri-aortic node sampling, multiple pelvic and diaphragmatic node biopsies are optional. Within 8 weeks of surgery, patients will be placed on BEP therapy: bleomycin IV push weekly for nine weeks, etoposide IV daily times five every three weeks for four courses, cisplatin IV daily times five, every three weeks for four courses. Complete responders or patients with nonmeasurable disease will undergo reassessment laparotomy not later than eight weeks following final course of therapy. To be evaluable for response, a patient will receive at least one course of chemotherapy. The efficacy of the three-drug combination will be evaluated by frequency of negative second-look and frequency and severity of acute toxicity.

Progress: This study was closed to patient entry, April 1997. One patient had disease detected at second look laparotomy in Sep 98. However, she still has no clinical evidence of disease.

Detail Summary Sheet

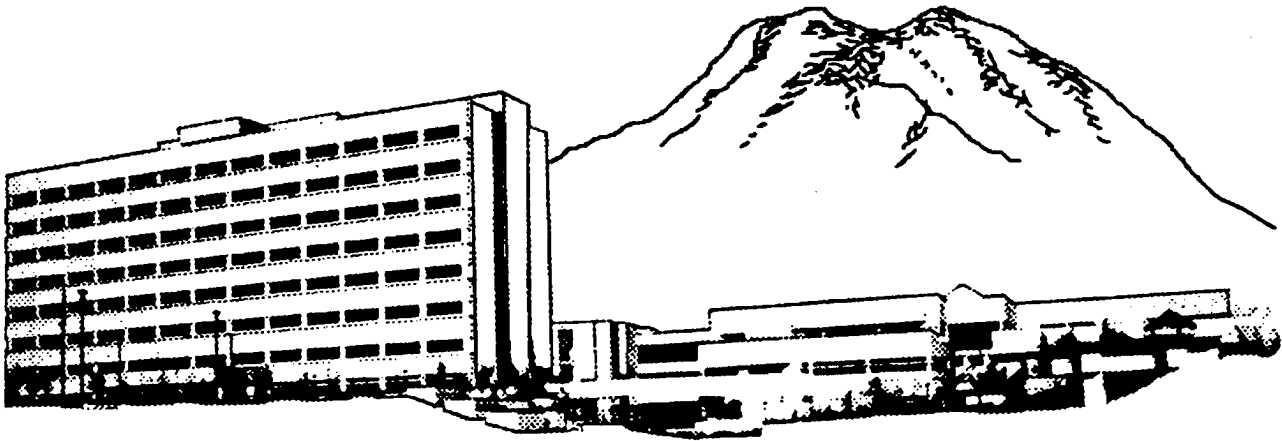
| | | |
|--|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 93/063 | Status: Ongoing |
| Title: GOG 0123: A Randomized Comparison of Radiation Therapy & Adjuvant Hysterectomy vs Radiation Therapy & Weekly Cisplatin & Adjuvant Hysterectomy in Patients with Bulky Stage IB Carcinoma of the Cervix | | |
| Principal Investigator: COL Mark E. Potter, MC | | |
| Department: GOG | | Facility: MAMC |
| Associate Investigator(s): None. | | |
| Start Date: 03/05/1993 | Est. Completion Date: Oct 97 | Periodic Review: 10/5/1999 |

Study Objective: To evaluate the addition of weekly chemotherapy with Cisplatin during radiation therapy in patients with bulky Stage IB carcinoma of the cervix.

Technical Approach: This study randomizes patients to two different treatment regimens. Both regimens include radiation therapy followed by hysterectomy. Regimen I - Radiation Therapy Plus Adjuvant Hysterectomy - Patients will undergo combined external and intracavitary radiation therapy followed by extrafascial hysterectomy (total doses of 13000 cGy). Regimen II - Radiation Therapy Plus Weekly Cisplatin Infusion Plus Extrafascial Hysterectomy. Patient will undergo radiation therapy to receive a total dose of 13000 cGy using a combination of external and intracavitary radiation therapy. Each week during external radiation therapy and during the intracavitary applications the patient will receive an infusion of cisplatin 40 mg/m² not to exceed 70 mg maximum in any single infusion, up to a maximum of 6 doses of cisplatin. Extrafascial hysterectomy will be carried out no later than six weeks following the last day of treatment in both regimens.

The principal parameters to determine the efficacy of weekly cisplatin during radiotherapy are: 1) Outcome variables (recurrence-free interval (RF), survival and local control rate); 2) Tumor characteristics; 3) Host characteristics; 4) Adverse effects; 5) Therapy administered.

Progress: This study was closed to patient entry, April 1997 One patient was enrolled who remains without evidence of recurrence of disease.



Detail Summary Sheets

National Surgical Adjuvant Breast and
Bowell Project (NSABBP)

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/001

Status: Ongoing

Title: NSABBP C-06: A Clinical Trial Comparing Oral Uracil/Ftorafur (UFT) Plus Leucovorin (LV) with 5-Fluorouracil (5-FU) Plus LV in the Treatment of Patients with Stages II and III Carcinoma of the Colon

Principal Investigator: LTC Kenneth A. Bertram, MC

Department:

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC; MAJ David E. McCune, MC

Start Date:

10/20/1998

Est. Completion Date:

Sep 02

Periodic Review:

10/26/99

Study Objective: (1) To compare the relative efficacy of UFT + LV with that of 5-FU + LV in prolonging DFS and S, (2) to evaluate the prognostic significance of the proposed biomarkers, alone or in combination, in patients treated with 5-FU + LV or UFT + LV, (3) to evaluate relationships of various biomarkers to each other and to evaluate their association with patient and tumor characteristics, (4) to compare QOL in patients with stage II or III carcinoma of the colon treated with either the 5-FU + LV regimen or the UFT + LV regimen.

Technical Approach: Patients will be randomized to one of two chemotherapy regimens following resection of stage II and III carcinoma of the colon. Group 1 will receive 5-Fluorouracil plus high-dose Leucovorin and Group 2 will receive Uracil/Ftorafur plus Leucovorin. Patients will be stratified according to the number of positive nodes.

Progress: This protocol was closed to patient accrual 31 Mar 99. One patient was enrolled in FY 99 at MAMC and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/147

Status: Ongoing

Title: NSABBP R-03: A Clinical Trial to Evaluate the Worth of Preoperative Multimodality Therapy (5-FU-LV and RTX) in Patients with Operable Carcinoma of the Rectum

Principal Investigator: LTC Kenneth A. Bertram, MC

Department:

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ John R. Caton, MC; MAJ Richard F. Williams, MC

Start Date:
08/06/1993

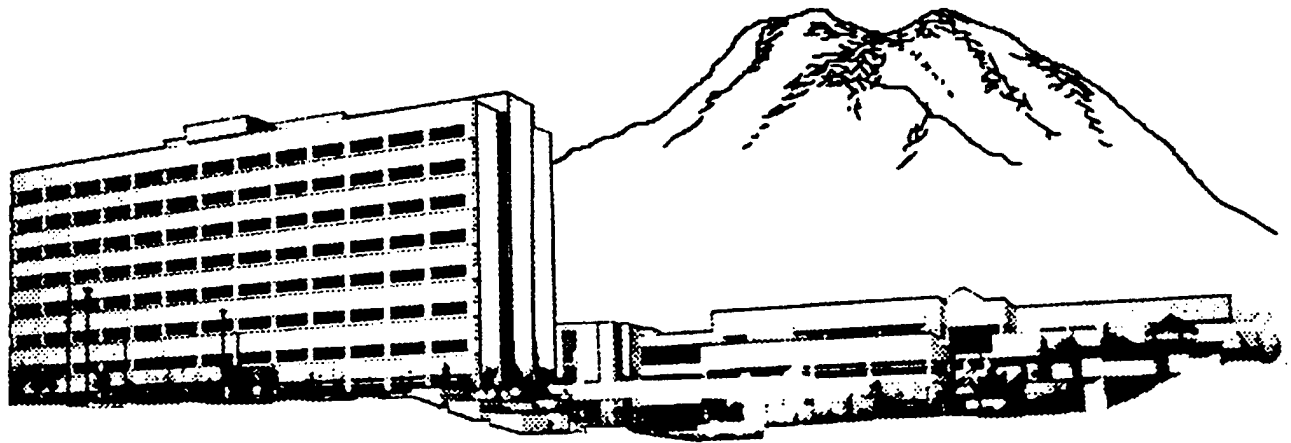
Est. Completion Date:
Jul 98

Periodic Review:
09/30/1998

Study Objective: 1). To determine whether the administration of chemotherapy (chemo) with radiotherapy (RTX) preoperatively is more effective than administration of chemo and RTX (C&R) postoperatively in improving disease-free survival and survival in patients with operable carcinoma of the rectum. 2). To determine if the administration of the above C&R preoperatively results in improvement local recurrence rates when compared with the regimen administered post-operatively in this population of patients. 3). To evaluate the response of rectal tumors to preoperative C&R and to correlate that response with disease-free survival and survival. 4). To assess the downstaging effect of preoperative C&R on the tumor size and pathologic status of regional lymph nodes. 5). To estimate the proportion of patients who can be converted to sphincter-saving surgical procedures from abdomino-perineal resection and local excision alone.

Technical Approach: Patients with operable adenocarcinoma of the rectum will receive seven cycles of 5-FU (FU) + leucovorin (LV) and radiotherapy (RTX), where the first three cycles are given preoperatively and the remaining four postoperatively, to seven cycles of FU-LV and RTX given postoperatively. The patients will be randomized into 2 groups. Group 1 patients, in cycle 1, will receive LV 500 mg/m² by IV infusion and FU 500 mg/m² will be started 1 hr later. Treatment will be given weekly for 6 weeks followed by a rest period. Treatment will be restarted 21 days after the date of administration of the sixth dose of the previous cycle. RTX will begin after completion of cycle 1. FU 325 mg/m²/day and LV 20 mg/m²/day will be given for 5 days during the first and fifth weeks of RTX (cycles 2 and 3). Surgery will be performed after completion of radiation therapy. After recovery from surgery, four more cycles of FU with LV, as in cycle 1, will be given for a total of seven cycles. Groups 2 patients should have surgery performed no later than 3 weeks after randomization. Chemo will begin after recovery from surgery is complete but no later than 4 weeks postoperatively. LV and FU will be administered as in Group 1. RTX will begin after completion of cycle 1. Cycle 4 should begin after completion of RTX when counts allow, but no later than 5 weeks. Four more cycles of FU with LV will be given for a total of seven cycles.

Progress: This protocol was closed to patient accrual 27 Aug 99. One patient was enrolled at MAMC and continues to be followed.



Detail Summary Sheets

Pediatric Oncology Group

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/072 **Status:** Completed

Title: POG 7837: Evaluation of Systemic Therapy for Children with Lymphoblastic Lymphoma Including T-Cell Disease

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
05/22/1998

Est. Completion Date:
Pend

Periodic Review:
06/22/1999

Study Objective: (1) To evaluate a program of intensified CNS therapy for patients with lymphoblastic lymphoma, including T-cell leukemia, treated with the Pediatric Oncology Group's most successful systemic therapy schedule for these patients. This protocol will serve as the control arm for a randomized study, (2) to assess the toxicity and rate of complications encountered by patients receiving POG modified LSA2L2 Therapy in comparison with patient who received therapy using POG 7839 Treatment Arm 1 or POG 7615, (3) to assess the value of cranial radiation therapy plus 3-drug intrathecal chemotherapy in treating occult T-cell leukemia of the central nervous system, using the rate of CNS relapse and the rate of CNS complications for comparison with responses achieved using POG 7837 Treatment Arm 1 and POG 7615 therapy in pediatric patients with T-cell acute lymphocytic leukemia, (4) to assess the therapeutic effectiveness as measured by disease-free survival of POG Modified LSA2L2 Therapy (POG 7837 Treatment Arm 2) compared with responses achieved with POG 7837 Treatment Arm 1 and POG 7615 in pediatric patients with lymphoblastic lymphoma and T-cell leukemia, (5) to provide uniform therapy for patients with lymphoblastic lymphoma, including T-cell leukemia, so as to examine the response of immunologically defined subgroups of T-cell patients to this therapy, and in those patients for who marker studies have been obtained, to correlate response with histopathology and serologic markers, (6) to provide a common protocol for the treatment of patients with widespread T-cell malignancy, offering the opportunity for comparison of response rates among patients who have differing extent of disease.

Technical Approach: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 1 patient being followed who was consented on an IRB approved 7837 study at Tripler AMC. Follow-up information on this patient will need to be sent to the POG Statistical Office per protocol requirements.

Progress: This protocol has been closed to patient accrual. The one patient being followed at MAMC has declined further follow-up; therefore, this protocol is now completed.

Detail Summary Sheet

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|--|--------------------------------------|---------------------------------------|
| Date: 30 Sep 99 | Number: 98/073 | Status: Ongoing |
| Title: POG 8602: Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC #14) | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Kelly J. Faucette, MC | | |
| Start Date: 05/22/1998 | Est. Completion Date: Pend | Periodic Review: 06/22/1999 |

Study Objective: (1) To test the concept that intensive asparaginase (ASP) therapy, designed to maintain low asparagine levels for the first six months of maintenance will improve the outcome for patients with standard risk acute lymphocytic leukemia (ALL) when added to pulses of intermediate dose methotrexate (IDM), as compared to intensification with IDM alone, (2) to study the effectiveness in standard risk patients of intensification with a potentially synergistic or additive drug pair, i.e., IDM plus arabinosyl cytosine (AraC), as compared to that of intensification with IDM pulses alone, (3) to determine if administering a pulse of IDM + AraC at three week intervals (early intensification) during the first 4 months of complete remission in children with ALL is superior to administering the same number of IDM + AraC pulses at 12 week intervals (late intensification) during the first two years of complete remission in children with ALL with either "lower" or "higher" risk of relapse, (4) to obtain further information on the immediate and delayed toxicity of the continuation chemotherapy program that incorporates these combinations of methotrexate (MTX) and AraC or MTX and ASP in moderately high doses, (5) to continue to characterize the biological features of acute lymphatic leukemia of childhood, and their independence and interaction (with therapy and each other) as prognostic factors for attaining and maintaining remission, (a) To assess the effectiveness of these regimens for the early pre-B (non-T, non-B, non-pre-B) and pre-B immunophenotypes of All, respectively, (b) To investigate the hypothesis that ploidy and/or the presence of structural chromosome abnormalities predicts prognosis, (6) to learn whether outcome is related to individual patient differences in methotrexate (MTX) availability as measured by sequential determinations of red blood cell (RBC) MTX and folate levels.

Technical Approach: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 3 patients being followed who were consented on IRB approved 8823 studies in other POG institutions. Follow-up information on these patients will need to be sent to the POG Statistical Office per protocol requirements.

Progress: Protocol is closed to patient accrual; however 3 patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/076 **Status:** Ongoing

Title: POG 8615: A Phase III Study of Large Cell Lymphomas in Children and Adolescents: A Comparison of Two Treatment Regimens - ACOP+ versus APO

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
05/22/1998

Est. Completion Date:
Indef

Periodic Review:
06/22/1999

Study Objective: (1) To determine the influence of alkylating agent (cyclophosphamide) therapy in advanced-stage large cell lymphomas in children and adolescents, by comparing in a randomized prospective study the efficacy and toxicity of a modified ACOP+ versus a modified APO regimen, (2) to reduce the adverse effects of treatments by elimination of involved field and cranial radiation in the treatment of large cell lymphomas, (3) to evaluate the adequacy of one year of total therapy for advanced large cell Non-Hodgkin's lymphoma (NHL), (4) to study clinical pathologic patterns and biologic characteristics of large cell lymphomas in children and adolescents, (5) to assess the feasibility of the total dose of Adriamycin of 300 mg/M2 on the APO arm (post closure of randomization).

Technical Approach: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 1 patient being followed who was consented on an IRB approved 8615 study at Stanford. Follow-up information on this patient will be sent to the POG Statistical Office per protocol requirements.

Progress: Protocol is closed to patient accrual; however 1 patient continues to be followed.

Detail Summary Sheet

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|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 93/141 | Status: Ongoing |
| Title: POG 8650: Intergroup National Wilms' Tumor Study - 4 | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC | | |
| Start Date: 06/09/1993 | Est. Completion Date: Oct 97 | Periodic Review: 06/22/1999 |

Study Objective: To compare 1) the relapse-free and overall survival percentages of patients with: Stage I and II favorable histology (FH) and Stage I anaplastic Wilms' tumor (Ana), using conventional versus pulse intensive (P/I) chemotherapy with vincristine and actinomycin D; 2) Stages 3 and 4 FH, and Stages 1-4 clear cell sarcoma of the kidney using conventional versus P/I vincristine, actinomycin D, and Adriamycin plus radiation therapy; 3) Stages 2-4 Ana treated with vincristine, actinomycin D, and Adriamycin versus the same 3 drugs plus cyclophosphamide, and radiation therapy; and 4) Stages 2-4 FH and Stage 1-4 clear cell sarcoma of the kidney treated for 6 versus 14 months after nephrectomy.

Technical Approach: All patients will be <16 years of age, have had no prior chemo-radiation therapy, will have undergone nephrectomy, and will meet other criteria as stated in the protocol. Patients will be randomized as follows: Stage II/FH & Stage I Ana receive A + V (24 wks) or P/I A + V (18 wks), Stage II/FH receive A + V (22 vs 65 wks) or P/I A + V (60 wks), Stages III & IV FH & clear cell (I-IV) receive A + V + D (26 vs 65 wks) plus RT or P/I A + V + D (24 vs 54 wks) plus RT, and Stages II-IV Ana receive A + V + D + C (65 wks) plus RT or A + V + D + C (65 wks) plus RT. Legend: A = actinomycin D, V = vincristine, D = doxorubicin (Adriamycin), C = cyclophosphamide, and RT = radiation therapy.

Progress: This protocol was closed to patient entry, 1 Sep 94. One patient was enrolled at MAMC in FY 93 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/074

Status: Ongoing

Title: POG 8823/34: Recombinant Alpha-Interferon in Childhood Chronic Myelogenous Leukemia

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
05/22/1998

Est. Completion Date:
Pend

Periodic Review:
06/22/1999

Study Objective: (1) To determine toxicity, response rate and duration of response to therapy with recombinant alpha interferon for newly diagnosed "adult" chronic myelogenous leukemia (ACML) in chronic phase, and for "juvenile" chronic myelogenous leukemia (JCML) occurring within the first two decades. (2) to obtain prospective clinical, laboratory, and genetic data on cases of ACML and JCML treated with recombinant alpha interferon.

Technical Approach: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 3 patients being followed who were consented on IRB approved 8823 studies at Walter Reed Army Medical Center. Follow-up information on these patients will need to be sent to the POG Statistical Office per protocol requirements.

Progress: Protocol is closed to patient accrual; however 3 patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/052 **Status:** Completed

Title: POG 8930: A Comprehensive Genetic Analysis of Brain Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC;
LTC Kelly J. Faucette, MC

Start Date:
12/16/1994

Est. Completion Date:
Nov 97

Periodic Review:
11/17/1998

Study Objective: 1) To determine prospectively the clinical significance of abnormalities of cellular DNA content, as measured by flow cytometry in pediatric brain tumors. 2) To determine the clinical implications of cytogenetic abnormalities found in pediatric brain tumors at diagnosis. 3) To determine the clinical significance of amplification or rearrangement of specific cellular proto-oncogenes or allelic loss of recessively-acting loci in DNA extracted from pediatric brain tumors. 4) To attempt to derive tumor cell lines and to provide a bank of frozen brain tumor tissue for use in further studies, especially molecular genetic studies.

Technical Approach: This is a non-therapeutic study intended to prospectively collect tissue from newly diagnosed patients with brain tumors. Flow cytometry, cytogenetics, and molecular studies will be used to characterize abnormalities of the DNA and correlate their findings with type of disease/diagnoses, tumor grade, and prognostic indicators.

Progress: This protocol closed to patient accrual, 5 Jan 99, as study goals have been met. No patients were enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/075 **Status:** Ongoing

Title: POG 9005: ALinC #15 - Dose Intensification of Methotrexate and 6-Mercaptopurine for ALL in Childhood - A Randomized Phase III Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
05/22/1998

Est. Completion Date:
Pend

Periodic Review:
06/22/1999

Study Objective: (1) To determine, in a randomized trial, whether intensification with intermediate-dose methotrexate (ID MTX), and intravenous 6-mercaptopurine (IV 6-MP) is superior or inferior to repeated low-dose, oral methotrexate (LD MTX) and IV 6-MP for prevention of relapse in children with ALL in first remission and at lower risk for relapse, (2) To compare, in a randomized trial, intensification with ID MTX alone versus ID MTX and IV 6-MP for prevention of relapse in children with lower risk ALL in first remission, (3) To determine if RBC MTX/folate levels can be correlated with event free survival.

Technical Approach: This study has been closed to patient accrual; however HHS guidelines has required IRB approval of closed studies when patients are being followed for survival information. Madigan currently has 5 patients being followed who were consented on IRB approved 9005 studies in other POG institutions, 4 military medical centers and two civilian. Follow-up information on these patients will need to be sent to the POG Statistical Office per protocol requirements.

Progress: Protocol is closed to patient accrual; however 5 patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/018

Status: Ongoing

Title: POG 9031: Treatment of Children with High Stage Medulloblastoma:
Cisplatin/VP-16 Pre vs Post-Irradiation

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC;
LTC Kelly J. Faucette, MC

Start Date:
11/18/1994

Est. Completion Date:
Nov 94

Periodic Review:
09/30/1998

Study Objective: To compare the 2-year event-free survival (EFS) of children with newly-diagnosed high-risk medulloblastoma who are treated with cisplatin and VP-16 pre-irradiation vs post-irradiation. To define the toxicity and activity of pre-irradiation cisplatin/VP-16 in patients with newly-diagnosed high-risk medulloblastoma. To determine whether achievement of a measurable tumor response (PR and CR) to pre-irradiation cisplatin/VP-16 has prognostic significance for children with high-risk medulloblastoma, compared with failure to achieve a measurable response (SD or PD). To define the toxicity and activity of post-irradiation cisplatin/VP-16 in patients with newly-diagnosed high-risk medulloblastoma. To determine if c-myc amplification in medulloblastoma is associated with an adverse prognosis.

Technical Approach: Studies in children and adults have demonstrated the ability to deliver pre-radiotherapy chemotherapy for patients with newly-diagnosed brain tumors without increasing neurotoxicity in association with the subsequent radiotherapy. This approach creates a phase II "window" allowing evaluation of response in these patients who are previously untreated except for surgery. The theoretical anti-neoplastic advantage of this approach is the potentially enhanced efficacy of the radiotherapy when given to "chemically debulked" patients. Half of the children diagnosed with medulloblastoma are now being successfully treated and are surviving for prolonged periods. Until recently, the survival of this group of patients was limited so that long-term effects of therapy were not a concern. As survival increases, one would expect to observe an increase in frequency of certain treatment-related toxicities. There are now a variety of long-term effects which need to be considered in this cohort of patients. Specific evaluations will be made on all patients entered onto this study, so that treatment-related problems may be detected in their early stages and intervention taken. This approach should ultimately improve the quality of life for children diagnosed and treated for brain tumors.

Progress: Protocol was closed to patient entry 26 March 96. One patient was enrolled in this study at MAMC in FY 95 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 93/164 **Status:** Ongoing

Title: POG 9047: Neuroblastoma Biology Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
09/03/1993

Est. Completion Date:
Feb 96

Periodic Review:
9/28/1999

Study Objective: 1) To obtain tissue for the analysis of DNA content of neuroblastoma cells by flow cytometry. 2) To characterize neuroblastoma tumor DNA from POG patients genetically by analysis of N-myc amplification and LOH for chromosome 1p. 3) To develop a reference bank of genetically characterized tumor tissue and DNA that would be available for other studies.

Technical Approach: This is a non-therapeutic study intended to collect tissue from newly-diagnosed neuroblastoma patients = 21 years. Viable tumor tissue, frozen tumor tissue (or marrow) and serum will be collected and forwarded to a designated study site.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 95/008 | Status: Completed |
|------------------------|-----------------------|--------------------------|

Title: POG 9153: Intergroup Rhabdomyosarcoma Study/Laboratory Evaluation of Tumor Tissue

Principal Investigator: LTC Stephen R. Palmer, MC

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|------------------------|-----------------------|
| Department: POG | Facility: MAMC |
|------------------------|-----------------------|

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

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|----------------------------------|--|---------------------------------------|
| Start Date: 11/04/1994 | Est. Completion Date: JUN 97 | Periodic Review: 11/17/1998 |
|----------------------------------|--|---------------------------------------|

Study Objective: 1) To prospectively correlate clinical features and outcome of newly diagnosed children with rhabdomyosarcoma with cytogenetic abnormalities of their tumors, 2) to measure cellular DNA content by flow cytometry of tumor cells and correlate the DNA index of tumor stem lines with clinical features and treatment response, 3) to determine prospectively the clinical significance of amplification or rearrangement of specific cellular proto-oncogenes or allelic loss of recessively acting loci in DNA extracted from pediatric rhabdomyosarcomas, 4) to attempt to derive tumor cell lines and to provide a bank of frozen rhabdomyosarcoma tumor tissue for use in further studies, especially molecular genetic studies, and 5) to determine the degree of specificity of monoclonal antibody probes, 4.2A8, 5.1H11, and 3.1G11, for childhood rhabdomyosarcoma.

Technical Approach: This is a non-therapeutic study intended to collect tissue from newly-diagnosed rhabdomyosarcoma and undifferentiated sarcoma patients < 21 years. Viable tumor tissue, frozen tumor tissue and involved marrow samples will be collected and forwarded to a designated study site.

Progress: This protocol closed to patient accrual 15 Mar 99 due to the activation of its successor study, protocol D9902. One patient was consented but never enrolled on this study. No patients have been enrolled on this protocol at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/084

Status: Ongoing

Title: POG 9182: HIV/Malignancy Biology Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC;
LTC Kelly J. Faucette, MC

Start Date:
03/17/1995

Est. Completion Date:
Apr 97

Periodic Review:
02/23/1999

Study Objective: 1) To establish a national registry of pediatric AIDS-associated lymphomas and other malignancies and a repository of well-characterized tumor tissue, cells and sera from affected patients. 2) To conduct prospective Phase I-III clinical trials of anti-cancer and anti-retroviral therapies aimed at improving outcomes and identifying critical determinants of risk. 3) To identify the presence and quantify the viral burden of human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), Human Herpes virus 6 (HHV6), and Herpes Simplex virus (HSV) in the tumor tissue, peripheral blood cells, plasma, and cerebrospinal fluid of pediatric patients with lymphomas and other malignancies; and to characterize the effect of anti-cancer and antiviral chemotherapy with regard to lymphoma stage, disease progression, host response, and toxicity. 4) To conduct the first large-scale molecular epidemiologic study of risk factors related to development of HIV-related NHL in children by means of a case-control analysis of HIV-infection characteristics such as co-infection with EBV, CMV, HHV6, Mycoplasma, the quantitative host viral burden, level of immunodeficiency, and other host characteristics. 5) For HIV+ and HIV- children, to characterize differences in NHL tumor tissue in terms of immunophenotype, immunoglobulin gene rearrangements and oncogene (c-myc) activation.

Technical Approach: Three groups of children are eligible for this protocol. The first, a "case" group, consists of children with a newly-diagnosed malignancy who are HIV positive. The second, a "malignancy control" group, consists of children with a newly-diagnosed malignancy who do NOT have HIV infection. The third group, a "non-malignancy control" group, consists of children with no evidence of malignancy, but who have a documented HIV infection. A total of 150, 150, and 300 patients, respectively is expected. The subject will be seen in the clinic at least every two months for up to two years, then every 6 months up to 3 years. At each visit blood will be drawn for testing. In addition, a small piece of tumor tissue or other body fluids (including spinal fluid and bone marrow), already obtained as part of routine clinical management may be examined. We will establish a database as a repository for characteristics of pediatric patients with HIV infection and malignancies. The database will include all appropriate clinical parameters, laboratory measures, and results of molecular and virologic studies. Descriptive analyses of clinical and laboratory data will use various criteria to characterize the study population and to correlate variation in infectious virus and total viral burden with clinical course and other laboratory measurements. Primary endpoints, which may include tumor response, disease-free survival and episodes of grade 3-4 toxicities, will be confined to those specified in POG therapeutic protocols. Contingency tables relating the laboratory variables with stage, age, primary tumor site, histopathology, and clinical response will be produced. Conditional logistic regression will be used to compare biological data for cases to matched controls. Frequency matching will be performed at the Statistics Office at the time of analysis. Kaplan-Meier life tables, log rank tests, and Cox regression will be used to explore the relationship of laboratory variables to outcome.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/056

Status: Ongoing

Title: POG 9201: ALINC #16 Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia, A Pediatric Oncology Group Phase III Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
12/16/1994

Est. Completion Date:
Dec 99

Periodic Review:
11/19/1999

Study Objective: 1) To confirm the outstanding results in patients with lesser risk not-T, non-B acute lymphoblastic leukemia (ALL) treated in a fashion similar to the least intensive arm of POG 8602 (AlinC 14, Arm A). 2) To study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405, and 9406.

Technical Approach: Patients on this study will be treated with a 3-drug induction regimen (vincristine, prednisone, and L-asparaginase) to bring about remission (a state of no apparent disease) in four weeks.

This will be followed by a consolidation phase including (6) six courses of intravenous (into vein) intermediate-dose methotrexate (each will require hospital stay) at 3-week intervals. After week 5, daily 6-mercaptopurine will be given by mouth until the end of planned treatment. Methotrexate will be given intramuscularly (into muscle) weekly. Periodic "pulses" (infrequent administration) of vincristine and prednisone will be given throughout the first two years of therapy. Additionally, triple intrathecal (into spinal fluid) therapy (TIT) consisting of methotrexate, hydrocortisone, cytosine arabinoside will be given at the start of treatment and periodically through the first two years of therapy to prevent the spread of leukemia to the central nervous system (CNS). The vitamin Leucovorin will be given to prevent methotrexate toxicity. After week 25, during the continuation phase, all medications will be on an outpatient basis.

The total duration of therapy is planned to be 2 1/2 years from initial diagnosis. If tests at that time indicate no evidence of leukemia, then all medications will be stopped and you (your child) will be followed closely to be sure that there is no evidence of return of the disease.

Progress: One patient enrolled in this study at MAMC in FY 96 and another patient was accepted in transfer. Both continue to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 94/033 **Status:** Ongoing

Title: POG 9219: Treatment of Localized Non-Hodgkin's Lymphoma, A POG Phase IV Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

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| Start Date: 11/05/1993 | Est. Completion Date: Jun 96 | Periodic Review: 04/27/1999 |
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Study Objective: 1. To maintain a high cure rate with minimum toxicity for children with localized non-Hodgkin's lymphoma in favorable sites.

2. To analyze in a large group of patients with localized non-Hodgkin's lymphoma (by pooling data from POG #83314, #8719 and the current study) prognostic factors which may predict subgroups of patients with a poor prognosis within the subgroup of patients with localized NHL.

Technical Approach: After staging, subjects that qualify will receive Vincristine 1.5 mg/M2 (max 2 mg) IV q wk x 6 weeks, prednisone 40 mg/M2/day in 3 divided doses x 28 days, Adriamycin 40 mg/M2/day IV days 1 & 22, and Cyclophosphamide 750 mg/M2/day IV days 1 & 22. Fluid intake is to be > 3000 ml/M2 on day of treatment. Triple intrathecal chemotherapy (TIT) will be given on days 1, 8, and 22 to those with head and neck primaries.

On day 43, or when blood counts recover, the patient will receive Adriamycin 40 mg/M2 IV, Cyclophosphamide 750 mg/M2 IV, Vincristine 1.5 mg/M2 (max 2 mg) IV, and Prednisone 50 mg/M2 in 3 divided doses x 5 days.

On day 64 and when blood counts have returned to normal following the prescribed induction and consolidation regimen, the patient will be assessed for remission status.

Progress: This protocol closed to patient accrual 2 Jul 99. Two patients were enrolled in this study at MAMC in FY 97. Both patients completed treatment and continue to be followed. No new patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/148

Status: Completed

Title: POG 9233/34: A Phase III Randomized Trial of standard vs Dose-Intensified Chemotherapy for Children Less Than 3 Years of Age With A CNS Malignancy Treated With or Without Radiation Therapy

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): COL Stephen R. Stephenson, MC; LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC

Start Date:
08/06/1993

Est. Completion Date:
Jun 95

Periodic Review:
04/27/1999

Study Objective: To develop effective methods of treatment for very young children with malignant brain tumors that will minimize late toxicities affecting immature and rapidly developing central nervous systems.

Technical Approach: Patients < 3 yrs of age with a primary intracranial malignancy will be randomized to one of two regimens. Patients assigned to Regimen A will receive six 12-week courses of chemotherapy, given over a total of 72 weeks. Each course consist of 3 drug cycles. Cycle A; vincristine and cyclophosphamide and Mesna will be given on weeks 1, 13, 25, 37, 49 and 61. Vincristine will be repeated on day 8 of this cycle. During Cycle B, patients will receive cisplatin on day 1 and VP-16 on days 3 and 4. Patients on Regimen B will receive eight 9-week courses of chemotherapy. Each course will consist of 2 consecutive cycles of one drug combination (Cycle X) followed by a cycle of another combination (Cycle Y). On Cycle X, vincristine, and Mesna will be given on day 1 of weeks 1, 4, 10, 13, 19, 22, 28, 31, 27, 40, 49, 55, 58, 64, and 67. On day 2 patients will receive cyclophosphamide and Mesna. On days 3-15 patients will receive G-CSF. On Days 8 and 15, vincristine will be given. Cycle Y will be given on weeks 7, 16, 25, 34, 43, 52, 61 and 70. On Day 1 of Cycle Y, cisplatin will be given. VP-16 will be given on days 3 and 4. On days 5-14 G-CSF will be administered.

Patients experiencing progression or recurrence of disease at any time during or within 12 months of chemotherapy will be encouraged to begin radiation therapy immediately. If disease recurs later than 12 months after completing chemotherapy, patients will be discontinued from the study.

Progress: No patients were enrolled in FY 98. One patient was enrolled in July 94 , completed treatment and was transferred to WRAMC Aug 96. Protocol closed to patient entry 8 May 1998 due to adequate patient accrual in all stratas.

Detail Summary Sheet

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|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 96/096 | Status: Ongoing |
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Title: POG 9315: A Phase III Study of Large Cell Lymphomas in Children and Adolescents; Comparison of APO vs. APO + IDMTX/HDARA-C

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC; MAJ Robert G. Irwin, MC

Start Date:
04/19/1996

Est. Completion Date:
Jun 99

Periodic Review:
04/27/1999

Study Objective: 1) To study whether intermediate-dose methotrexate/high dose ARA-C (ID MTX/HRARA-C), administered during the maintenance phase can improve the event-free survival (EFS) of patients with advanced-stage large cell lymphoma (LCL); 2) to further characterize the immunophenotypic and morphologic correlates of pediatric LCL; and 3) to compare efficacy and cardiotoxicity of doxorubicin given by continuous versus bolus infusion.

Technical Approach: Patients will be randomized at registration to Regimen A or B. Patients who present with CNS disease will go after induction directly to Regimen B. Induction for both regimens will be the same, with additional intrathecal for patients with CNS disease. Maintenance A consists of 8 cycles of ID MTX/HD Ara-C alternating with 5 cycles of VCR/6-MP/ADR/Pred and 2 cycles of VCR/6-MP/MTX/Pred; a total of 15 cycles given at 3 week intervals. Maintenance B consists of 5 cycles of ADR/V/6-MP/Pred followed by 10 cycles of MTX substitution for ADR; a total of 15 cycles will be given at 3 week intervals. Following completion of therapy, examinations will be every month for the first 6 months; thereafter every 3 months until year 2 off therapy and then every 6 months until 5 years off therapy, then annually. Cardiac exams after completion of therapy will be required during first, third and fifth years off treatment.

Progress: One patient was enrolled in this study at MAMC in FY 97; however, she was transferred to a civilian hospital prior to her sponsor's separation from the military. This study remains open for patient accrual. No patients were enrolled in FY 99.

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 94/072 | Status: Completed |
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Title: POG 9317: Chemotherapy for Children with Advanced Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B Cell ALL

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
03/04/1994

Est. Completion Date:
May 99

Periodic Review:
04/27/1999

Study Objective: 1) To evaluate the efficacy of adding VP-16/Ifosfamide intensification to the treatment of patients with advanced-stage B-cell malignancies: Stage III & IV DU NHL and B-cell acute lymphoblastic leukemia (B-ALL). 2) To compare the toxicity and efficacy of high-dose Ara-C given by intermittent bolus (q 12 hour x 4) vs bolus/continuous infusion over 48 hours.

Technical Approach: In this groupwide protocol, we propose to add, in a randomized study, two agents active in the treatment of aggressive NHL: Ifosfamide 2.8 g/M² with VP-16 100 mg/M² qd x 5. All patients in this study will be randomized at diagnosis to receive, throughout therapy, high-dose Ara-C by continuous infusion (CI) or by bolus (actually a 3 hour infusion). The CI Ara-C dose is based on the POG pilot study #9190 with a starting dose of 3.8 g/M²/48 hours (80 mg/M²/hr) following 9.5 g/m² bolus. The bolus Ara-C dose is taken from POG #8617: 3 g/M² q 12 hr X 4 doses.

All patients will receive therapy based on POG #8617/8616, with a reduction in duration. After a common induction with fractionated cyclophosphamide, vincristine, Adriamycin, methotrexate by 24-hour infusion, and Ara-C, patients with Stage III disease will receive these drugs without Adriamycin and patients with Stage IV/B-ALLL will receive these 5 drugs including Adriamycin during consolidation.

Patients will also be randomized to receive or not to receive VP-16/ifosfamide intensification, except for patients with CNS involvement who will be assigned to receive VP/16 ifosfamide. The study question is being posed in a randomized 2 X 2 factorial design.

Progress: This protocol was closed to patient accrual 5 Mar 99. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/168

Status: Ongoing

Title: POG 9323: Interferon-Alpha 2b Plus Hydroxyurea and Ara-C for Chronic Phase ACML in Children, A POG Pilot Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:
07/21/1995

Est. Completion Date:
Jul 99

Periodic Review:
06/22/1999

Study Objective: 1) To assess the toxicity of the combination of Hydroxyurea (HU) and Ara-C combined sequentially with interferon-alpha 2b (IFN) in children with adult type chronic myelogenous leukemia (ACML). 2) To determine the frequency and duration of hematologic and cytogenetic response, and the length of time needed to achieve response during two years of such treatment.

Technical Approach: Therapy will be divided into 2 induction phases and a consolidation phase. Induction 1: Therapy will begin with two, or possibly three, weekly courses of hydroxyurea and Ara-C. Each course will consist of treatment given on three consecutive days as follows: after consuming clear fluids only for breakfast, hydroxyurea will be taken by mouth. Two hours later, Ara-C will be administered intravenously over 15 minutes. This will be repeated on the second and third day of each course. Subjects will receive at least two courses, beginning days 1 and 8. If blood counts are still above certain values on day 15, a third course will be given. Induction 2: Once blood counts have adequately recovered from the above chemotherapy, IFN treatment will begin. Subjects will receive IFN given as a subcutaneous injection daily for 14 days. Consolidation: IFN will then be continued at this dosage every Monday, Wednesday and Friday. IFN therapy will be interrupted for at least one week, approximately every 6 weeks, for a threeday course of hydroxyurea/Ara-C. This six-week cycle (IFN three times weekly for five weeks followed by a course of hydroxyurea/Ara-C), will be repeated for a total treatment time of approximately two years, assuming a good response to treatment. Most therapy will be administered at home (IFN) or in the outpatient clinic (hydroxyurea/Ara-C), with the exception being the first course of hydroxyurea/Ara-C and the first few days of IFN therapy, for which hospitalization is recommended. Every effort will be made to continue treatment for at least 90 days. All patients who have signs of progressive (worsening) disease within the first 90 days will be evaluated for possible discontinuation of this therapy. All other patients will continue on treatment for a total of 24 months. For those patients continuing on therapy past 90 days, the treatment will be discontinued (prior to 24 months) if there are signs of progressive disease at any time; if there is no evidence of any improvement by six months or if side effects develop which cannot be tolerated even with reduction in the drug dosages. Therapy may also be stopped at any time if a suitable marrow donor has been found and the physician decides that bone marrow transplantation would be in the patient's best interest. If the patient is still on therapy and responding well after 24 months, then the physician may offer to continue therapy with IFN alone. This will be offered as further therapy, but it will not be part of this study. It is not known how many years interferon may be safely given. The dosage schedule described above is to be considered a guideline. It is very possible that modification will need to be made depending on the side effects encountered.

Routine blood tests will be done during the first four to six weeks of therapy (the "induction" phase), and then every one to two weeks while on therapy. A bone marrow aspirate and biopsy will be done prior to start of induction therapy, then twice more at about three month intervals, and then every six months thereafter unless removed from the study because of no response, progressive disease (increased severity), or bone marrow transplantation. A

Chromosomal analysis will be completed on each bone marrow aspirate to find out if the Philadelphia chromosome is present. Each bone marrow aspirate will be followed by an ultrasound study of the spleen in order to determine the size of the spleen.

Progress: This protocol was closed to patient accrual 27 Jan 99. One patient was enrolled in this study at MAMC in FY95. She was taken off study July 97 to pursue bone marrow transplant and continues to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/092

Status: Ongoing

Title: POG 9351/CCG 7921: Trial of Doxorubicin, Cisplatin, and Methotrexate With and Without Ifosfamide, With and Without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
04/01/1994

Est. Completion Date:
Jun 99

Periodic Review:
04/27/1999

- Study Objective:**
- 1) To improve the survival of patients with osteogenic sarcoma.
 - 2) To compare the results of a prospective, randomized trial of two chemotherapeutic regimens in the treatment of osteogenic sarcoma.
 - 3) To compare the results of a combined chemotherapeutic regimen (high-dose methotrexate, cisplatin, and doxorubicin) given pre-operatively and post-operatively to a similar regimen using the same drugs and adding ifosfamide.
 - 4) To test whether the early introduction of ifosfamide results in a higher rate of good histologic response at the time of definitive surgery.
 - 5) To determine whether histologic response assessed after longer pre-operative chemotherapy with more drugs predicts disease-free survival with the same power as observed in CCG-782 which used a shorter period of pre-operative chemotherapy and fewer drugs.
 - 6) To determine whether liposomal muramyl tripeptide-phosphatidyl ethanolamine (MTP-PE, CGP 19835a), a stimulator of macrophage function, can improve disease-free survival for patients with osteogenic sarcoma.
 - 7) To determine whether multiple drug resistance gene-encoded P-glycoprotein expression is useful for determine prognosis or assigning therapy.

Technical Approach: This study is a phase III, prospective, randomized trial of two chemotherapy regimens for the treatment of newly diagnosed, previously untreated osteogenic sarcoma. One regimen calls for the administration of high-dose methotrexate, doxorubicin, and cisplatin. The other regimen calls for the administration of these agents plus ifoxfamide. Chemotherapy is administered for 10 weeks prior to surgical resection of the primary tumor and any metastatic disease (CCG patients). Patients also are randomly assigned either to receive muramyl tripeptide (MTP-PE) with maintenance chemotherapy or to receive maintenance chemotherapy alone.

Progress: Protocol was closed to patient accrual 25 Nov 97 due to adequate patient enrollment. Two patients were entered in this study at MAMC in FY 96. One patient chose to discontinue treatment early. The other patient completed therapy. Both patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/087

Status: Ongoing

Title: POG 9362: A Phase II Study of Alpha Interferon in HIV-Related Malignancies

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC;
LTC Kelly J. Faucette, MC

Start Date:
03/17/1995

Est. Completion Date:
Jun 99

Periodic Review:
03/23/1999

Study Objective: 1) To estimate the complete response rate for HIV related malignancies treated with interferon (aIFN). 2) The secondary objectives are to estimate the one year disease free survival and to evaluate the toxicity of aIFN alone or in combination with anti-retroviral therapy.

Technical Approach: This study will require all patients to be enrolled in POG 9182 and compliance with all specimen submission requirements of that protocol. The study will minimize additional tissue, CSF or blood sampling except as required for monitoring for toxicity and tumor response. This study will take advantage of the demonstrated antitumor and antiviral activity of aIFN alone or in combination with other antiretroviral agents to treat HIV positive children with refractory or newly diagnosed malignancies. As the duration of response is one of the goals of this study, responders will continue on therapy indefinitely. Patients on this study will be treated using a interferon by subcutaneous injection every day for 14 days; then if your child's/adolescent's evaluation allows further treatment he/she will receive a interferon three times a week. This treatment will need to be monitored by a treating physician and blood tests will be performed in order to insure that the treatment is well tolerated and that the dose is appropriate. For that purpose 10cc of blood will be taken once a week. The physician and/or staff will be checking closely to see if any of these side effects are occurring. Routine physical exams, laboratory tests and tests such as biopsy or bone marrow aspiration may be necessary to monitor the effect of the treatment. Side effects usually disappear after the treatment is stopped. In the meantime, the doctor may prescribe medication to keep these side effects under control.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/058 **Status:** Ongoing

Title: POG 9400: ALinC 16 Classification (C) Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC;
LTC Kelly J. Faucette, MC; MAJ Robert G. Irwin, MC

Start Date:
12/16/1994

Est. Completion Date:
Dec 99

Periodic Review:
11/19/1999

Study Objective: 1) To continue to characterize the biologic findings of the acute lymphoblastic and undifferentiated leukemias (immunologic markers, ploidy (DNA index), karyotyping, morphology) and their relationship, as prognostic factors for attaining and maintaining remission.

2) To apply to therapy selection, the determination that ploidy and certain structural chromosomal abnormalities predict poor prognosis.

3) To evaluate the usefulness of PCR technique in detecting minimal residual disease in patients with disease demonstrating t (9; 2 2) or t (1; 19) chromosomal abnormalities. (optional)

4) To apply to therapy selection molecular testing for 11q23 translocation in infants < 12 months of age with acute lymphocytic leukemia.

5) To determine the roll of p53 and pl6 tumor suppressor genes in T-ALL. (optional)

6) Individual patient outcome will be compared with the leukemia cell proliferation response to ask if proliferation in response to a myeloid growth factor is associated with an increased risk of developing AML. (optional)

7) To determine risk group assessment using Fluorescent In-Situ Hybridization (FISH) screening for Trisomies 4 and 10 in Non-T, Non B ALL.

8) To determine if drug sensitivity profiles of blast cells for three commonly used chemotherapeutic agents - Adriamycin, Methotrexate, and Cytarabine correlate with a) initial response b) subsequent development of relapse.

Technical Approach: A bone marrow aspirate (a needle stick in hip bone to draw marrow into syringe) will be done to prove or disprove diagnosis of leukemia. If leukemia is present, it is important to identify the exact type and subtype of leukemia, in order to plan treatment. This typing requires that several laboratory tests be run on the leukemia cells in the bone marrow. As we perform the bone marrow aspiration we will be removing enough bone marrow (about 2-1/2 teaspoons) to run the laboratory tests. We may also need to draw some blood (about 2-1/2 teaspoons) from a vein to send for studies. Some of these tests will be done here and some will be sent to reference laboratories in other Pediatric Oncology Group institutions for different kinds of special tests to identify the characteristics of the leukemia cells.

Progress: Two patients enrolled in this study at MAMC in FY95, one patient enrolled in FY 96 and one patient in FY 97 for a total enrollment of four. Two patients were enrolled in FY 99 for a total of 6 patients enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/144

Status: Ongoing

Title: POG 9404: T-Cell #4 Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:

07/19/1996

Est. Completion Date:

Aug 04

Periodic Review:

06/22/1999

Study Objective: 1) To determine, in a randomized trial, the effectiveness of high dose methotrexate (HD MTX) when added to a multi-agent chemotherapy backbone (DFCI 87-0001) proven effective in T-Cell acute lymphoblastic leukemias (T-ALL) and advanced stage non-Hodgkin's lymphoma (Lymphoblastic NHL); 2) to determine, in a randomized trial, the role of the cardioprotectant Zinecard (DZR) in preventing cardiotoxicity in children with T-ALL and advanced stage Lymphoblastic NHL receiving an anthracycline based regimen; 3) to study the biology of T-Cell lymphoid malignancies by accumulating data on the concurrent ALL classification study (POG 9400) and analyzing the data relative to outcome; 4) to evaluate the correlation of minimal residual disease with event-free survival utilizing the TAL 1 proto-oncogene; 5) to determine the role of p53 and p16 tumor suppressor genes in T-ALL; and 6) to determine if drug sensitivity profiles of blasts cells to Doxorubicin, methotrexate and cytarabine correlate with initial response and subsequent development of relapse.

Technical Approach: Patients will receive induction therapy (weeks 1-6), vincristine every week for 4 weeks, prednisone for 21 days starting day 1 and doxorubicin on days 1, 2, and 22, with or without ZINECARD. During this phase, the drug methotrexate will be given on day 2. Patients will be randomized to receive high dose methotrexate on day 22. Intrathecal methotrexate, Ara-C and hydrocortisone will be given to prevent central nervous system disease throughout the entire three phases of treatment. Once remission has been achieved, patients will receive consolidation therapy (weeks 7-33). Drugs will be given in three week cycles (6-mercaptopurine for 14 days, vincristine and doxorubicin on day 1 of the cycle, prednisone for 21 days) with or without ZINECARD. Asparaginase will also be given during the consolidation phase once a week during weeks 7-26. Patients who received high dose methotrexate on day 22 of induction will also receive it on weeks 7, 10 and 13 of consolidation. At weeks 22-24, all patients will receive radiation therapy to the brain. During continuation (weeks 34-108), patients will receive vincristine, prednisone (every day for five days) and 6-MP (every day x 14 days) every three weeks. Methotrexate, will be given every week except during those weeks when patients receive intrathecal medications.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/059 **Status:** Ongoing

Title: POG 9405: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
12/16/1994

Est. Completion Date:
Dec 99

Periodic Review:
11/19/1999

Study Objective: 1) To determine in a randomized trial, the efficacy of a higher (2.5 gms/mt) versus standard (1 gm/m²) dose methotrexate (MTX) infusion during consolidation. The major endpoint will be eventfree survival among those achieving a complete remission. Secondary comparisons will include sitespecific events and adverse drug reactions. 2) To determine in a randomized comparison, the efficacy of delivering oral 6-MP on a once versus twice daily schedule during continuation. 3) To study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405 and 9406. 4) To assess the prognostic significance of the percent of marrow blasts after two weeks of induction therapy.

Technical Approach: In this research study, the subject will receive intensive combination chemotherapy for 4 weeks to eliminate visible disease (remission induction). This induction chemotherapy involves standard combinations of such agents as Prednisone, given orally (by mouth) for 28 days; vincristine, given by a quick intravenous infusion (IV push) on days 1, 8, 15, and 22; L- asparaginase, injected into a muscle (IM) on days 2, 5, 8, 12, 15, and 19. The drugs methotrexate, Icotosine arabinoside (Ara-CI, and hYdrocortisone will be administered intrathecally (injected into the spinal fluid) at various intervals throughout both the induction and intensive periods to prevent the leukemia from coming back in the central nervous system. After Induction the subject will be randomized (assigned by chance, such as flipping a coin), to a specific regimen to include either standard or high dose IV Methotrexate and receiving oral 6MP once or twice daily. During the period of consolidation (weeks 5-28), the subject will receive the drugs methotrexate and 6- mercaDtoPurine (6-MP). The Methotrexate will be given at a standard or higher dose. In the first week, methotrexate will be injected into a vein followed by a 24-hour infusion. The vitamin Leucovorin will be given orally or as an infusion to help protect the patient from the toxicity of methotrexate. Immediately after the methotresate, 6-MP will be given by IV infusion over 20 minutes followed by an infusion over 6 hours. On the second week of therapy, the subject will receive methotrexate injected into a muscle (IM) on day 1 and 6-MP daily by mouth for 7 days. This 2 week treatment will be repeated for a total of 12 cycles. During the period of continuation (weeks 20-130), 6-MP will be given orally each day, and methotrexate injected into a muscle (IM) once each week. Patients randomized onto regimens B & D will receive 6MP orally twice daily. The subject will be taken off study in case of relapse in the bone marrow, or any other site, or if the subject fail to achieve a complete remission during the induction phase of the study. At the time of bone sarrow aspiration, blood sampling, or spinal tap, cells obtained may be used for research studies. These studies will help the doctor to better understand this form of cancer and how treatment can be improved in the future. Chemotherapy given intrathecally into the spinal fluid may cause pain at infusion site, pain in the back, legs or head, fever, headache, vomiting; rarely stiff neck, convulsions, paralysis. Bone marrow aspiration may cause bruising and soreness over the bone from which the marrow sample is taken.

Progress: This protocol closed to patient accrual 26 Dec 95 due to excessive neuro toxicity. Two patients were enrolled at MAMC. One patient enrolled in this study at MAMC in FY95 was taken off study but continues to be followed. The other patient enrolled in FY 96 was transferred to Beaumont Naval Med Center.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/060 **Status:** Ongoing

Title: POG 9406: ALinC #16 - Protocol for Patients With Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG **Facility:** MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|-------------|-----------------------|------------------|
| 12/16/1994 | Dec 99 | 11/19/1999 |

Study Objective: 1) To determine the efficacy of a 2.5 gm/m² dose versus 1 gm/m² dose intravenous methotrexate infusions during intensified continuation therapy. The major endpoint will be event-free survival among those achieving a complete remission. Secondary comparison will include site-specific events and adverse drug reactions. 2) To determine whether intensified continuation therapy delivering pulses of Ara-C (3 gm/m² x 4 doses) with asparaginase rescue is superior to standard intensified continuation with pulses of VM-26/Ara-C. The major endpoint will be event-free survival among those achieving a complete remission. Secondary comparison will include site-specific events (including secondary AML) and adverse drug reactions. 3) To study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405, and 9406. 4) To assess the prognostic significance of the percent of marrow blasts after two weeks of induction therapy.

Technical Approach: In this research study, a child will receive intensive combination chemotherapy for 4 weeks to eliminate visible disease (remission induction). This induction chemotherapy involves standard combinations of such agents as prednisone, given orally for 28 days; vincristine, given by a quick intravenous infusion on days 1, 8, 15, and 22; L-asparaginase, injected IM on days 2, 5, 8, 12, 15, and 19. The drugs methotrexate, cytosine, arabinoside (Ara-c), and hydrocortisone will be administered intrathecally at various intervals throughout the induction and intensive periods to prevent the leukemia from coming back in the central nervous system. Daunomycin will be given on days 8, 15, and 22 intravenously. After the previous treatment, subjects will be randomized to a specific regimen to include either standard or high dose Methotrexate or low or high dose Ara-C. During the period known as consolidation, the subject will receive the drugs methotrexate and 6-mercaptopurine (6-MP) during weeks 5-6, 10-11, 15-16, 25-26, and 30-31. In the first week of each of these periods, methotrexate (either the standard or the intensified higher dose) will be injected into a vein followed by a 24-hour infusion. The vitamin Leucovorin will be given orally or as an infusion to help protect the patient from the toxicity of methotrexate. Immediately after the methotrexate, 6-MP will be given by IV infusion over 20 minutes followed by an infusion over 6 hours. On the second week of therapy, the subject will receive methotrexate injected into a muscle (IM) on day 1 and 6-MP daily by mouth for 7 days.

At weeks 7, 17, and 27 the subject will receive Ara-C as a continuous infusion for 72 hours (higher dose) or injected under the skin (lower dose). VM-26 will be given as a 45-minute IV infusion before the start of Ara-C and on day 2 with standard dose Ara-C. If the subject receives intensified Ara-C, the subject will also receive the drugs PEG and G-CSF. PEG is a drug that may lessen the toxic effects of Ara-C, and G-CSF is used to increase the blood count to decrease the risk of infection.

At weeks 12, 22, and 32, Ara-C will be infused over 72 hours as described above. Daunomycin (DNR) will be given as a 30-minute infusion before the start and at the end of the

Ara-C. In addition to DNR/Ara-C, vincristine is given IV on days 1 and 8, prednisone by mouth on days 1 and 7, and PEG-L-asparaginase IM on day 1.

During the period known as continuation, weeks 35-130, standard dose 6-MP will be given orally each day, and methotrexate injected into a muscle (IM) once a week. The total time of planned therapy is 130 weeks (2 1/2 years).

The subject will be taken off study in case of relapse in the bone marrow, or any other site, or if the subject fails to achieve a complete remission during the induction phase of the study. Radiation therapy will be suggested if the subject has CNS leukemia at diagnosis.

At the time of bone marrow aspiration, blood sampling, or spinal tap, cells obtained may be used for research studies.

Progress: One patient was enrolled in this study in FY 96, however due to an adverse event during induction was taken off study and continues to receive therapy. Another patient accepted in transfer from SUNY relapsed while on therapy and went on to a bone marrow transplant. Both patients continue to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/089

Status: Ongoing

Title: POG 9421: Phase III Evaluation of Standard vs. High Dose ARA-C Induction Followed by the Randomized Use of Cyclosporine A As An MDR Reversal Agent, Compared to Allogeneic BMT, in Childhood AML

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; COL Bruce A. Cook, MC; LTC Kelly J. Faucette, MC

Start Date:
03/17/1995

Est. Completion Date:
Jan 01

Periodic Review:
02/23/1999

Study Objective: 1) To determine the effect of high dose vs. standard dose Ara-C induction on CR (clinical remission) and EFS (event free survival) in Childhood AML. 2) To compare EFS in Childhood AML after 3 cycles of consolidation with or without the MDR (multidrug resistance) modulator CSA (cyclosporine A). 3) To compare the EFS between patients genetically randomized between allogeneic BMT and chemotherapy. 4) To evaluate the impact of EFS of various clinical and laboratory factors such as cytogenetics and MDR expression. 5) To confirm the superior response of Down syndrome patients utilizing standard induction and non-CSA containing consolidation, and identify specific biologic and pharmacokinetic characteristics in these patients.

Technical Approach: Phase III evaluation of standard vs. high dose Ara-C induction followed by the randomized use of Cyclosporine A as an MDR (multidrug resistant) reversal agent, compared to allogeneic BMT, in childhood AML. Patients will be randomized (assigned by chance, such as flipping a coin) at the time of diagnosis to receive either standard doses or high doses of ARA-C during the initial course of therapy. The chances of receiving any of the therapies is approximately equal. Later in the course of therapy, patients (according to how they were previously randomized) will or will NOT receive the drug Cyclosporine A in combination with the chemotherapy agents, Mitoxantrone and Etoposide. Patients with Down syndrome will not be randomized, but will receive the standard therapy. Earlier studies have shown the three year event-free survival rate for Down syndrome children significantly superior to children without Down syndrome using standard therapy. Also, for this reason Down syndrome patients will not receive Cyclosporine A. If a sibling who is matched for bone marrow transplantation, will receive bone marrow transplantation, which has been shown to be a more effective treatment in controlling AML compared to chemotherapy, providing that consent from the sibling donor can be obtained. If not a sibling donor, studies have shown chemotherapy is superior to matched unrelated donor BMT. However, should the patient choose to pursue an unrelated matched BMT instead of continuing with consolidation chemotherapy, the subject may discontinue the study. At the time of bone marrow aspiration, blood sampling, or spinal tap, cells obtained may also be used for research studies.

Progress: One patient accepted in transfer from WRAMC is off protocol therapy and continues to be followed. One patient was enrolled in FY 99.

Detail Summary Sheet

| | | |
|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 97/071 | Status: Ongoing |
| Title: POG 9425: Advanced Stage Hodgkin's Disease, A POG Phase III Study | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC | | |
| Start Date: 03/21/1997 | Est. Completion Date: Jul 03 | Periodic Review: 03/23/1999 |

Study Objective: 1) To test the efficacy of DBVE-PC, an intensive treatment regimen for advanced stage Hodgkins disease that administers doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide with G-CSF at 3 week intervals in a dose intensive manner (using cumulative drug doses that may minimize long term toxicity), followed by consolidative radiotherapy; 2) To tailor therapy based on rapidity of response in order to minimize cumulative drug dosages. Those in CR after 3 cycles of DBVE-PC will receive only low dose RT. Those who are not in CR will receive 2 additional cycles of DBVE-PC (+ low dose RT); 3) To determine, in a randomized trial, whether the addition of Dexrazoxane reduces pulmonary and cardiac toxicity of DBVE-based therapy without compromising response. This randomization will include all patients with Hodgkins's disease on POG 9425 (advanced stage) and 9426 (early stage) or not to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 3 cycles of the drug combination etoposide, vincristine, bleomycin, doxorubicin cyclophosphamide, prednisone combination with G-CSF in 3 week intervals. Patients will be restaged after receiving these three chemotherapy courses. Those showing large tumor response will go on to radiation therapy, while those showing partial response will receive 2 additional cycles of chemotherapy and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis after completion of therapy.

Technical Approach: Registered study patients will be randomized to receive or not to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 3 cycles of the drug combination etoposide, vincristine, bleomycin, doxorubicin cyclophosphamide, prednisone combination with G-CSF in 3 week intervals. Patients will be restaged after receiving these three chemotherapy courses. Those showing large tumor response will go on to radiation therapy, while those showing partial response will receive 2 additional cycles of chemotherapy and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis after completion of therapy.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/054

Status: Ongoing

Title: POG 9426: Response Dependent Treatment of Stages IA, IIA, and IIIA(1-micro) Hodgkin's Disease with DBVE and Low Dose Involved Field Irradiation with or without Zinecard

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC; MAJ Robert G. Irwin, MC

Start Date:
02/21/1997

Est. Completion Date:
Jul 03

Periodic Review:
02/23/1999

Study Objective: 1) To tailor chemotherapy courses based on the patients' initial response to therapy; 2) To examine the activity of variable courses of doxorubicin, bleomycin, vincristine, and etoposide (DBVE) and low-dose involved field irradiation; 3) To monitor safety and feasibility of the response-dependent approach, and morbidity, immediate and long term toxicities of the above regimen; 4) To evaluate if limited therapy is adequate for patients with early response; 5) To examine if addition of Zinecard can reduce pulmonary toxicity while not significantly reducing response rate or event-free survival; 6) To determine if the frequency and magnitude of myocardial injury during therapy, as measured by an elevation of cardiac Troponin-T in the serum, is reduced by the addition of Zinecard.

Technical Approach: Registered study patients will be randomized to receive the investigational drug Zinecard just prior to the administration of the chemotherapy drugs bleomycin and doxorubicin. Following disease staging with radiologic imaging and laboratory evaluations, patients will receive 2 courses of the four drug combination etoposide, vincristine, bleomycin and doxorubicin at 28 day intervals. Patients will be restaged after receiving these two chemotherapy courses. Those showing remission will go on to radiation therapy, while those showing residual disease will receive 2 more courses of the four drug combination and then go on to radiation therapy. Follow-up will continue for a minimum of 10 years at least on a yearly basis.

Progress: One patient was enrolled in this study at MAMC in FY 98. No patients were enrolled in FY 99.

Detail Summary Sheet

| | | |
|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 96/097 | Status: Ongoing |
| Title: POG 9440: National Wilms Tumor Study - 5: Therapeutic Trial and Biology Study | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC | | |
| Start Date: 04/19/1996 | Est. Completion Date: Jul 02 | Periodic Review: 04/27/1999 |

Study Objective: 1) To increase the survival rate of children with favorable histology Wilms tumor and other renal tumors of childhood; 2) to determine if loss of heterozygosity for chromosome 16q markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms tumor; 3) to determine if loss of heterozygosity for chromosome 1p markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms tumor; 4) to determine if increased DNA content in tumor cells is associated with a poorer prognosis; 5) to decrease the acute and long term morbidity of treatment of children with Wilms tumor; 6) to improve the survival of patients with unfavorable histology tumors including Wilms tumor with diffuse anaplasia and clear cell sarcoma of the kidney by using a new treatment regimen that includes etoposide and cyclophosphamide; 7) to improve survival of patients with malignant rhabdoid tumor of the kidney; 8) to study biology and pathology of patients who present with bilateral Wilms tumor; 9) to conduct hypothesis-driven trials led by diagnostic radiologists in order to develop guidelines; and 10) to establish a biological samples bank containing touch preparations, paraffin blocks, frozen tumor, normal kidney tissue, and serum and urine.

Technical Approach: Wilms tumor is the most frequent malignant renal tumor in children. This proposed therapeutic trial involves a number of experimental regimens that are designed either to reduce treatment for the subgroup of patients with the most favorable prognosis, or to intensify treatment for several subgroups with the least favorable prognosis. Patients will be stratified into the appropriate treatment regimens by age, size of tumor at diagnosis and staging of the tumor (Stages 1-V) with favorable/unfavorable histology, including rhabdoid, clear cell sarcomas and Wilms tumor with diffuse or focal anaplasia. Treatment will include nephrectomy or surgical debulking of tumor, radiation therapy to abdomen and/or lungs, and appropriate chemotherapy regimens.

Progress: One patient was enrolled in this study at MAMC in FY 96 and was transferred to Portsmouth Naval Hospital. One patient was accepted in transfer from Tripler AMC, Honolulu, Hawaii and continues to be followed. No new patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/090 **Status:** Ongoing

Title: POG 9442: National Wilms Tumor Late Effects Study

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
07/17/1998

Est. Completion Date:
Jul 03

Periodic Review:
06/22/1999

Study Objective: To determine (1) the frequency of Wilms tumor and other cancers in family members of Wilms tumor patients in order to estimate the recurrence risk in siblings and offspring; test the plausibility of specific genetic modes of inheritance in homogeneous subgroups; and identify familial cancer syndromes (if any) that may involve Wilms tumor, (2) To determine fertility rates of Wilms tumor patients and rates of perinatal mortality, low birth-weight and adverse pregnancy outcomes in relation to the type and amount of cancer treatment received in childhood, (3) To estimate the rates of selected congenital defects and of specified single gene disorders (sentinel phenotypes) in the offspring of Wilms tumor patients, (4) to estimate the rates of second malignancy neoplasms in relation to the dosage of radiation therapy and the use of specific chemotherapeutic agents (actinomycin D, doxorubicin, cytoxan and etoposide) received in childhood, (5) to compare the incidence rate of congestive heart failure among Wilms tumor survivors in relation to the dose of radiation therapy received to abdomen and/or lungs and to the use of specific chemotherapeutic agents.

Technical Approach: The large number of Wilms tumor survivors ascertained by the NWTS during its first twenty years of operation constitutes an ideal cohort for the study of familial risk and late effects of treatment. Four protocol studies have been conducted; treatment protocols and results for the first three studies have been published. A large fraction of the total national U.S. incidence of Wilms tumor has been registered on these studies, probably as much as 70% of an estimated 450-500 cases occurring nationally since 1980. Over 2,500 children who were followed on NWTS treatment protocols have now survived 5 or more years since their original diagnosis. Many of those treated more than a decade ago have reached sexual maturity, so that their reproductive history and the status of their offspring may be evaluated by entry into this study.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/039

Status: Ongoing

Title: POG 9457: Intensive Therapy with Growth Factor Support for Patients with Ewing's Tumor Metastatic at Diagnosis

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Luke M. Stapleton, MC; LTC Kenneth A. Bertram, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; LTC Kelly J. Faucette, MC

Start Date:
12/15/1995

Est. Completion Date:
Sep 99

Periodic Review:
11/19/1999

Study Objective: 1) To evaluate the response rate, and duration of response in patients with Ewing's tumor, metastatic at diagnosis, treated with maximally intensified therapy. (2) To evaluate the response to new agents utilized in an upfront window. Initially, topotecan will be used as a single agent. When the maximally tolerated dosages of the combination of topotecan and cyclophosphamide are available, the combination will be employed. (3) To assess the role of surgical treatments with regard to local control of primary and metastatic sites and disease course. (4) To determine whether individual variability in ifosfamide and cyclophosphamide metabolism correlated with toxicity and/or response. (5) To evaluate the rise in the absolute neutrophil count following one dose of G-CSF just prior to a chemotherapy cycle as a measure of bone marrow reserve and subsequent myelosuppression.

Technical Approach: In the absence of effective new agents in Ewing's Tumor, attempts to increase the rate of cure have recently centered around increasing dose intensity. Ifosfamide will be used at a dosage level 25% higher than that currently being used, for the first 3 cycles. The dosage will be reduced for the 2 continuation cycles. Cyclophosphamide will also be used in increased dosage with vincristine and adriamycin. This study will encourage the use of surgery for local control, with irradiation of the primary tumor bed, unresectable primary tumors and selected metastatic sites. Topotecan is a camptothecin, a topoisomerase I inhibitor. Initially, this study will use 2 cycles of single agent topotecan 3 weeks apart. At least 14 patients will be registered. When the maximum tolerated dosages of the combination of topotecan and cyclophosphamide are available, subsequent patients will be treated with the combination.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 98/048 | Status: Completed |
|------------------------|-----------------------|--------------------------|

Title: POG 9464: Cyclophosphamide Plus Topotecan in Children with Recurrent or Refractory Solid Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

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| Department: POG | Facility: MAMC |
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Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
02/20/1998

Est. Completion Date:
Jul 03

Periodic Review:
01/26/1999

Study Objective: To determine the response rate of recurrent or refractory solid tumors and brain tumors to cyclophosphamide plus topotecan and to further define the toxicity of cyclophosphamide plus topotecan in children.

Technical Approach: Following evaluation, patients will be hospitalized to receive IV fluid hydration for 30 minutes prior to receiving cyclophosphamide and topotecan, both administered IV over a period of 30 minutes each. This entire sequence will be repeated for 5 consecutive days. On day 6, G-CSF will be administered until the absolute neutrophil count is recovered from the effects of the chemotherapy. Patients entering the study are expected to complete 2 courses of therapy unless significant toxicity occurs. Evaluations will be repeated prior to the second and third courses of therapy. Patients will be removed from the study if clear evidence of progressive disease is documented after the first course of topotecan and cyclophosphamide or after any subsequent courses. Patients should continue treatment with the study drugs after the second course as long as CR, PR, or NR/SD is present unless alternative therapy is planned. Patients may be electively removed from the study to pursue such therapy after the second course.

Progress: This protocol was closed to patient accrual 28 Jan 99 as study goals have been met. One patient was entered in this study at MAMC in FY 98; however he was taken off study due to disease progression and died.

Detail Summary Sheet

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|--|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 96/035 | Status: Ongoing |
| Title: POG 9490: Topotecan Followed by Multimodal, Multiagent Therapy for Children and Adolescents with Newly Diagnosed Stage IV/Clinical Group IV Rhabdomyosarcoma, an IRS-V Pilot Study | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC | | |
| Start Date: 11/17/1995 | Est. Completion Date: Jun 97 | Periodic Review: 09/30/1998 |

Study Objective: 1) To evaluate the toxicity of the topoisomerase I inhibitor, topotecan, when given alone at a maximum tolerated dose by bolus injection daily X 5 days/course for 2 courses to untreated children and adolescents with Stage IV and/or Clinical Group IV rhabdomyosarcoma, all patients with metastatic disease. (2) To estimate the response rate (complete or partial) of such patients to topotecan. (3) To evaluate the toxicity of a new chemotherapy combination comprising topotecan, cyclophosphamide, and vincristine (VTC) given in alternating cycles with vincristine, actinomycin D, and cyclophosphamide (VAC) to patients who have achieved an objective response partial response (PR) or complete response (CR) to topotecan.

Technical Approach: Patients with rhabdomyosarcoma, clinical stage IV disease will receive Topotecan upfront at 2.0 mg/M²/day X 5 IV. Following evaluation, patients with partial response or complete response will go on to VAC treatment, alternating with VTC treatment. Those with stable or progressive disease will proceed to VAC alone. Radiation therapy will begin following evaluation at week 15 in conjunction with vincristine and cyclophosphamide. Continuation therapy begin following evaluation at week 25 with VAC/VTC for patients showing PR and CR.

Progress: Closed to patient accrual 1 Nov 96. One patient was enrolled in this study at MAMC in FY 96 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/089

Status: Ongoing

Title: POG 9553: A Phase II of Neoadjuvant Vincristine, Ifosfamide, Doxorubicin, and G-CSF in Children with Advanced Stage Non-rhabdomyosarcoma Soft Tissue Sarcomas

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:

04/18/1997

Est. Completion Date:

Jul 03

Periodic Review:

04/27/1999

Study Objective: 1) To estimate the response rate to the combination of vincristine, ifosfamide, and doxorubicin (VID), with G-CSF support, in children with newly diagnosed inoperable or metastatic non-rhabdomyosarcoma soft tissue sarcomas; 2) To estimate the 2-year survival and event-free survival of children treated with VID in combination with radiotherapy and/or surgery; 3) To establish a bank of frozen tissue (tumor and peripheral blood) for use in further molecular studies.

Technical Approach: Registered study patients will receive the three drug combination Vincristine, Ifosfamide, and Doxorubicin; two courses within a 6 week period. Cyclophosphamide will be substituted for those patients who cannot tolerate Ifosfamide. Patients will then be evaluated for response. If the tumor shrinks, patients will go on to XRT/chemotherapy, with or without prior surgical resection at this time. If the tumor has grown or stayed the same, patients will be taken off study treatment and offered other therapy. After XRT and chemotherapy, patients will be reimaged and another six weeks of chemotherapy will be given at this time unless the tumor has grown or come back.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/120

Status: Ongoing

Title: POG 9605: ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:

05/17/1996

Est. Completion Date:

Jul 03

Periodic Review:

05/27/1999

Study Objective: 1) To determine in a randomized trial whether the addition of 6 months of delayed intensification with divided dose oral methotrexate (ddMTX) improves event-free survival (EFS) of children with standard risk acute lymphoblastic leukemia; 2) to determine in a randomized trial the effect on EFS of delivering oral 6-mercaptopurine (6-MP) on a divided (twice daily) vs once a day schedule, during delayed intensification and continuation; 3) to study how laboratory data from POG 9400 correlates with outcome by pooling studies 9201, 9405, 9605, and 9406; 4) to assess the prognostic significance of the percent of marrow blasts after two weeks of induction therapy; 5) to describe the occurrence of elevated transaminases and correlation of these with outcome.

Technical Approach: This treatment protocol involves 130 weeks of chemotherapy beginning with standard induction therapy of generally 4 (but up to 6) weeks of chemotherapy consisting of vincristine, prednisone, and L-asparaginase plus triple intrathecal therapy of combined methotrexate, hydrocortisone and Ara-C. Post induction, the treatment is divided into consolidation, intensification, and maintenance phases of therapy. Registration on study occurs post induction therapy at which time patients are randomized to receive 1 of 4 regimens which vary beginning in the intensification phase of therapy.

Progress: One patient enrolled in this study at MAMC in FY 96 was transferred to WRAMC. Three patients have been accepted as transfers from other POG institutions. Two patients were enrolled in FY 99. Six patients are currently being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/045

Status: Ongoing

Title: POG 9631: A Phase II Feasibility Study of Oral Etoposide Given Concurrently with Radiotherapy Followed with Dose Intensive Adjuvant Chemotherapy for Children with Newly-Diagnosed High Stage Medulloblastoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
02/23/1999

Est. Completion Date:
Feb 05

Periodic Review:
N/A

Study Objective: 1. To estimate the response rate and toxicity of children with newly diagnosed high-stage medulloblastoma who are treated with 2 cycles of oral etoposide, given concurrently with radiation therapy.

2. To compare the response rate and toxicity of these patients to historical control patients registered on POG study # 9031 TRT 2 (RT alone followed by adjuvant chemotherapy).

3. To estimate the 2-year event-free survival and overall survival of patients treated with 2 cycles of oral etoposide, given concurrently with radiation therapy.

4. To compare the 2-year event-free survival and overall survival of these patients to historical control patients registered on POG study # 9031.

5. To evaluate the toxicity of dose intensive chemotherapy following craniospinal irradiation using oral etoposide, cisplatin, cyclophosphamide and vincristine.

Technical Approach: The goal of this study is to maximize response to initial therapy using oral etoposide concurrently with radiotherapy in children with newly diagnosed high stage medulloblastoma. Adjuvant therapy will continue after radiation using dose intensive chemotherapy.

Progress: No patients have been enrolled in FY 99.

Detail Summary Sheet

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|-----------------|----------------|-----------------|
| Date: 30 Sep 99 | Number: 98/065 | Status: Ongoing |
|-----------------|----------------|-----------------|

Title: POG 9641: Primary Surgical Therapy for Biologically Defined Low-Risk Neuroblastoma; A Pediatric Oncology Group Children's Cancer Group, Phase III, Intergroup Study

Principal Investigator: LTC Stephen R. Palmer, MC

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| Department: POG | Facility: MAMC |
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Associate Investigator(s): LTC Kelly J. Faucette, MC

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|---------------------------|---------------------------------|--------------------------------|
| Start Date: 03/20/1998 | Est. Completion Date: Jul 03 | Periodic Review: 03/23/1999 |
|---------------------------|---------------------------------|--------------------------------|

Study Objective: 1) To determine if low risk INSS stage 2A/2B asymptomatic neuroblastoma patients treated with surgery alone will have a three year survival (S) rate of 95%, (2) To determine if low risk INSS stage 1 asymptomatic neuroblastoma patients treated with surgery alone will have a three year S rate of 95%, (3) To determine if low risk INSS stage 4S asymptomatic neuroblastoma patients treated with surgery alone will have a three year S rate of 95%, (4) To estimate the response and 3 year event-free survival (EFS) rates of symptomatic patients with chemotherapy, (5) To estimate the EFS and S rates in patients who relapse or progress after initial treatment with surgery alone, (6) To determine the acute and long-term morbidity/toxicities associated with treating low-risk neuroblastoma with surgery alone or with surgery and chemotherapy, (7) To further define and evaluate the prognostic importance of other biologic factors as determined on studies POG #9047 (or its successor), CCG #B973, and by International Neuroblastoma Risk Group criteria, (8) To collect resource utilization data regarding number of hospital days, the extent of transfusion support, and the use of diagnostic imaging, and to compare these with historical CCG study 3881 data.

Technical Approach: Patients in this study will be stratified by stage and extent of disease to either surgery alone or surgery with chemotherapy. Further studies done on patient's tumor specimens may change their classification to "intermediate" or "high" risk neuroblastoma, in which case they will be taken off study and more intensive chemotherapy will be administered.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/064

Status: Ongoing

Title: POG 9701 (A09701): A Phase II Study of Temodal (SCH 52365; Temozolomide, IND #52797) in Children and Adolescents with Recurrent Central Nervous System (CNS) Tumors

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
03/20/1998

Est. Completion Date:
Jun 03

Periodic Review:
3/23/1999

Study Objective: To determine the response rate to Temodal in several strata of recurrent CNS tumors of childhood and to further assess the toxicity of Temodal in a larger group of patients treated at the recently defined maximally tolerated dose (MTD).

Technical Approach: The study is divided into two treatment strata; prior history of craniospinal (CSI) or total spinal radiotherapy. Patients without prior CSI will receive Temodal(r) 200 mg/m²/day orally for five consecutive days, following overnight fast. Patients may not eat for two hours after administration of capsules. Subsequent courses may begin on day 28, if all toxicities have resolved.

Patients with prior CSI will receive Temodal(r) 180 mg/m²/day orally for five consecutive days, following overnight fast. Patients may not eat for two hours after administration of capsules. Subsequent courses may begin on day 28, if all toxicities have resolved.

Patients benefiting from Temodal(r) after 2 courses (patients with stable disease or a response) may continue up to 10 additional courses. Treatment must be stopped when disease progresses or when a total of 12 total courses of Temodal(r) have been administered.

Progress: One patient entered in this study at MAMC in FY 98 and continues to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

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|---|--|---------------------------------------|
| Date: 30 Sep 99 | Number: 98/066 | Status: Ongoing |
| Title: POG 9720: Idarubicin and Cladribine in Recurrent and Refractory Acute Myeloid Leukemia: A Pediatric Oncology Group Phase II Study | | |
| Principal Investigator: LTC Stephen R. Palmer, MC | | |
| Department: POG | Facility: MAMC | |
| Associate Investigator(s): LTC Kelly J. Faucette, MC | | |
| Start Date: 03/20/1998 | Est. Completion Date: Jul 03 | Periodic Review: 03/23/1999 |

Study Objective: 1) To determine the CR rate of the combination of Idarubicin (IDA) and Cladribine (CDA) in patients with recurrent AML, 2) To determine the CR rate of the combination of IDA and CDA in patients with primary refractory AML, 3) To determine the CR rate of the combination of IDA and CDA in patients with recurrent or primary refractory secondary AML and myelodysplastic syndromes (not related to Down's Syndrome), 4) To determine the toxicities of the combination of IDA and CDA, 5) To define the pharmacokinetics of CDA administered as a 2 hour infusion.

Technical Approach: Eligible patients will be stratified and receive a five day treatment consisting of IV Idarubicin daily for 3 days and IV Cladribine, 2 hours daily for 5 days. Twenty-four hours after completion of chemotherapy, patients will begin daily subcutaneous injections of G-CSF until blood counts stabilize. A bone marrow aspirate will be done at 3 weeks to assess response. A second course may be given. If patients have progressive disease they will be taken off study.

Progress: No patients enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/088

Status: Ongoing

Title: POG A9961: A Phase III Prospective Randomized Study of Craniospinal Radiotherapy Followed by one of Two Adjuvant Chemotherapy Regimens (CCNU, CDDP, VCR, or CPM, CDDP, VCR) in Children with Newly-Diagnosed Average Risk Medulloblastoma

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Shirley E. Reddoch, MC; LTC Kelly J. Faucette, MC

Start Date:
04/18/1997

Est. Completion Date:
Apr 03

Periodic Review:
04/27/1999

Study Objective: 1) To determine if a cyclophosphamide arm will increase the rate of progression-free survival compared to a CCNU containing arm for children with average-risk medulloblastoma; 2) To determine the progression-free survival and overall survival of children treated with craniospinal (2340 cGy) and local boost radiotherapy (3240 cGy) for a total dose of 5580 cGy, and adjuvant vincristine, CCNU and cisplatin chemotherapy; 3) To determine the progression-free survival and overall survival of children treated with craniospinal (2340 cGy) and local boost radiotherapy (3240 cGy) for a total dose of 5580 cGy, and adjuvant vincristine, cyclophosphamide and cisplatin chemotherapy; 4) To determine the long-term neurocognitive, endocrinologic and cardiopulmonary sequelae of radiotherapy plus adjuvant chemotherapy in children with average-risk medulloblastoma treated with 2340 cGy of craniospinal radiation therapy, local boost radiotherapy, and either one of two drug regimens and to determine if the replacement of CCNU with cyclophosphamide will alter the incidence and degree of sequelae experienced; 5) To determine if cellular/biologic parameters, including tumor molecular genetic analysis, DNA ploidy, mitotic activity markers and immunohistochemical analysis are correlated with progression-free survival, survival and the pattern of disease relapse in children with average-risk medulloblastoma; 6) To determine the utility of routine MR surveillance studies of the head and spine to detect subclinical recurrent disease.

Technical Approach: A9961 is an intergroup research study which plans to evaluate the overall progression-free survival of children with average-risk medulloblastoma treated with craniospinal radiation and local boost radiotherapy plus one of two adjuvant chemotherapy regimens differing in the replacement of CCNU by cyclophosphamide. The long-term neurocognitive, endocrinologic and cardiopulmonary sequelae of radiotherapy with adjuvant chemotherapy will be determined, as well as the feasibility of routine surveillance scans to detect subclinical recurrent disease. Another objective of this study will be to evaluate the sensitivity of molecular and biochemical techniques (i.e., molecular genetic analysis, DNA ploidy, mitotic activity markers and immunohistochemical analysis, to predict progression-free survival and disease relapse.

Following surgery, patients will be randomized to receive Regimen A or B of treatment. Both regimens will include 2340 cGy of craniospinal radiation and 3240 cGy of boost radiation directly to the primary tumor with weekly vincristine doses. Six weeks following the completion of radiotherapy, patients will begin 8 cycles of maintenance chemotherapy for Regimen A (CCNU, cisplatin and vincristine) or Regimen B (cyclophosphamide, cisplatin and vincristine).

The study is expected to accrue between 240 and 300 patients over a minimum of 4 year accrual period.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/145

Status: Ongoing

Title: POG D9602: Actinomycin D and Vincristine with or without Radiation Therapy for Newly Diagnosed Patients with Low-Risk Rhabdomyosarcoma or Undifferentiated Sarcoma: An IRS-V Protocol

Principal Investigator: LTC Stephen R. Palmer, MC

Department: POG

Facility: MAMC

Associate Investigator(s): LTC Kelly J. Faucette, MC

Start Date:
09/19/1997

Est. Completion Date:
Jul 03

Periodic Review:
9/28/1999

Study Objective: 1) Treatment of IRS-V low-risk patients with actinomycin D (AMD) and vincristine (VCR), plus local radiotherapy (XRT) for microscopic or gross residual tumor, will result in a failure-free survival rate of 88% at 2 years and an overall survival rate of about 95% at 5 years from initial diagnosis; 2) Treatment of IRS-V low-risk patients with alveolar rhabdomyosarcoma or undifferentiated sarcoma with vincristine and actinomycin D plus cyclophosphamide (collectively called VAC) will result in a failure-free survival rate of greater than or equal to 70% at two years and an overall survival rate of about 80-90% at 5 years; 3) Reduction in radiation therapy dose for patients with Clinical Group II disease to 36 Gy (from 41.3 Gy) and for Group III patients with orbital disease to 45 Gy (from 50-S' Gy) will result in local control rates of about 90%.

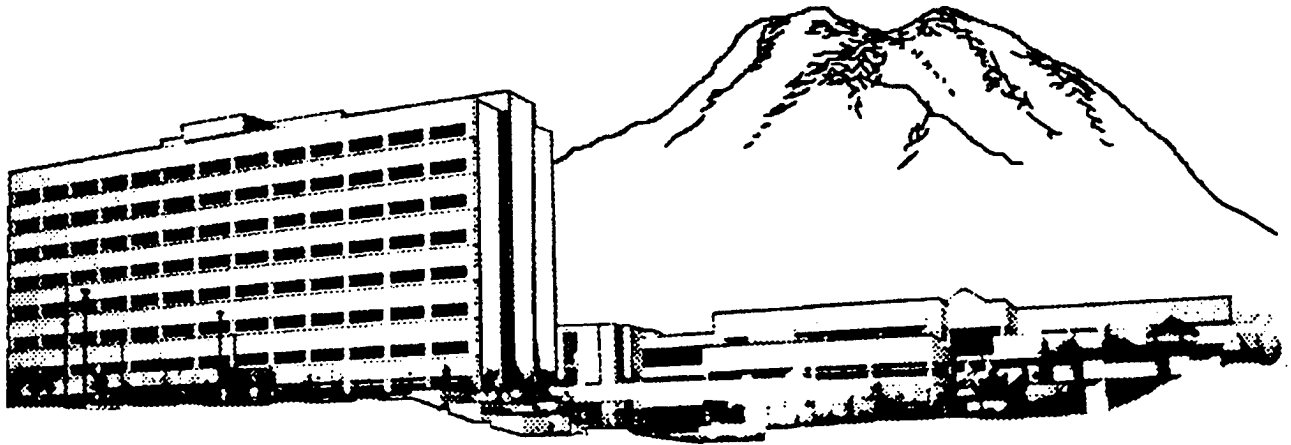
Technical Approach: Patients in Group I have no residual tumor following surgery and will receive no radiation therapy. Patients in Group II have microscopic residual tumor and will receive radiation therapy at a dose lower than the current standard. Patients in Group III, orbit tumor only, have visible residual tumor after biopsy and will receive radiation therapy. The results will be compared to current intergroup rhabdomyosarcoma study results.

All patients will begin chemotherapy with the two-drug combination of vincristine and actinomycin D, given over a 3-week period while their tumor specimen is being classified at the IRS Group Pathology Center in Columbus, Ohio.

Patients whose tumor is classified as embryonal or botryoid rhabdomyosarcoma will continue to receive vincristine and actinomycin D, given at weeks 12 through 21, 24 through 33, and 36 through 45.

Patients whose tumor is classified as alveolar rhabdomyosarcoma or undifferentiated sarcoma will have the chemotherapy drug cyclophosphamide added to the combination of vincristine and actinomycin D, given at weeks 3, 6, 9, 12, 15, 18, 24, 27, 30, 36, and 42. Cyclophosphamide will be added on Week 0 for these patients who show molecular genetic or cytogenetic evidence of the t(2;13) or t(1;13) translocation, or the PAX 3-FRHR or PAX 7-FRER gene fusion product.

Progress: No patients were enrolled in FY 99.



Detail Summary Sheets

Radiological Diagnostic Oncology Group

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 95/136 **Status:** Completed

Title: RDOG(5) 6881: Stereotactic Fine Needle Aspiration Biopsy and Core Needle Biopsy in the Work-up of Lesions Detected by Mammography

Principal Investigator: MAJ Donald V. Smith, MC

Department: RDOG **Facility:** MAMC

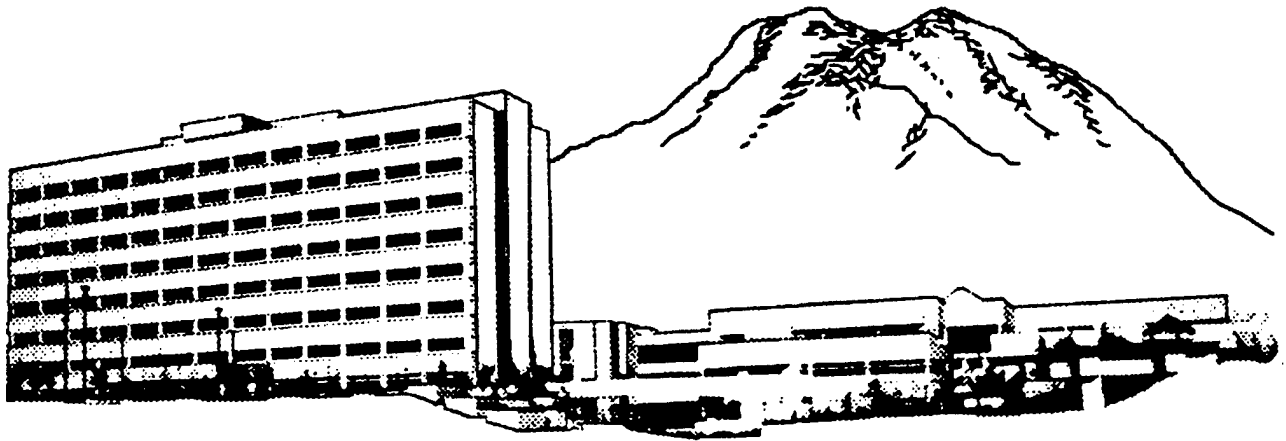
Associate Investigator(s): Charlene P. Holt, M.D.; MAJ Vincent B. Ho, MC; LTC William C. Williard, III, MC; Preston L. Carter, M.D.; MAJ Barbara A. Crothers, MC; MAJ Janice C. Stracener, MC; COL Sankaran S. Babu, MC; MAJ Mark A. Myers, MC

| Start Date: | Est. Completion Date: | Periodic Review: |
|--------------------|------------------------------|-------------------------|
| 06/16/1995 | Jun 98 | 09/30/1998 |

Study Objective: The overall objective of this research protocol is to conduct a randomized clinical trial to study whether stereotactically-guided and/or ultrasound-guided fine needle aspiration (FNA) and/or core needle biopsy (CNB) can replace open surgical biopsy in the diagnostic evaluation of nonpalpable mammographically-detected breast lesions.

Technical Approach: This is a randomized clinical trial to be carried out in mammographic centers nationwide within two consortia. This offers the opportunity to cover the spectrum of experience, equipment and patient populations, all using an agreed protocol to evaluate the use of fine needle and core biopsy used in the work-up of non-palpable breast lesions. The two consortia will enroll a total of 3,600 patients with an expected average MAMC enrollment of two subjects per day for the length of the study. Women having had the appropriate mammographic evaluation and meeting the inclusion criteria will be entered either to stereotactic or ultrasound arms of the study. Those in the stereotactic arm will be randomized to FNA followed by CNB, or CNB alone, both followed by open surgical biopsy or when indicated, 6, 12, and 24 month follow-ups. Those in the ultrasound arm will be randomized to FNA/CNB or CNB. All mammograms will have second readings by experts, and all pathology and cytology will have second readings by reference experts. Data analysis will consist of accuracy determination, agreement analysis, and logistic regression modeling for evaluation of important co-variants on the estimates. In addition, analysis of observer variability, insufficient sample rates, and predictive ability of specific mammographic characteristics will be conducted.

Progress: Study is closed to patient entry. 38 subjects entered at MAMC, none during FY 99, following subjects with the last patient finishing in October 1998.



Detail Summary Sheets
Southwest Oncology Group

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 77/054 **Status:** Terminated

Title: SWOG 7406: Advanced Hodgkin's Disease: Remission Induction (MOPP #5).
Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC;
LTC Howard Davidson, MC

Start Date:
02/18/1977

Est. Completion Date:
Feb 82

Periodic Review:
02/20/1998

Study Objective: (1) To compare the effectiveness of two MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) + bleomycin + adriamycin combinations against MOPP + bleomycin for remission induction in patients with advanced Hodgkin's disease without prior chemotherapy; (2) To evaluate systematic restaging of patients in apparent complete remission; (3) To assess the length of unmaintained remission after intensive induction with ten courses of treatment and after documentation of complete remission (CR) status by careful restaging; (4) To evaluate by crossover design the remission induction potential of the other study combinations for patients who relapse during unmaintained remission.

Technical Approach: All previously untreated patients with Ann Arbor Stages IIIB or IV A+B Hodgkin's disease who meet the other criteria as outlined in the protocol will be randomized to one of the induction programs as specified in the protocol. Ten courses of treatment at 4-week intervals will constitute remission induction. If induction results in a CR and this is confirmed by restaging, then no further treatment will be given. If at least a partial remission (PR) is indicated another 4 courses will be administered in a second attempt to achieve a CR. Persistence of disease after 14 courses will constitute an induction failure and the patient will be taken off study. Relapsing patients will be crossed over to one of the other induction combinations.

Progress: Closed to patient entry 31 Aug 78. Two patients were entered in previous years, one patient is still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 77/053 | Status: Terminated |
|------------------------|-----------------------|---------------------------|

Title: SWOG 7433: Non-Hodgkin's Lymphomas (Stages I, IE, II, and IIE). A Phase III Study.

Principal Investigator: LTC Kenneth A. Bertram, MC

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| Department: SWOG | Facility: MAMC |
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Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

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| Start Date: 02/18/1977 | Est. Completion Date: Feb 82 | Periodic Review: 02/20/1998 |
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Study Objective: To compare the remission rate, remission duration and survival in patients with non-Hodgkin's lymphoma, pathologic stages I, IE, II and IIE treated with extended field radiotherapy (supradiaphragmatic mantle or abdominal field) alone or with extended Hydroxyl-daunorubicin (adriamycin), Oncovin (vincristine), and Prednisone.

Technical Approach: Patients newly diagnosed (no type of prior therapy) with non-Hodgkin's lymphoma except mycosis fungoides and diffuse lymphocytic well differentiated lymphoma will be thoroughly evaluated for extent of disease and then randomized to either radiation therapy or radiation therapy plus chemotherapy. If the patient does not achieve a complete remission after completion of his treatment course, he will be removed from the study. Those achieving complete remission will be followed for two years or until relapse.

Progress: This protocol was closed to patient entry 1 Oct 82 and was previously reported as closed. In fact, 2 patients were entered at MAMC, 1 has died and the other is still being followed. The protocol was reactivated in December 1993 in order to allow SWOG to continue to collect data on these patients. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 77/024 **Status:** Completed

Title: SWOG 7436: Combined Modality Therapy of Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; LTC H. Irving Pierce, MC;
LTC Howard Davidson, MC

Start Date:
01/21/1977

Est. Completion Date:
Jan 82

Periodic Review:
1/15/1999

Study Objective: To compare the effect of two adjuvant chemotherapy programs upon the time to recurrence and upon the percentage of recurrences in post-operative breast carcinoma patients who have a high risk of developing metastases. To compare the effect of these adjuvant chemotherapy programs upon the survival pattern of such patients.

Technical Approach: Melphalan and combination (5-Fluorouracil, Methotrexate, Vincristine, Cyclophosphamide, Prednisone) will be used as chemotherapy as outlined in the protocol. The adjuvant chemotherapy will be instituted (regardless of radiation therapy) two weeks after radical mastectomy, unless local or systemic post-operative complications of surgery contraindicate onset of therapy. In such cases, therapy will be instituted when the primary physician involved feels it is not contraindicated by the clinical condition of the patient. The interval between surgery and the institution of adjuvant chemotherapy cannot be greater than six weeks for entry into the study. All therapy will be discontinued after one year.

Progress: This protocol was closed to patient entry in 1 Nov 1979 and was previously reported as closed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on 10 patients that had been entered. One patient expired in FY 97, 18 years after treatment. Five other patients expired previously and four patients are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 77/018 | Status: Terminated |
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Title: SWOG 7510: Intensive Adjuvant Chemotherapy with or without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel

Principal Investigator: LTC Kenneth A. Bertram, MC

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| Department: SWOG | Facility: MAMC |
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Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

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| Start Date: 10/15/1976 | Est. Completion Date: Oct 81 | Periodic Review: 02/20/1998 |
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Study Objective: To determine the efficacy of adjuvant chemotherapy with the highly effective combination of Methyl CCNU (MeCCNU) and 5-Fluorouracil (5-FU) and to determine whether this is added to by immunotherapy with oral Bacillus Calmette-Suerin (BCG) on the disease-free interval and survival of patients with Duke C large bowel adenocarcinoma.

Technical Approach: Patients will be randomly assigned to either of the two following regimens; (1) chemotherapy alone - Methyl CCNU, given orally on day 1, plus intravenous 5-Fluorouracil, given intravenously weekly for three doses would constitute one course. Courses would be every eight weeks; (2) chemotherapy plus immunotherapy - Chemotherapy as described above plus immunotherapy in the form of oral BCG given every two weeks.

Progress: This protocol was closed to patient entry 20 Aug 1980 and was previously reported as closed. 11 patients were entered at MAMC, 8 have died, 3 are still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 78/002 **Status:** Terminated

Title: SWOG 7713/14: Chemoimmunotherapy in Non-Hodgkin's Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy: Levamisole vs No Maintenance After Remission Induction

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): LTC H. Irving Pierce, MC; COL Friedrich H. Stutz, MC; LTC Howard Davidson, MC

Start Date:
10/21/1977

Est. Completion Date:
Jun 79

Periodic Review:
10/17/1997

Study Objective: 1) To compare the effectiveness, in terms of rate of response of two chemoimmunotherapy regimens (CHOP + levamisole vs CHOP + levamisole + BCG) against CHOP for remission induction in previously untreated patients with non-Hodgkin's lymphoma; (2) For patients proven to be in complete remission after induction, to compare the duration of documented complete response obtained by continued maintenance immunotherapy with levamisole vs no maintenance therapy; (3) For patients with impaired cardiac function (not eligible for treatment with adriamycin), with mycosis fungoides, or with only a partial response to 11 courses of treatment with levamisole + BCG, to estimate the complete response rate obtained by continued chemoimmunotherapy with COP + levamisole; (4) To estimate the CNS relapse rate in patients with diffuse lymphomas when CNS prophylaxis with intrathecal cytosine arabinoside is used; (5) To continue to evaluate the impact of systematic restaging of patients judged to be in complete remission and the value of expert hematopathology review of diagnostic material from all cases; (6) To establish baseline and serial data on immunologic status in both chemoimmunotherapy groups.

Technical Approach: Patients with a diagnosis of non-Hodgkin's lymphoma established by biopsy with no prior chemotherapy are eligible. Patients with chronic lymphocytic leukemia are ineligible. Patients with preexisting cardiac disease or mycosis fungoides are ineligible for the CHOP programs, but will be treated with COP + levamisole. Patients will be stratified according to nodular or diffuse histologies, adequate or impaired bone marrow reserves, presence or absence of bone marrow involvement, and performance status. Initial drug doses are based on bone marrow reserve. Treatment plans as outlined in the protocol.

Progress: This protocol was closed to patient entry 1 Oct 1982 and was previously reported as completed. 4 patients were entered at MAMC, 3 have died, one patient is still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 78/047

Status: Terminated

Title: SWOG 7808: Combination Modality Treatment for Stage III and Stage IV Hodgkin's Disease, MOPP #6

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; LTC H. Irving Pierce, MC; Suresh B. Katakhar, M.D., DAC; LTC Howard Davidson, MC

Start Date:
07/31/1978

Est. Completion Date:
Jan 88

Periodic Review:
10/17/1997

Study Objective: To attempt to increase the complete remission rate induced with MOP-BAP (nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, and bleomycin) alone utilizing involved field radiotherapy in patients with Stages III and IV Hodgkin's disease achieving partial remission at the end of 6 cycles; and to determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when complete remission has been induced with 6 cycles of MOP-BAP in Stages III & IV Hodgkin's.

Technical Approach: Patients (>15 yrs) must have histologic diagnosis of Hodgkin's disease; no prior chemotherapy. Patients with a history of congestive heart failure, valvular heart disease, or serious obstructive or restrictive pulmonary disease will be excluded. Normal marrow patients will receive six cycles of MOP-BAP. Impaired bone marrow patients will receive six cycles of MOP-BAP with dose modifications. Complete Remission (CR) patients with prior radiotherapy will be randomized to Treatment 3 (no treatment) or Treatment 4 (levamisole). CR patients without prior radiotherapy will receive Treatment 5 (radiotherapy). Partial remission (PR) patients without prior radiotherapy or residual bone marrow involvement will receive Treatment 6 (radiotherapy). PR patients with prior radiotherapy or those with residual bone marrow involvement will receive Treatment 7 (4 additional cycles of MOP-BAP); after 10 total cycles of MOP-BAP, patient will continue study on MOP-BAP therapy at the discretion of the investigator.

Progress: This study was closed to patient entry 1 Dec 87. Thirteen patients were enrolled in previous years and 5 are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 84/018

Status: Terminated

Title: SWOG 8216/38: Comparison of BCG Immunotherapy and Adriamycin for Superficial Bladder Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL William D. Belville, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Thomas M. Baker, MC; MAJ Alfred H. Chan, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; LTC Howard Davidson, MC

Start Date:
11/18/1983

Est. Completion Date:
Sep 85

Periodic Review:
10/17/1997

Study Objective: To compare the effectiveness of intravesical BCG immunotherapy with intravesical Adriamycin in chemotherapy with respect to disease-free interval and two-year recurrence rate; to compare the toxicity of topical immunotherapy and chemotherapy; and to obtain experience regarding disease-free interval and the recurrence rate in patients who develop tumor recurrence and are then crossed over to the alternative treatment arm.

Technical Approach: Following a standard transurethral resection, patients will be stratified by the presence or absence of documented carcinoma in situ and as to prior chemotherapy and then randomized to receive BCG immunotherapy or Adriamycin chemotherapy. Patients who develop tumor recurrence following treatment will be eligible for crossover to the other treatment arm.

Progress: This study was closed to patient entry 20 Dec 85. Three patients were enrolled at MAMC and are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 85/076 | Status: Terminated |
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Title: SWOG 8269: Concurrent Chemo-Radiotherapy for Limited Small Cell Carcinoma of the Lung, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

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| Department: SWOG | Facility: MAMC |
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Associate Investigator(s): COL Irwin B. Dabe, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; MAJ Thomas M. Baker, MC; LTC Howard Davidson, MC

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| Start Date: 08/23/1985 | Est. Completion Date: Jun 87 | Periodic Review: 10/17/1997 |
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Study Objective: To explore the response rate with the concurrent use of radiation therapy plus chemotherapy utilizing cis-platinum, VP-16, and vincristine in limited small cell carcinoma of the lung and to observe the toxicities of this combined modality program.

Technical Approach: Patients will be started on chemotherapy consisting of cis-platinum, VP-16, and vincristine and concurrent radiation therapy to the primary site. After completion of radiation therapy to the chest, prophylactic cranial radiation therapy will be given. After a brief rest period, the patients will be treated with 12 more weeks of conventional chemotherapy consisting of adriamycin, cytoxan, VP-16, vincristine, and methotrexate. Patients who show a complete response will be followed. Patients with less than a complete response will be taken off study and offered alternative therapy.

Progress: This study was closed to patient entry 19 March 86. It was previously reported as completed. In fact, two patients were entered and one is still being followed. The protocol was reactivated in December 1993 so that SWOG could continue to collect data on these patients. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 83/056 | Status: Ongoing |
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Title: SWOG 8294: Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC James E. Congdon, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Timothy J. O'Rourke, MC; MAJ Alfred H. Chan, MC; MAJ Thomas M. Baker, MC; LTC Howard Davidson, MC

Start Date:
03/18/1983

Est. Completion Date:
Feb 85

Periodic Review:
02/23/1999

Study Objective: To assess the impact of short-term intensive chemotherapy with CMFP to prevent disease recurrence and prolong survival in node negative patients with any size estrogen receptor negative tumors and node negative patients with estrogen receptor positive tumors whose pathological size is >3 cm; to assess the impact of surgical procedure, estrogen receptor status, menopausal status and tumor size; to develop guidelines referable to histopathological features of node negative tumors which are reproducible and to assess their prognostic impact for disease-free survival and survival; to assess the value to CEA in predicting recurrence and survival rates; to assess the natural history of a subgroup with node negative, estrogen receptor positive small tumors (3 cm).

Technical Approach: Patients will have laboratory evaluations to ensure that there is no evidence of disseminated disease. They will be stratified into a number of treatment groups based on the site of tumor, estrogen receptor status, age, and menopausal status. Patients with primary tumors less than 3 cm in diameter who are estrogen receptor positive will be followed by close observation only to determine the natural history of their tumor. All other patients who have a somewhat greater likelihood of relapse will be randomized to receive either close observation only or 6 cycles of systemic chemotherapy. The chemotherapy will consist of 4 agents: cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone given for six 28 day cycles. The dosage of the individual agents will be determined by body height and weight.

Progress: This study was closed to patient entry 15 May 88. Twelve patients were enrolled in previous years and nine continue to be followed. Three have expired.

Detail Summary Sheet

Date: 30 Sep 99

Number: 84/059

Status: Terminated

Title: SWOG 8313: Multiple Drug Adjuvant Chemotherapy for Patients with ER Negative Stage II Carcinoma of Breast, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; MAJ Thomas M. Baker, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; LTC Howard Davidson, MC

Start Date:
05/18/1984

Est. Completion Date:
May 86

Periodic Review:
10/17/1997

Study Objective: To compare through a randomized prospective study the recurrence rates and disease-free intervals for postoperative axillary node positive estrogen receptor negative breast cancer patients given adjuvant therapy with either short term intense chemotherapy (FAC-M) or one year standard chemotherapy (CMFVP); to compare the effect of these two adjuvant therapies on survival; to compare the relative toxicity of the two therapies; to compare the quality of life of patients with operable breast cancer randomized to receive one year of CMFVP or a short intensive regimen of FAC-M x 4 courses; and to compare a multiple item questionnaire for assessing quality of life.

Technical Approach: Women who have histologically proven breast cancer with axillary lymph node metastasis and negative estrogen receptors will be entered 14-21 days post-lumpectomy or within 14-42 days post-mastectomy and randomly assigned to receive: Arm I a tapering course of oral prednisone for 6 weeks, weekly IV vincristine for 10 weeks, weekly IV methotrexate, and weekly IV 5-FU plus daily oral cyclophosphamide for a total of one year; or Arm II four cycles of adriamycin (IV day 1), cyclophosphamide (IV day 1), 5-FU (IV days 1 and 8), and methotrexate (IV day 22). Each cycle will be five weeks and total duration of therapy in this arm is approximately 20 weeks. Questionnaires to compare quality of life will be completed at 72 hours prior to chemotherapy. Added to this protocol will be a sub-study to determine the prognostic significance of circulating human mammary epithelial antigens. This will involve blood tests prior to chemotherapy and then once every three months.

Progress: This study was closed to patient entry 15 Jun 90. Three patients were enrolled, 2 have died and 1 continues to be followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 86/007 **Status:** Terminated

Title: SWOG 8417/19: Evaluation of Two Consolidation Regimens in the Treatment of Adult Acute Lymphoblastic Leukemia, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; LTC Howard Davidson, MC; MAJ Thomas M. Baker, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; MAJ Paul C. Sowray, MC

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| Start Date: 10/18/1985 | Est. Completion Date: Sep 87 | Periodic Review: 10/17/1997 |
|----------------------------------|--|---------------------------------------|

Study Objective: To compare the effects on remission duration and survival of two consolidation regimens: the L-10-M consolidation used in SWOG 8001 versus a regimen employing daunomycin, cytosine, arabinoside, 6-thioguanine and escalating methotrexate/Lasparaginase in patients with adult lymphoblastic leukemia and to compare the toxicities of the two consolidation regimens.

Technical Approach: Patients will begin remission induction with vincristine, prednisone, adriamycin, methotrexate, cyclophosphamide, and adriamycin (36 days), followed by a 14 day rest period. On day 30, patients will have an Ommaya reservoir placed in the frontotemporal area of the skull. Patients failing to achieve an A1 marrow status on induction therapy will go off study. Patients with complete remission will be randomized to one of the following consolidation regimens: ARM I (L-10-M) methotrexate and Ara-c, daily x 5 on days 1, 36, and 71; Ara-c and 6-thioguanine every 12 hr for 12 doses on days 15, 50, and 85; methotrexate days 15, 17, 57, and 59; vincristine and prednisone days 50 and 57; L-asparaginase beginning day 99, three times weekly for a total of 6 doses, and cyclophosphamide day 110 following last dose of L-asparaginase. Arm II: daunomycin days 1-3, Ara-C continuous infusion days 1-5, 6-thioguanine every 12 hr days 15, followed by a 21-28 day rest period. Methotrexate every 10 days from 28-98, L-asparaginase every 10 days 29-99. After a 2-week rest period, maintenance therapy will begin with vincristine, prednisone, adriamycin, 6-mercaptopurine, methotrexate (IT), methotrexate PO, dactinomycin, vincristine, prednisone, BCNU, cyclophosphamide, 6-mercaptopurine, and methotrexate (repeated every 21 weeks for 36 months or until relapse. An adequate trial will be the completion of remission induction.

Progress: This study closed to patient entry 15 Nov 91. Seven patients were enrolled MAMC. All original patients enrolled at MAMC have died but one patient has transferred in (previous FY) and is being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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|------------------------|-----------------------|---------------------------|
| Date: 30 Sep 99 | Number: 87/107 | Status: Terminated |
|------------------------|-----------------------|---------------------------|

Title: SWOG 8507: Maintenance versus No Maintenance BCG Immunotherapy of Superficial Bladder Cancer, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; COL William D. Belville, MC; COL Victor J. Kiesling, MC; LTC Lauren K. Colman, MC; MAJ Thomas M. Baker, MC; MAJ David M. Dunning, MC; MAJ Ruben D. Sierra, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC

Start Date:
08/21/1987

Est. Completion Date:
Aug 90

Periodic Review:
10/17/1997

Study Objective: To compare the effectiveness of intravesical and percutaneous BCG immunotherapy given on a maintenance versus no maintenance schedule with respect to disease-free interval and rate of tumor recurrence in patients with transitional cell carcinoma of the bladder; to assess the toxicity of maintenance and no maintenance BCG immunotherapy; and to assess the association of intermediate strength PPD skin test reactivity with disease free status in patients treated with BCG immunotherapy.

Technical Approach: Patients will be stratified according to prior chemotherapy, disease type, and PPD skin test conversion. One week following a standard transurethral resection, BCG, 120 mg lyophilized BCG organisms will be diluted in 50.5 cc of sterile, preservation-free saline. Fifty cc will be administered intravesically and 0.5 cc will be administered percutaneously. The BCG administration will be repeated weekly for a total of six weeks. Patients will then be randomized to the BCG maintenance or no maintenance arms. The BCG maintenance arm will consist of weekly intravesical and percutaneous BCG immunotherapy administrations repeated for three consecutive weeks at three months, six months, and every six months thereafter for a total treatment period of 36 months. Patient removal from the study will be determined by the type of tumor. Any patient with progression of disease, defined by an increase in tumor grade or stage beyond the highest previous grade or stage or an increase in the number or frequency or recurrences will be removed from the study.

Progress: This study closed to patient entry 15 Dec 88. Eleven patients were entered in the study and 10 are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 86/080

Status: Terminated

Title: SWOG 8516: A Phase III Comparison of CHOP versus m-BACOD versus ProMACE-CytaBOM versus MACOP-B in Patients with Intermediate or High-Grade Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Thomas M. Baker, MC; COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; MAJ David M. Dunning, MC; CPT David R. Bryson, MC; LTC Howard Davidson, MC

Start Date:
08/15/1986

Est. Completion Date:
Jul 89

Periodic Review:
10/17/1997

Study Objective: To compare in a randomized group-wide setting the complete response rate, response duration, and survival of patients with intermediate and high grade non-Hodgkin's lymphoma treated with one of four combination chemotherapy regimens: CHOP, m-BACOD, ProMACE-CytaBOM, or MACOP-B; and to compare the toxicities of each regimen in this patient population.

Technical Approach: Patients with prior chemotherapy or radiotherapy are ineligible. Arm I (CHOP every 3 weeks for 8 consecutive cycles): cyclophosphamide (IV), doxorubicin (IV), vincristine (IV) and prednisone (PO). Arm II (m-BACOD every 3 weeks x 10): cyclophosphamide (IV), doxorubicin (IV), vincristine (IV), bleomycin (IV), dexamethasone (PO), methotrexate (IV), and calcium Leucovorin rescue after each MTX dose. Arm III (Pro-MACE-CytaBOM every 21 days, treated until complete remission plus 2 additional cycles): cyclophosphamide (IV), doxorubicin (IV), VP-16 (IV), Prednisone(PO), Ara-C (IV), bleomycin (IV), vincristine (IV), methotrexate (IV), calcium leucovorin rescue after each MTX dose, and trimethoprim-sulfamethoxazole (PO). Arm IV (MACOP-B will be given over 12 weeks): methotrexate (IV), calcium leucovorin rescue after each MTX bolus, doxorubicin (IV), cyclophosphamide (IV), vincristine (IV), bleomycin (IV), prednisone (PO), and trimethoprim-sulfa (PO). Patients with documented progressive disease may be taken off study at any time; however patients will preferably be restaged upon completion of the treatment program to assess response. Patients with less than a complete response at restaging will be taken off study. Patients whose clinical disease has disappeared and who appear to be in complete remission will undergo a complete and thorough laboratory and radiographic search for evidence of persistent lymphoma approximately one month after completion of therapy. If complete remission is confirmed, the patient will be observed with no further therapy.

Progress: This study was closed to patient entry 15 June 1991, and was previously reported as completed. However, two patients were transferred in to MAMC from another Army medical center so it was reactivated in Dec 93. MAMC now follows these patients. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 85/073

Status: Ongoing

Title: SWOG 8590: Phase III Study to Determine the Effect of Combining Chemotherapy with Surgery and Radiotherapy for Resectable Squamous Cell Carcinoma of the Head and Neck, Phase III Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Thomas M. Baker, MC; COL Friedrich H. Stutz, MC; COL Irwin B. Dabe, MC; COL William J. Gernon, MC; MAJ Timothy J. O'Rourke, MC; MAJ Michael D. Stone, MC; CPT David R. Bryson, MC; LTC Donald B. Blakeslee, MC; LTC Howard Davidson, MC

Start Date:
06/28/1985

Est. Completion Date:
May 87

Periodic Review:
10/17/1997

Study Objective: To test whether the addition of chemotherapy to surgery and radiotherapy prolongs disease-free survival and survival between the two study groups; to test whether the addition of chemotherapy to surgery and radiotherapy increases local control rates at the primary site and/or the cervical neck nodes; and to determine if the patterns of failure have been changed with the addition of chemotherapy.

Technical Approach: After surgery, patients will be randomized to either chemotherapy plus radiation therapy or radiation therapy alone. In the chemotherapy plus radiation therapy group, the chemotherapy will start 2-4 weeks after surgery and the radiotherapy will start approximately two weeks after completing chemotherapy. In the radiation therapy alone group, the radiation therapy will begin 2-4 weeks after surgery. Chemotherapy will be cisplatinum give day 1 and 5 FU given days 1-5 and repeated every 21 days for three courses. Patients who develop local or distant recurrence following therapy will be treated at the physician's discretion.

Progress: This study was closed to patient entry 1 Feb 90. Three patients were entered in previous years and are still being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 87/045

Status: Terminated

Title: SWOG 8600: A Randomized Investigation of High-Dose Versus Standard Dose Cytosine Arabinoside with Daunorubicin in Patients with Acute Non-lymphocytic Leukemia

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; LTC Lauren K. Colman, MC; LTC Howard Davidson, MC; MAJ Thomas M. Baker, MC; MAJ David M. Dunning, MC; MAJ Ruben D. Sierra, MC; CPT David R. Bryson, MC; MAJ Paul C. Sowray, MC

Start Date:
02/27/1987

Est. Completion Date:
Feb 90

Periodic Review:
02/20/1998

Study Objective: To compare, among patients with acute nonlymphocytic leukemia, the rate of complete remission produced by induction regimens of either standard dose cytosine arabinoside and daunorubicin or high-dose cytosine arabinoside and daunorubicin; to compare the duration of complete remission and of disease-free survival among patients who receive one of the three combinations of induction and consolidation regimens listed below; to determine the comparative toxicities of these three programs, and to determine the feasibility of implementing a predetermined approach to supportive care for these patients in a multi-institutional cooperative group setting.

Technical Approach: Patients will be stratified according to age and institution. Induction therapy will consist of standard dose Ara-C plus daunorubicin (Arm I) or high dose Ara-C + daunorubicin (Arm II). Patients requiring a second cycle of induction will receive the same doses as cycle 1, following the recovery of hematologic toxicities. Consolidation chemotherapy will begin when bone marrow and blood counts have recovered or on day 28 after the last induction cycle. Patients initially randomized to Arm I will be randomized to Arm III (high dose, one cycle only) or Arm IV (standard dose, two cycles). Patients initially randomized to Arm II (high dose) will be assigned to Arm III. Following the completion of consolidation, no further therapy will be given and patients will be followed only. Supportive care will include a predetermined antibiotic regimen determined by the physician.

Progress: This study was closed to patient entry 1 Dec 91. Of the seven patients enrolled at MAMC, 5 have died and 2 are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

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| Date: 30 Sep 99 | Number: 88/065 | Status: Terminated |
| Title: SWOG 8736: Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy | | |
| Principal Investigator: LTC Kenneth A. Bertram, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): COL Irwin B. Dabe, MC; CPT Denis Bouvier, MC; LTC Steven S. Wilson, MC; MAJ Rahul N. Dewan, MC; LTC Howard Davidson, MC | | |
| Start Date: 07/15/1988 | Est. Completion Date: Jun 91 | Periodic Review: 10/17/1997 |

Study Objective: To evaluate, in a cooperative group setting, the difference in survival, time to treatment failure, and toxicity of two curative approaches to the treatment of patients with localized, intermediate or high grade non-Hodgkin's lymphoma.

Technical Approach: All patients must have biopsy proven non Hodgkin's lymphoma of intermediate or high grade histology except lymphoblastic lymphoma. Patients must have had all visible tumor removed (excisional biopsy) and must have clinically adequate liver and myocardial function to begin treatment at full doses. Patients with known central nervous system disease, previous cancer with a possibility for recurrence which might affect survival or prior chemo or radiotherapy will be ineligible. All patients will be stratified at the time of initial registration by the following: (1) age (<65 years vs >65 years); (2) Stage (I or Ie vs nonbulky II or IIe); (3) histology (diffuse large cell vs other); (4) location of disease (GI involved vs non-GI, abdominal vs non-GI, other); (5) all disease resected vs residual measurable disease. Patients will be randomized to CHOP (Arm I) or to CHOP plus radiation therapy (Arm II). A complete course of chemotherapy on Arm I will consist of the administration of CHOP every 21 days for eight consecutive cycles unless progressive disease develops. A complete course of chemotherapy for Arm II will consist of the administration of CHOP every 21 days for three consecutive cycles unless progressive disease develops. Radiation therapy will begin immediately after the third cycle of CHOP. Radiation therapy dose, duration, and treatment volume will be determined jointly by the radiation oncologist and the medical oncologist. All patients will be followed at three month intervals until death. CHOP: Cyclophosphamide, 750 mg/m² IV, day 1; Doxorubicin, 50 mg/m² IV, day 1; Vincristine, 1.4 mg/m² IV, day 1; Prednisone, 100 mg/day po, days 1-5.

Progress: This study closed to patient entry 15 June 95. Nine patients have been enrolled at MAMC. Two have expired, so seven continue to be followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/119

Status: Ongoing

Title: SWOG 8794: Treatment of Pathologic Stage C Carcinoma of the Prostate With Adjuvant Radiotherapy

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL John N. Wettlaufer, MC; COL John C. Norbeck, MC; LTC Kurt L. Hansberry, MC; CPT Timothy O. Taylor, MC; CPT Michael D. Bagg, MC; CPT Bradley F. Schwartz, MC; MAJ J. Brantley Thrasher, MC; LTC Luke M. Stapleton, MC; LTC Kenneth A. Bertram, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Raymond S. Lance, MC

Start Date:
06/03/1994

Est. Completion Date:
Jun 98

Periodic Review:
10/17/1997

Study Objective: 1) To compare in a randomized study, the disease-free survival rates in completely resected patients with pathologic Stage C (T3N0M0) carcinoma of the prostate assigned to be treated with adjuvant external beam radiotherapy to that in patients assigned to receive no adjuvant therapy. 2) To assess the qualitative and quantitative toxicities of patients with pathologic Stage C (T3N0M0) carcinoma of the prostate when treated with external beam radiotherapy.

Technical Approach: Patients who have undergone radical prostatectomy and pelvic lymphadenectomy for clinical Stage A or B disease with a histologically proven diagnosis of pathologic Stage C (T3N0M0) carcinoma of the prostate will be randomized to receive either postoperative adjuvant radiation therapy (ARM I) or no adjuvant therapy (ARM II). The studies primary objective is to determine whether adjuvant radiation therapy has an effect on local control of the cancer and cancer-specific survival.

Progress: This study was closed to patient entry 17 Jan 97. One patient was enrolled at MAMC and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 88/066 **Status:** Ongoing

Title: SWOG 8796: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III Intergroup (INT 0074)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC

Start Date:
07/15/1988

Est. Completion Date:
Jun 91

Periodic Review:
10/17/1997

Study Objective: To compare the effectiveness of the MOPP/ABV hybrid with sequential MOPP-->ABVD in patients with advanced or recurrent Hodgkin's disease and to determine which regimen is superior with respect to the following parameters: complete response rate, duration of complete response, freedom from progression, and survival.

Technical Approach: Patients must have histologic confirmation of Hodgkin's disease with no prior chemotherapy. Patients will be stratified according to age, prior radiotherapy, bulky disease, and performance status. They will then be randomized to MOPP repeated every 28 days for 6 cycles (Arm I) or to MOPP/ABV Hybrid repeated every 28 days for six cycles (Arm II). Patients on Arm I with a complete response will go on to ABVD repeated every 35 days for three cycles. Those with partial response will receive two MOPP cycles and then go on to ABVD for three cycles. Those with no change will go off study. Those patients on Arm II with complete response will receive two more cycles of MOPP/ABV. Those with partial response will continue MOPP/ABV to complete response or until a maximum of 12 cycles. Those with no change will be taken off study. MOPP: Nitrogen mustard, 6 mg/m² IV, days 1 and 8, Vincristine, 1.4 mg/m² IV, days 1 and 8, Procarbazine, 100 mg/m² PO per day x 14 days, Prednisone 40 mg/m² PO per day x 14 days. ABVD: Adriamycin, 25 mg/m² IV, days 1 and 15, Bleomycin, 10 units/m² IV, days 1 and 15, Vinblastine, 6 mg/m² IV days 1 and 15, DTIC, 375 mg/m² IV, days 1 and 15. The MOPP/ABV hybrid consist of the MOPP regimen plus adriamycin, 35 mg/m² IV, day 8; bleomycin, 10 units/m² IV day 8; and vinblastine, 6 mg/m² IV, day 8.

Progress: This study was closed to patient entry 1 Aug 89. One patient was enrolled at MAMC (FY88) and is still being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 89/080

Status: Ongoing

Title: SWOG 8814 (ECOG 4188, NCCTG 883051): Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Breast Cancer Having Involved Axillary Nodes and Positive Hormone Receptors

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:
09/15/1989

Est. Completion Date:
Sep 99

Periodic Review:
10/17/1997

Study Objective: To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen and/or progesterone receptors treated with standard adjuvant therapy with long-term Tamoxifen or with chemoendocrine therapy with CAF, followed by long-term Tamoxifen or with concurrent chemoendocrine therapy with Tamoxifen and CAF and to compare the relative toxicity of the three therapies.

Technical Approach: Tumors must be pathologic stage T1, T2, or T3; N; MO (Stage II or selected Stage IIIA). Patients must have histologically proven adenocarcinoma of the breast with at least one positive lymph node (tumor and/or nodes must not be fixed). Patients must have undergone a radical, modified radical, or breast sparing procedure plus axillary dissection (level I or level II). Patients with bilateral breast cancer are ineligible. Estrogen and progesterone receptors must be assayed and one and/ or the other must be positive by the institutional laboratory standards of >10 fmol/mg protein. Prestudy studies must reveal no evidence of metastatic disease. Prior hormonal or chemotherapy is not allowed and prior postmenopausal estrogen therapy is allowed but must be discontinued before registration. Stratification factors will include: involved nodes (1-3, >4); PgR+ (ER positive or negative) vs PgR(ER positive); time from surgery to randomization (<6 vs >6 weeks). Patients will be randomized to one of three treatment arms: Arm I: Tamoxifen x 5 years, Arm II: Intermittent CAF x 6 courses followed by Tamoxifen x 5 years, Arm III: Intermittent CAF x 6 courses with concurrent Tamoxifen x 5 years.

Progress: This study closed to patient entry 1 Aug 95. Seven patients have been entered in this study at MAMC. One patient expired in FY 96, 6 others are still being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 90/027

Status: Ongoing

Title: SWOG 8851 (EST 5811, INT-0101): Phase III Comparison of Combination Chemotherapy (CAF) and Chemohormonal Therapy (CAF + Zoladex or CAF + Zoladex + Tamoxifen) in Premenopausal Women with Axillary Node-Positive, Receptor- Positive Breast Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:
01/19/1990

Est. Completion Date:
Dec 99

Periodic Review:
1/15/1999

Study Objective: To compare the recurrence rates, disease-free intervals, relative toxicities, and hormone-receptor-positive survival for premenopausal women with axillary lymph node-positive breast cancer given adjuvant therapy with combination chemotherapy using cyclophosphamide, doxorubicin, and 5-FU (CAF) alone or CAF followed by Zoladex, or CAF followed by Zoladex plus Tamoxifen; and to assess the effect of CAF, CAF plus Zoladex, and CAF plus Zoladex and Tamoxifen on hormone levels (LH, FSH, and estradiol) in these patients.

Technical Approach: Patients will be nonpregnant females who have undergone excision of the primary breast tumor mass, proven histologically to be invasive breast adenocarcinoma and must have one or more pathologically involved axillary nodes. Patients who undergo total mastectomy may receive post-operative radiotherapy at the discretion of the investigator. Patients who have had prior hormonal therapy or chemotherapy for breast cancer are ineligible. Patients will be randomized to CAF alone for six cycles or to CAF for 6 cycles followed by monthly Zoladex for 5 years, or to CAF for 6 cycles followed by daily Tamoxifen and monthly Zoladex for 5 years. Adjuvant therapy will be instituted as soon as possible after mastectomy or lumpectomy. The interval between definitive surgery and initiation of adjuvant chemotherapy will not be >12 weeks. When planned, radiation therapy may be administered prior to or after (within 4 weeks of) completion of 6 cycles of adjuvant chemotherapy.

Progress: This study closed to patient entry 15 Feb 94. Six patients have been enrolled at MAMC in previous years. One patient has been lost to follow-up, five are still being followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 91/067

Status: Ongoing

Title: SWOG 8855: Prognostic Value of Cytometry Measurements of Cellular DNA Parameters in Locally Advanced, Previously Untreated Head and Neck Cancer Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Patrick L. Gomez, MC

Start Date:
06/14/1991

Est. Completion Date:
Jun 94

Periodic Review:
9/28/1999

Study Objective: To evaluate the prognostic value of cellular DNA parameters of degree of DNA aneuploidy (DNA index) and proliferative activity (SPF) in predicting treatment response, time to treatment failure, and survival in patients with squamous cell carcinoma of the head and neck treated initially with cytotoxic therapy and to assess the correlation of DNA index and SPF with other patient clinical characteristics.

Technical Approach: Squamous cell cancers of the head and neck display a high degree of responsiveness to chemotherapy and/or radiotherapy, but a significant minority are exquisitely resistant to these treatment modalities. This will be a companion study to all SWOG head and neck cancer protocols utilizing chemotherapy as initial treatment and will use the patients registered on those studies. This study will use flow cytometrically determined cellular parameters, particularly cellular DNA content, to help identify prognostic outcome in this group of tumors. Specimens will be obtained at the time of biopsy for diagnosis, at completion of therapy if the tumor persists, or if a biopsy is performed to confirm a clinical complete response or document recurrence. All resected specimens will be sent for flow cytometry analysis. The degree of DNA aneuploidy (DNA index) and proliferative activity (SPF) will be determined by flow cytometry. These measurements will be correlated with the clinical characteristics of the patient at the time of biopsy to help predict treatment response, time to treatment failure, and survival in patients with squamous cell carcinoma of the head and neck.

Progress: Four patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 90/029

Status: Ongoing

Title: SWOG 8897 (EST-2188, CALGB-8897, INT-0101): Phase III Comparison of Adjuvant Chemotherapy With or Without Endocrine Therapy in High-Risk, Node Negative Breast Cancer Patients, and a Natural History Follow-up Study in Low-Risk, Node Negative Patients

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC

Start Date:
01/19/1990

Est. Completion Date:
Jan 93

Periodic Review:
1/15/1999

Study Objective: To compare disease-free survival and overall survival of high risk primary breast cancer patients with negative axillary lymph nodes treated with standard adjuvant chemotherapy for 6 cycles; either CMF (cyclophosphamide, methotrexate, 5-FU) or CAF (cyclophosphamide, adriamycin, 5-FU); to assess the value of the addition of tamoxifen for five years compared to no tamoxifen in these patients; to compare the toxicity of the therapies; to assess the prognostic significance of DNA flow cytometry in patients with small, occult invasive breast cancer treated by local therapy only; and to evaluate the disease-free survival and survival of low risk invasive breast cancer patients determined by receptor status, tumor size, and % S phase treated by local therapy only.

Technical Approach: Patients must have undergone a radical, modified radical, or breast sparing procedure plus level 1 and 2 axillary lymph node dissection. Patients with bilateral breast cancer, prior hormonal or chemotherapy, or previous or concurrent malignancy are ineligible. Low risk patients will be followed but will not receive adjuvant therapy. High risk patients will be randomized to: (1) CMF x 6 cycles; (2) CAF x 6 cycles; (3) CMF x 6 cycles followed by tamoxifen; or (4) CAF x 6 cycles followed by tamoxifen. Patients will start adjuvant chemotherapy within 12 weeks of definitive surgery. Patients who have had a breast sparing procedure and axillary dissection will receive radiation therapy, either before or after CMF or CAF (at the discretion of the treating physician). Radiotherapy and tamoxifen may be given together. Patients will be removed from the study for unacceptable toxicity, development of local/regional or metastatic disease; or noncancer related illnesses that prevent continuation of therapy or regular follow-up. Patients will be followed until death.

Progress: This study was closed to patient entry 15 Jan 93. Nine patients were enrolled in previous years, one expired in FY 97 and one was lost to further follow-up. The other seven continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 89/021

Status: Ongoing

Title: SWOG 8899: A Prospectively Randomized Trial of Low-Dose Leucovorin + 5-FU, High-Dose Leucovorin + 5-FU, Levamisole + 5-FU, or Low-Dose Leucovorin + 5-FU + Levamisole Following Curative Resection in Selected Patients with Durke's B or C Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Irwin B. Dabe, MC; MAJ Mark H. Kozakowski, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; MAJ Everardo E. Cobos Jr., MC

Start Date:
02/17/1989

Est. Completion Date:
Feb 92

Periodic Review:
01/26/1999

Study Objective: To assess the effectiveness of 5-FU + high-dose Leucovorin as surgical adjuvant therapy for resectable colon cancer, when compared to surgery alone.

Technical Approach: Patients must have received a potentially curative surgery for colon cancer with neither gross nor microscopic evidence of residual disease following the complete resection. The resected specimen must pathologically verify a diagnosis of modified Duke's B-2, B-3, or C. The primary tumor must be above the peritoneal reflection. Patients may not have had any prior chemotherapy nor exposure to 5-FU. Patients must be maintaining oral nutrition and be ambulatory 50% of the day and have adequate bone marrow function. Patients may not have a concurrent second malignant disease nor any previous malignant tumor within three years. Patients will be stratified by extent of invasion (limited to bowel wall vs into or through serosa vs perforation vs adherence to adjacent organs vs invasion of adjacent organs); extent of regional nodal metastases (none vs 0-4 vs >4); regional/ mesenteric implants resected enbloc (yes/no); and obstruction (yes/no). RANDOMIZE TO: (1) Observation; (2) Leucovorin 20 mg/m² + 5-FU 425 mg/m²; days 1-5; repeat at 4 and 8 wks, then every 5 wks for a total of 6 courses; (3) Leucovorin 500 mg/m² + 5-FU 600 mg/m²; Leucovorin by IV 2 hour infusion, 5-FU IV push beginning 1 hr after start of Leucovorin infusion, repeated weekly for 6 wks, followed by a 2-wk rest period, each 8-wk cycle (1 course) will be repeated for 4 courses. Revision (Jan 90): Observation arm closed (due to positive results seen in SWOG 8591); two new arms added (5-FU + levamisole & 5-FU + low dose leucovorin + levamisole).

Progress: Eighteen patients were enrolled at MAMC prior to closure to patient entry on 30 Jul 92. One patient was lost to follow-up, seven patients have died from their disease and 10 continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 91/089

Status: Ongoing

Title: SWOG 8947: Central Lymphoma Serum Repository Protocol; Companion Protocol to SWOG Studies 8516, 8736, 8809, and 8816

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; MAJ Everardo E. Cobos Jr., MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC; LTC Luke M. Stapleton, MC

Start Date:
08/02/1991

Est. Completion Date:
Aug 95

Periodic Review:
07/27/1999

Study Objective: To establish a central lymphoma serum repository that will serve as a resource to provide specimens for current and future scientific studies and to utilize the Southwest Oncology Group clinical data base to perform clinicopathologic correlations with the results of those studies.

Technical Approach: No therapy will be utilized in this study and patient treatment will not be based on this study. Patients must meet the eligibility criteria and be registered to one of the following SWOG protocols: 8516, 8809, 8736, or 8816. Ten cc's of blood will be drawn prior to protocol treatment and shipped to the SWOG Lymphoma Serum Repository at Loyola University Medical School.

Progress: This is a companion protocol to other SWOG studies. Two specimens have been collected in previous years .

Detail Summary Sheet

Date: 30 Sep 99

Number: 90/056

Status: Ongoing

Title: SWOG 8997 (ECOG 3887): Phase III Chemotherapy of Disseminated Advanced Stage Testicular Cancer with Cisplatin Plus Etoposide with Either Bleomycin or Ifosfamide

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Paul C. Sowray, MC; MAJ Mark H. Kozakowski, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Patrick L. Gomez, MC; CPT Denis Bouvier, MC; LTC Howard Davidson, MC; LTC Robert L. Sheffler, MC; LTC John A. Vaccaro, MC

Start Date:
03/16/1990

Est. Completion Date:
Mar 93

Periodic Review:
02/23/1999

Study Objective: To determine the objective response rate and duration of remission of BEP compared to VIP combination chemotherapy; to determine the toxicity of VIP compared to BEP combination chemotherapy; to confirm the efficacy and toxicity of intravenous Mesna as a urothelial protective agent.

Technical Approach: Patients must have a histologic diagnosis of advanced disseminated germ cell tumor and no prior chemotherapy or radiation therapy. Patients will be randomized to VIP (cisplatin, ifosfamide, mesna, and etoposide) to BEP (cisplatin, etoposide, and bleomycin). The regimen will be repeated every three weeks for four cycles. Bleomycin will be omitted for postsurgery chemotherapy in BEP patients. Patients in complete remission at the end of four courses of therapy will receive no further treatment. If there is radiographic or serologic evidence of persistent disease and residual tumor is surgically resectable, surgery will be performed. Patients who have complete or near complete resection of residual radiographic abnormalities with the pathologic finding of fibrosis/necrosis and those who have complete resection of mature or immature teratoma will receive no further treatment. Patients who have complete resection of residual disease which histologically shows viable carcinoma will receive two more courses of the original induction therapy. If residual tumor is deemed unresectable, patients will be followed monthly until disease progression with no further therapy. If relapse occurs in complete or partial responders less than 4 weeks after day 1 of the last course of induction therapy, the patient will be taken off study.

Progress: Prior to closure to patient entry (1 Apr 92) two patients had been enrolled at MAMC. One patient is still being followed (one died Jan 93).

Detail Summary Sheet

| | | |
|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 91/094 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: SWOG 9007: Cytogenetic Studies in Leukemia Patients, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC

Start Date:
09/06/1991

Est. Completion Date:
Aug 94

Periodic Review:
8/24/1999

Study Objective: To compare these primary aspects of quality of life, according to treatment assignment: 1) Treatment specific symptoms 2) Physical Functioning 3) Emotional functioning To compare three secondary quality of life variables, according to treatment assignment: 1) General symptoms 2) Global perception of quality of life 3) Social functioning.

Technical Approach: This is a companion to SWOG 8794. Patients will be assigned to the same treatment groups as in the companion protocol (prostatectomy followed by adjuvant radiotherapy versus prostatectomy alone) and must be able to complete a quality of life questionnaire prior to registration and randomization on SWOG-8794. Standardized instructions will be read to the patients by the nurse/data manager at each site. Additional questionnaires will be completed at week 6, 6 months, 12 months, and then yearly for the next 4 years. Quality of life profiles will be compared for the two treatment groups at different points in time: baseline, where no differences are expected six weeks, where the two treatment groups are expected to show maximum differences on some measures; six months, one year and annually for a total for five years, where the treatment means for quality of life measures are expected to come together and level off. For key continuous variables, repeated measures analyses of variance should help to make comparisons at fixed points in time and across time. For the discrete variables such as occurrence or non-occurrence of specified complications, standard methods of categorical data analysis will be employed.

Progress: Five patients have been enrolled in previous years. One patient continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 91/033

Status: Ongoing

Title: SWOG 9013 (RTOG 89-11, INT-0113): A Prospective Randomized Comparison of Combined Modality Therapy for Squamous Carcinoma of the Esophagus: Chemotherapy Plus Surgery Versus Surgery Alone for Patients with Local REgional Disease

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ William A. Phillips; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; COL Joseph F. Homann, MC; COL Daniel G. Cavanaugh, MC; MAJ Everardo E. Cobos Jr., MC; MAJ Paul C. Sowray, MC

Start Date:
02/01/1991

Est. Completion Date:
Jan 94

Periodic Review:
01/26/1999

Study Objective: To compare, using a prospective controlled randomized study design, the outcomes of therapy of surgery alone versus pre and postoperative chemotherapy and surgery for patients with local regional esophageal cancer (outcome is defined as survival and relapse pattern); to assess the toxicities of a multimodality approach to esophageal carcinoma involving systemic chemotherapy and surgery (the toxicities of surgical resection as initial therapy or following chemotherapy will be assessed as operative morbidity and mortality); to compare the local and distant control rates with the two approaches and to define the pattern of failure; and to compare the impact on overall and disease free survival of multimodality therapy with surgery alone.

Technical Approach: Esophageal cancer is seen in over 10,000 patients a year in the United States and only about 7% of these patients are cured as demonstrated by a five year survival. This study is designed to see whether or not giving chemotherapy will improve that survival. To be eligible patients must have histologic proof of squamous cell carcinoma of the esophagus, disease limited to the total regional area (clinical stage T1-T3, NX,MO), no prior surgery, radiation therapy, or chemotherapy, and adequate bone marrow, liver function, renal function, and pulmonary reserve. Patients must be physiologically fit for proposed chemotherapy and surgery and be greater than 18 years of age. Patients will be randomized to surgery alone, or to receive three cycles of preoperative cisplatin and 5-FU and then to undergo definitive surgery followed by two more cycles of cisplatin and 5-FU, starting two to six weeks after surgery.

Progress: This study was closed to patient entry 31 Dec 95. Three patients have entered this study in previous years. Two are being followed and one died of the disease.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/143

Status: Terminated

Title: SWOG 9019: A Phase III, Randomized, Prospective Comparison Between Chemotherapy Plus Radiotherapy, and the Same Chemotherapy Plus Radiotherapy Together With Surgery for Selected Stage IIIA (Positive Mediastinal Nodes) and Selected Stage IIIB (No Malignant Effusion) Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:
06/09/1993

Est. Completion Date:
May 98

Periodic Review:
10/17/1997

Study Objective: 1) To assess whether concurrent chemotherapy and radiotherapy, followed by surgical resection, results in a significant improvement in progression-free, overall, and long-term survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIa (N2 Positive) and selected IIIB non-small cell lung cancer. 2) To evaluate the patterns of local and distant failure for patients enrolled in each arm of the study, in order to assess the impact of the therapy on local control and distant metastasis.

Technical Approach: Patients with regionally advanced non-small cell lung carcinoma will be randomized to one of two arms. Arm I: patients will receive induction radiation therapy to a "tight" field to 4500 cGy. They will receive concurrent cisplatin on days 1 and 8 and on days 29 & 36 with VP-16 days 1-5, repeated on days 29-33 (2 cycles). After completion of induction, patients will be re-evaluated for extent of disease. If there is no progression of the disease, patients will go to exploratory thoracotomy for complete removal of the primary lesion and sampling of nodes.

If the tumor is unresectable or the margins are positive or the mediastinal nodes are positive, an additional 2 cycles of chemotherapy with a radiation boost will be given. Patients who complete the induction phase but have persistent supraclavicular node metastases will also receive 2 more cycles of concurrent chemo-radiotherapy will not go to surgery.

Arm II patients receive "standard" lung field radiation therapy to 4500 cGy and concurrent cisplatin and VP-16 for 2 cycles.

One week prior to completing radiation therapy, patients will be re-evaluated for response. Those patients with no evidence of distant metastases or local progression will continue radiation therapy with no break for an additional 1600 cGy with a boost. They will also receive 2 more cycles of chemotherapy concurrent with radiation.

Any patient who shows local or distant progression after induction chemo-radiation will be taken off protocol.

Progress: This study was closed to patient entry 1 Dec 95. Two patients have been enrolled in this study in previous years (1 in FY95). One patient continues to be followed and the other died of the disease. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 92/052

Status: Terminated

Title: SWOG 9031: A Double Blind Placebo Controlled Trial of Daunomycin and Cytosine Arabinoside With or Without rhG-CSF in Elderly Patients With Acute Myeloid Leukemia, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert B. Ellis, MC; LTC Robert L. Sheffler, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC

Start Date:
04/03/1992

Est. Completion Date:
Jun 94

Periodic Review:
10/17/1997

Study Objective: To compare the complete response rates and duration of survival in patients 56 or older with acute myeloid leukemia (AML) when treated with standard doses of cytosine arabinoside (Ara-C) and daunorubicin (DNR), with or without recombinant human granulocyte-colony stimulating factor (rhG-CSF); to assess the frequency and severity of toxicities of the two treatment regimens; to compare the duration of neutropenia and thrombocytopenia, the total number of febrile days, the number of days of antibiotic therapy, the number and type of infection episodes, and the number of hospital days in patients treated with or without rhG-CSF; and to correlate biological parameters including cell surface immunophenotype, ploidy, and cytogenetics with clinical response.

Technical Approach: Patients aged 56 and older with AML will be randomized to receive treatment with either Ara-C/DNR plus rhG-CSF or Ara-C/DNR plus placebo (Ara-C days 1-7, C/DNR days 1-3, and blinded drug begins on day 10) Patients who had regrowth of leukemia during this course of treatment will receive a second identical course of treatment except the blinded drug will not be started until the marrow shows <5% blasts. The blinded drug will not be given in the second induction course if the patient has regrowth of leukemia following the first induction course. Following completion of induction therapy, patients who achieve complete remission will be registered to receive two cycles of post-remission therapy, utilizing the same regimen to which they were originally randomized.

Progress: This protocol closed to patient accrual 15 Jan 95. One patient was enrolled at MAMC in FY 93 and continues to be followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/062

Status: Ongoing

Title: SWOG 9035: Randomized Trial of Adjuvant Immunotherapy with an Allogeneic Melanoma Vaccine for Patients with Intermediate Thickness, Node Negative Malignant Melanoma, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Richard F. Williams, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ John R. Caton, MC

Start Date:
01/20/1995

Est. Completion Date:
Jan 99

Periodic Review:
1/15/1999

Study Objective: 1) To compare disease-free survival and overall survival between patients with T3NOM0 malignant melanoma who receive adjuvant immunotherapy with an allogeneic melanoma vaccine versus no adjuvant treatment. 2) To evaluate the toxicity of adjuvant immunotherapy with an allogeneic melanoma vaccine in patients with T3NOI10 malignant melanoma. 3) To explore the interaction between the patients' defined HLA types (i.e., whether they are compatible with the HLA phenotypes of the vaccine) and the vaccine treatment effectiveness in terms of disease-free survival and overall survival.

Technical Approach: The study is a randomized study of Interferon Alfa-2b as adjuvant immunotherapy in patients with T3NOM0 malignant melanoma following complete resection. After complete staging, including assessment of any abnormal lymph nodes by biopsy, patients will be randomized either to treatment with four cycles of intramuscular vaccine therapy or observation only and will be followed until death for recurrence.

Progress: This protocol closed to patient accrual, 15 Nov 96. One patient was enrolled in FY 95 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 91/069

Status: Ongoing

Title: SWOG 9040 (CALGB-9081, INT-0014): Intergroup Sectal Adjuvant Protocol, A Phase III Study

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Everardo E. Cobos Jr., MC; MAJ Paul C. Sowray, MC; MAJ Patrick L. Gomez, MC; MAJ Rahul N. Dewan, MC; LTC Steven S. Wilson, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; LTC Howard Davidson, MC

Start Date:
06/14/1991

Est. Completion Date:
May 93

Periodic Review:
10/17/1997

Study Objective: To determine the relative efficacy of: 5-FU; 5-FU plus leucovorin; 5-FU plus levamisole; and 5-FU plus leucovorin and levamisole when combined with pelvic radiation therapy in the treatment of Stages B-2 and C (TNM Stage II and III) rectal cancer. End points used will include local recurrence rates, probability of distant metastases, disease free survival rates, and overall survival.

Technical Approach: This will be a 4-armed study with the same radiation therapy program in all arms, but with varying drug regimens as listed in the objective. 5-FU with radiation therapy will comprise the control arm of the study. Patients will be randomized to treatment arms and they will be stratified by type of operation (abdominal perineal or anterior resection); nodal involvement (none, 1-3, or >3); and invasion through bowel wall or into adjacent organs (none, through muscularis propria, or adherence to or invasion of adjacent organs or structures). Each drug regimen will be given alone on days 1-5 and 29-33, followed by radiation therapy (five weeks) with concomitant chemotherapy on days 57-60 and 85-88. The chemotherapy regimen will then be repeated beginning 28 days after the completion of radiation therapy on days 1-5 and 29-33. If evidence of recurrence is obtained, protocol treatment will be discontinued and the patient followed until death. In the absence of recurrent disease, follow-up observations will be continued for a minimum of 5 years after surgery.

Progress: This study was closed to patient entry on 22 Nov 92. Three patients were enrolled in previous years and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/104

Status: Ongoing

Title: SWOG 9041: Chemoprevention of Recurrent Adenomas and Second Primary Colorectal Carcinoma. A Phase III Pilot Study.

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
05/06/1994

Est. Completion Date:
May 98

Periodic Review:
9/28/1999

Study Objective: This is a preliminary effort towards the long-term research goal of determining whether calcium, as a nutritional supplement, can prevent colorectal adenomas and new primary carcinomas in surgically treated colorectal carcinoma (CRC) patients.

Technical Approach: Patients with previously resected colon cancer, Stages 0, I, or II or rectal carcinomas, Stages 0, I are eligible to participate in this study. During the 3 month Run In period, patients will be placed on placebo 3 tablet a day. After successful completion of the Run In (patients must have taken > 80% of tablets) patients will be randomized to regimen A (3 - 600 mg tablets of calcium carbonate daily for 5 years) or regimen b (3 placebo tablets daily for 5 years). The pills will be provided to the patients every three months for the first two years and every six months for the next three years. Patients will be monitored for compliance, hypercalcemia, renal toxicity and gastrointestinal or hepatic toxicity. Endpoint is the efficacy of supplemental oral calcium in reducing recurrence of adenomas or second primary carcinomas.

Progress: This protocol closed to patient accrual 22 Nov 98. Sixteen patients have been enrolled and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/096

Status: Ongoing

Title: SWOG 9059 (E1392, INT-0126): Phase III Comparison of Standard Radiotherapy versus Radiotherapy plus Simultaneous Cisplatin, versus, split-Course Radiotherapy plus Simultaneous Cisplatin and 5-Fluorouracil, in Patients with Unresectable Squamous Cell Carcinoma of the Head and Neck

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
05/16/1997

Est. Completion Date:
Apr 00

Periodic Review:
04/17/1998

Study Objective: 1) To compare the effectiveness of standard radiation therapy alone to radiation therapy and simultaneous chemotherapy with cisplatin to split-course radiation therapy with cisplatin and 5-fluorouracil infusion in patients with unresectable Stage III and IV squamous cell carcinoma of the head and neck. Endpoints will include complete response rate, time to treatment failure, and overall survival. 2) To compare the relative toxicities of these treatment arms, in this patient population. 3) To compare patterns of relapse or treatment failure among these regimens. 4) To further assess the role, timing, and success of surgery in patients achieving a response to non-operative therapy.

Technical Approach: Unresectable Squamous Cell Carcinoma has a dismal prognosis with 3 year survivals in the 25% range. Several studies have shown that adding chemotherapy to radiation therapy may improve response rates and may allow some patients to get surgery after therapy. There are two approaches to adding chemotherapy to radiation therapy. One way is to give concurrent therapy with Cisplatin alone with combined continuous radiation therapy (Al Sarraf regimen) or to give combination Cisplatin and 5-FU with split course (Adelstein Regimen). These two regimens have met with some success in single ARM Phase II studies and have resulted in some patients having subsequent surgeries translating into longer survivals. It is thus the aim of this study to evaluate efficacy of three different regimens with continuous radiation therapy alone serving as the third ARM. Toxicities from these regimens are reasonable.

Progress: Two patients have been enrolled in this study at MAMC and continue to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/032

Status: Ongoing

Title: SWOG 9061 (EST-2190, INT 0121): A Phase III Study of Conventional Adjuvant Chemotherapy vs High Dose Chemotherapy and Autologous Bone Marrow Transplantation or Stem Cell Transplantation as Adjuvant Intensification Therapy Following Conventional Adjuvant Chemotherapy in Patients with Stage II and III Breast Cancer at High Risk of Recurrence

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:
12/04/1992

Est. Completion Date:
Nov 95

Periodic Review:
11/19/1999

Study Objective: To compare the sites and rates of recurrence, disease-free survival and overall survival, and toxicity of adjuvant chemotherapy (CAF) with adjuvant chemotherapy plus high-dose therapy with cyclophosphamide and the TEPA with autologous marrow infusion in patients with breast cancer with 10 or more positive lymph nodes.

Technical Approach: Patients will be stratified according to estrogen receptor status, age, and menopausal status and then randomized to receive radiotherapy plus tamoxifen or high-dose chemotherapy and autologous bone marrow transplantation. Both arms will receive cyclophosphamide 100 mg/m² PO X 14 days, doxorubicin 30 mg/m² IV days 1 & 8, and flurouracil 500 mg/m² IV days 1 & 8 repeated every 28 days x 6 cycles (CAF). Patients receiving CAF without bone marrow transplantation will begin radiation therapy within 4 weeks of the last dose of chemotherapy or when the WBC > 2900 and Platelets > 100,000. Patients randomized to receive high-dose chemotherapy will have bone marrow harvested no sooner than 4 weeks nor longer than 8 weeks after the last previous dose of myelotoxic chemotherapy. The CBC must be normal and the bone marrow normocellular and free of tumor by bilateral iliac crest biopsy within 4 weeks prior to storage. After the bone marrow is harvested, high-dose chemotherapy of cyclophosphamide 6000 mg/m²/96 hr and ThioTEPA 800 mg/m²/96 hr (4 days), will be given by continuous infusion over 4 days, days -6 to -2. Autologous bone marrow reinfusion will be on day 0. Patients receiving BMT will again be randomized to receive GM-CSF as a daily 2, 6 or 24 hour intravenous infusion beginning 2-4 hours after bone marrow infusion. GM-CSF will be initiated at a dose of 250 mcg/m²/d. Treatment will continue until the patient has achieved an absolute neutrophil count (ANC) of = 1000 cells/ul on 3 consecutive days or a planned duration of 28 days of treatment.

Tamoxifen 20 mg PO q.d. will be given to all patients who are estrogen or progesterone receptor positive after the completion of all chemotherapy for 5 years. For patients not randomized to receive transplant, Tamoxifen should be initiated 28 days after the start of the last CAF cycle. Patients randomized to receive transplant should begin Tamoxifen following transplant when WBC > 4000 and/or ANC > 2000. Patients will be taken off-study if there is development of metastatic disease at any time while therapy is ongoing.

Measurement of effect is recurrence, disease-free survival or survival (survival is measured from the date of randomization to date of death).

At measured times during the study a Breast Chemotherapy Questionnaire (BCQ) will be completed to separately document the changes in psychosocial function that occur on the two

regimens. Not all subjects will complete the questionnaire at all time points, but if at least 150 per arm have complete data, the width of a 95% confidence interval on the mean change in scores would be about ± 0.09 .

The BCG will also be used to make comparisons between regimens. A 2 degree of freedom test based on the difference of the means of the 36 week evaluation and the difference of the means of the 52 week evaluation will be used. Then using the variance information given above, the variance of the difference of means at either time should have a variance of about 0.0099, and the covariance between the two times should be about 0.0079. If there is a constant difference in the scores, then the distribution of the test statistic would be approximately noncentral chi-square with 2 degrees of freedom and centrality parameters $113*d*d$. For a 5% level test, this gives a power of 82% for detecting a difference of $d = 0.3$.

Progress: This protocol closed to patient accrual 3 Aug 98. One patient was enrolled in this study at MAMC and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 92/017

Status: Terminated

Title: SWOG 9125: A Phase II Trial of CVAD/Verapamil/Quinine for Treatment of Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Howard Davidson, MC; MAJ Paul C. Sowray, MC; LTC Luke M. Stapleton, MC; MAJ Patrick L. Gomez, MC; LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; CPT Jennifer L. Cadiz, MC; MAJ James S. D. Hu, MC

Start Date:
12/06/1991

Est. Completion Date:
Oct 92

Periodic Review:
10/17/1997

Study Objective: 1) To evaluate the effectiveness of the CVAD chemotherapy regimen (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) when administered in combination with chemosensitizers (verapamil and quinine) which are intended to block the emergence of multidrug resistance in previously untreated patients with intermediate and high grade non-Hodgkin's lymphoma. The effectiveness of CVAD plus verapamil and quinine will be based on the estimate of the complete response rate and the time to treatment failure. 2) To assess the toxicities and side effects associated with the CVAD regimen when combined with verapamil and quinine. Secondary objectives are to further investigate the utility of the proliferative rate (determined by Ki-67 monoclonal antibody), the importance of cell-cell recognition molecules, the role of host response, and the value of detectable levels of p_glycoprotein as prognostic indicators of outcome in conjunction with companion study SWOG 8819; and to further utilize the central serum repository enabling clinicopathologic correlations with the results of studies on the material collected (see companion study SWOG 8947).

Technical Approach: Currently, regardless of the regimen used, 30 to 60% of advanced stage non-Hodgkin's lymphoma patients will relapse and the emergence of clinical drug resistance is a significant problem in these patients. In this study, patients will receive oral verapamil and quinine on days 1-6 as chemosensitizers. They have been shown to reverse the multidrug resistance associated with P-glycoprotein. Starting on day 2, patients will receive a continuous infusion of Adriamycin and vincristine for four days, Cytosan will be given IV on Day 2 and oral decadron will be given days 2-5. Patients with documented progressive disease at any time will be taken off protocol treatment. Patients with stable disease will receive 2 courses (6 weeks) of chemotherapy. Patients responding to treatment will receive a maximum of 8 courses of chemotherapy. Patients will be restaged upon completion of the treatment program to assess response, with a complete laboratory and radiographic evaluation one month after the completion of therapy. All patients will be followed until death.

Progress: This study was closed to patient entry 15 Feb 93. Two patients were enrolled in previous years and are still being followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/097

Status: Ongoing

Title: SWOG 9133: Randomized Trial of Subtotal Nodal Irradiation versus Doxorubicin Plus Vinblastine and Subtotal Nodal Irradiation for Stage I-IIA Hodgkin's Disease, Phase III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:
05/06/1994

Est. Completion Date:
Sep 01

Periodic Review:
9/28/1999

Study Objective: The main objective of this study is to compare progression-free and overall survivals of clinically stage (non-laparotomized) patients with early stage (IA,IIA), good-prognosis Hodgkin's Disease treated with either standard subtotal nodal irradiation or with short-course chemotherapy plus standard irradiation. In addition, the study will attempt to identify subgroups of patients who may do better with one approach or the other, and to follow patients for long-term toxicities associated with either regimen.

Technical Approach: Patients will be clinically staged by standard methods and then, if they appear to have localized, good-prognosis disease, they will be randomized to receive either standard radiotherapy to mantle and para-aortic fields (subtotal nodal irradiation) or three cycles (6 doses) of chemotherapy followed by the same radiotherapy. Management of both patient groups will be identical apart from the chemotherapy.

Progress: Two patients were enrolled in this study, both in FY 94, and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/042

Status: Ongoing

Title: SWOG 9201 (RTOG 91-11): Phase III Trial to Preserve the Larynx: Induction Chemotherapy and Radiation Therapy versus Concomitant Chemotherapy and Radiation Therapy Versus Radiation

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; LTC Steven S. Wilson, MC; MAJ Nyun C. Han, MC; MAJ Mark E. Shaves, MC; CPT Brent L. Kane, MC

Start Date:
12/19/1996

Est. Completion Date:
Nov 00

Periodic Review:
11/19/1999

Study Objective: The normal treatment of cancer of the throat is surgery with removal of the voice box. The purpose of this study is to try to preserve the larynx by using a non-surgical treatment. Three treatments will be compared: 1) chemotherapy followed by radiation, or 2) chemotherapy given at the same time as radiation, or 3) radiation alone.

Technical Approach: Treatment 1: Cisplatin and 5-FU will be given twice 3 weeks apart. Treatment 2: Cisplatin will be given once every 21 days (for three doses on Days 1, 22, and 43) during radiation which is given once a day, 5 days a week for 7 weeks. Radiation can be given on an outpatient basis. Cisplatin is given into the vein over 20-30 minutes. 5-FU is given into the vein by continuous infusion over 120 hours following cisplatin administration in Treatment 1.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

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|--|--|--------------------------------------|
| Date: 30 Sep 99 | Number: 93/097 | Status: Ongoing |
| Title: SWOG 9205: Central Prostate Cancer Serum Repository Protocol | | |
| Principal Investigator: LTC Kenneth A. Bertram, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Robert L. Sheffler, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Timothy P. Rearden, MC | | |
| Start Date: 05/07/1993 | Est. Completion Date: Mar 95 | Periodic Review: 9/28/1999 |

Study Objective: 1) To store serum of patients with confirmed adenocarcinoma of the prostate entered onto clinical trials conducted by the SWOG Genitourinary Committee. 2) To provide the serum of the above patients entered onto SWOG studies for specific clinical-laboratory investigations outlined on separate SWOG protocols approved by the Genitourinary Committee Tumor Biology Subcommittee.

Technical Approach: This serum bank is to provide the opportunity for study of new or existing markers or other tests in a prospective or retrospective fashion, in order to test their usefulness as diagnostic or management tools in prostate cancer at all stages. Specific information regarding the nature of individual tests to be conducted on the serum samples of these patients will be described in individual protocols.

All serum samples (approx. 3 - 5 cc) will be collected from patients in the frequency and timing indicated on specific protocols. Samples will be spun 15 minutes after collection and stored at a minimum of -20°C. Samples will be frozen and shipped to the Serum Bank Coordinator.

Progress: Two patients were enrolled in this serum study in FY 97. Two patients were enrolled in previous years; one expired in FY 96. Three patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/115

Status: Ongoing

Title: SWOG 9208: Health Status and Quality of Life in Patients With Early Stage Hodgkin's Disease: A Companion Study to SWOG 9133

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
06/03/1994

Est. Completion Date:
Jun 98

Periodic Review:
9/28/1999

Study Objective: 1) To evaluate prospectively the health status and quality of life (QOL) of early stage Hodgkin's Disease patients receiving either subtotal nodal irradiation or short course chemotherapy plus subtotal nodal irradiation. 2) To describe the short-term, acute effects of two treatments for early stage Hodgkin's Disease patients on patient report of symptoms and on patient QOL. 3) To evaluate the intermediate and long-term effects of two treatments for early stage Hodgkin's Disease patients on patient QOL over five years.

Technical Approach: Patients enrolled in the companion protocol, SWOG-9133, will be asked to complete questionnaires before registration into this study, at 6 months; and annually for seven years. These questionnaires seek to identify and quantitate those differences pertaining to quality of life issues that the added chemotherapy may have in early stage Hodgkin's disease patients.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 94/010 **Status:** Ongoing

Title: SWOG 9217: Chemoprevention of Prostate Cancer with Finasteride (Proscar), Phase III, Intergroup

Principal Investigator: LTC Raymond A. Costabile, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): MAJ J. Brantley Thrasher, MC; MAJ Raymond S. Lance, MC

Start Date:
10/01/1993

Est. Completion Date:
Nov 03

Periodic Review:
9/28/1999

Study Objective: The primary objective of this trial will be to determine if finasteride can reduce the development of prostatic cancer in males 55 years and older.

Technical Approach: Men who have attained 55 years of age have never been diagnosed as having prostatic cancer will be randomized to receive Finasteride 5 mg or Matched Placebo PO daily for 7 years. Patients will be followed with clinic visits at 6 months, 1 year and then annually. Annual laboratory screening will include PSA. Triggers are in place to initiate prostatic biopsies. The final endpoint is biopsy proven presence/absence of carcinoma of the prostate after seven years.

Progress: Approximately 50 patients have been enrolled in this study and continue to receive treatment. The protocol has been closed to patient entry 1 Jan 97.

Detail Summary Sheet

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|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 93/136 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: SWOG 9221, MDACC ID 91-025, INT-191-001: Phase III Double-Blind Randomized Trial of 13-Cis Retinoic Acid (13-cRA) to Prevent Second Primary Tumors (SPTs) in Stage I Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert D. Vallion, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; MAJ Timothy P. Rearden, MC; CPT Diana S. Willadsen, MC

Start Date:
07/02/1993

Est. Completion Date:
Jul 98

Periodic Review:
9/28/1999

Study Objective: To evaluate: (1) the efficacy of 13-cis-retinoic acid (13-cRA) in reducing the incidence of SPTs in patients who have been treated for Stage I non-small cell lung cancer with complete surgical resection; (2) the qualitative and quantitative toxicity of 13-cRA in a daily administration schedule; and (3) compare the overall survival of patients treated with 13-cRA vs. patients treated with placebo.

Technical Approach: Patients enrolling into this study will be stratified according to histology, T stage and smoking status then registered into a Single-Blind, 8 week run-in period to test compliance. All patients will receive placebo during this period. After Run-in the patients will be randomized into a double-blind trial to receive 13-cRA (30 mg p.o./d x 3 yrs vs. Placebo (30 mg p.o./d x 3 yrs). Each group will have a 4 year follow-up period.

The final analysis will be undertaken shortly after seven years. The primary hypothesis for the study is whether 13-cRA lowered the rate of second primary tumors (SPT). All patients randomized will be grouped according to the assigned treatment. Patients who are either purely lost to follow up or died without a SPT occurring will be included in the actuarial analysis with a censored status on the last day of contact. The primary hypothesis of treatment benefit will be tested using the proportional hazards model.

Progress: The protocol closed to patient accrual 9 Apr 97. Ten patients have been enrolled in this study (1 in FY 97). Two died in FY 96, and one was transferred to Keesler AFB. Seven continue to be followed at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/108

Status: Ongoing

Title: SWOG 9237: Evaluation of Topotecan in Refractory and Relapsing Multiple Myeloma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC

Start Date:
05/07/1993

Est. Completion Date:
May 98

Periodic Review:
10/17/1997

Study Objective: 1) To evaluate the response rate for refractory myeloma treated with topotecan; 2) To evaluate the qualitative and quantitative toxicities of topotecan administered in a Phase II study; 3) To measure topoisomerase levels in multiple myeloma cells.

Technical Approach: Patients with proven multiple myeloma, with protein criteria present, who have received exactly one prior regimen, and have shown, in the opinion of the investigator, to have disease progression are eligible for this study. All patients will receive topotecan 1.25 mg/m² q.d. IV over 30 minutes on days 1-5 repeated q 21 days. This schedule will continue as long as patients show complete remission, partial remission or stable disease and toxicity is acceptable. Topotecan dosage can be adjusted on nadir counts of the preceding cycle.

It is assumed that topotecan will be of interest if a true response rate of 20% or more is achieved in the treatment of patients with relapsed or refractory multiple myeloma.

Progress: This study closed to patient accrual 15 Feb 95. One patient was entered in this study in FY93 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/092

Status: Ongoing

Title: SWOG 9245: Central Lymphoma Repository Tissue Procurement Protocol for Relapse or Recurrent Disease

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; CPT Jennifer L. Cadiz, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; CPT Diana S. Willadsen, MC; LTC Robert D. Vallion, MC

Start Date:
04/02/1993

Est. Completion Date:
May 95

Periodic Review:
03/23/1999

Study Objective: 1. To acquire fresh snap-frozen lymphoma tissue from patients who relapse or have recurrent disease after being treated on Southwest Oncology Group treatment protocols. 2. To establish a standard set of procedures for routine acquisition, banking, and study of lymphoma tissues within the cooperative group. 3. To use the repository tissue to establish clinical correlations via presently activated phenotyping studies and future projected molecular studies assessing specimen DNA and RNA status. 4. To examine the biology of therapy failure in relationship to changes in pretreatment and post-therapy immunophenotypic data.

Technical Approach: Fresh frozen tissues will be acquired from relapsed patients for basic science protocols, both current and future, designed to better define the biology of relapsed non-Hodgkins's lymphoma. This is not a treatment protocol, nor will results be used to guide treatment decisions.

Fresh biopsies (from any organ site) will be snap-frozen and submitted with one stained (Hematoxylin and Eosin) histologic section with accompanying pathology report to The Department of Pathology at the University of Arizona in Tucson.

Progress: No patients have been enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/161

Status: Ongoing

Title: SWOG 9250 (INT-0136): Phase III Intergroup Prospectively Randomized Trial of Perioperative 5-FU After Curative Resection, Followed by 5-FU/Levamisole for Patients With Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert B. Ellis, MC; MAJ Timothy P. Rearden, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
09/21/1994

Est. Completion Date:
Sep 98

Periodic Review:
8/24/1999

Study Objective: To determine if (1) adjuvant therapy with one week of continuous 5-FU given within 24 hours of a curative colon resection followed by 12 months of 5-FU/Levamisole is effective in prolonging the disease free interval and increasing survival in patients who are treated with 5-FU/Levamisole only. Endpoints include: treatment failure - as described by recurrence of local/regional or distant metastases - and survival. (2) To establish within ECOG a Central Tissue Repository for paraffin blocks and a frozen tissue bank.

Technical Approach: Patients with primary colon cancer will be randomized to either receive 7 days of continuous intravenous 5-fluorouracil (5-FU) within 24 hours completion of colon surgery or not to receive any perioperative chemotherapy. The only investigational part of this protocol is the administration of chemo-therapy during the period right after subjects colon operation. The operation and the use of 5-FU/levamisole are all standard treatment.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/073

Status: Ongoing

Title: SWOG 9300: A Randomized Phase II Evaluation of All Trans-Retinoic Acid with Interferon-Alfa 2a or All Trans-Retinoic Acid with Hydroxyurea in Patients with Newly Diagnosed Chronic Myelogenous Leukemia in Chronic Phase

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Mark E. Robson, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
03/04/1994

Est. Completion Date:
Mar 94

Periodic Review:
02/23/1999

Study Objective: 1). To estimate whether treatment of Chronic Myelogenous Leukemia (CML), with all-trans retinoic acid in combination with either hydroxyurea or interferon alfa-2a is sufficiently effective based on either hematologic or cytogenetic response, to justify its investigation in phase III trials. 2). To assess the toxicities associated with all-trans retinoic acid plus hydroxyurea or itnerferon alfa-2a in chronic phase CML.

Technical Approach: Patients qualifying for this study will be stratified by age (< 45 vs >=45), splenomegaly (present vs absent), prior hydroxyurea (yes or no), and ANC at diagnosis (<50,000 ul). Patients will then be randomized to one of two treatment arms as follows: Arm I: ATRA and HU or Arm II: ATRA and IFN. This randomization will be dynamically balanced to assure roughly equal numbers of patients within levels of the stratifying factors.

All patients in both arms will begin treatment with HU to control or keep the WBC <= 20,000/ul and platelets <=800,000/ul. All therapy will include allopurinol. Patients will receive this HUS treatment for a minimum of 21 days and a maximum of 42 days. Patients with WVA <= 20,000/ul, platelets <=800,00/ul, and no evidence of progressive splenomegaly after 21 - 42 days of HU will then bergin treatment on their assigned regimens. Patients who do not achieve a WBC <= 20,000/ul, platelets <=800,000/ul, and absence of progressive splenonegaly after 42 days will be removed from protocol treatment.

Arm I patients will receive ATRA 150/mg/M2/d x 7 days followed by 7 days rest and HU 500 mg qd adjusted to maintain WBC and platelets to predefined levels.

Arm II patients will receive acetaminophen 650 mg 1/2 hr before administration of IFN initiated a 3 MIU/M2/d 5 days/week escalated by 1 MIU/M2 each week to a maximum of 5 MIU/M2day/ and ATRA 150 mg/M2/d x 7 days followed by 7 days rest.

Treatment regimens will continue until the onset of accelerated or blast phase or relapse from CR or PR. Bone marrow aspiration and biopsy to monitor disease status are required at 3 and 6 months and every 6 months thereafter. Serial blood and urine specimens will be obtained for laboratory analysis.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 93/166

Status: Ongoing

Title: SWOG 9303: Phase III Study of Radiation Therapy, Levamisole, and 5-Fluorouracil versus 5-Fluorouracil and Levamisole in Selected Patients With Completely Resected Colon Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
09/03/1993

Est. Completion Date:
Oct 98

Periodic Review:
10/17/1997

Study Objective: To determine whether 5-FU, levamisole and radiation therapy results in superior overall survival when compared to 5-FU and levamisole without radiation therapy in the management of patients with completely resected pathologic stage T4BN0-2 colon cancer and selected patients with T3N1-2 colon cancer.

Technical Approach: This randomization clinical trial will compare radiation therapy, 5FU and levamisole with 5FU and levamisole in patients with completely resected colon cancer at high risk for local-regional recurrence and limited risk for system disease.

We will compare 5FU and levamisole, as delivered in the prior intergroup study, with one month of 5FU and levamisole followed by 5-5 1/2 weeks of 5FU, levamisole, and local-regional RT (45-50.4 Gy in 25-28 fractions), followed by 43 weeks of 5FU and levamisole.

Progress: This study was closed to patient entry 17 Dec 96. One patient was enrolled in this study at MAMC in FY 95 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/111

Status: Ongoing

Title: SWOG 9304: Postoperative Evaluation of 5-FU by Bolus Injection vs 5-FU by Prolonged Venous Infusion Prior to and Following Combined Prolonged Venous + Pelvic XRT vs Bolus 5-FU +Leucovorin + Levamisole Prior to and Following Combined Pelvic XRT + Bolus 5-FU + Leucovorin in Patients with Rectal Cancer, Phase III Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
05/06/1994

Est. Completion Date:
May 98

Periodic Review:
9/28/1999

Study Objective: 1) To compare the effectiveness of 5-FU by bolus injection vs. 5-FU by prolonged venous infusion given prior to and following combined pelvic x-ray (XRT) therapy + protracted venous infusion (PVI) vs. 5-FU by bolus injection plus LV plus LEV given prior to and following combined pelvic XRT plus bolus 5-FU plus LV in the treatment of modified Aster-Coller Stages B2, B3 and C rectal cancer. This will be evaluated in terms of survival and relapse-free survival.

2) To obtain descriptive information regarding relapse patterns and tolerance.

Technical Approach: Patients entering this study will be randomized to one of three treatment arms. Patients in all arms will receive pelvic radiotherapy. Those randomized to Arms A and B will receive concomitant 5-FU by PVI (225 mg/M2/d) during radiotherapy. Each patient will be randomly allocated to receive 5-FU +/- LV and levamisole for 2 months prior to and for 2 months following combined chemo-radiotherapy. Patients will be randomized to chemotherapy prior to and following chemo-radiotherapy as follows:

- a. Arm A: bolus IV injection of 5-FU alone
- b. Arm B: protracted venous infusion of 5-FU alone
- c. Arm C: bolus 5-FU + LV + levamisole before and after pelvic radiotherapy; bolus 5-FU + LV during pelvic radiotherapy.

After completion of all therapy patients will be followed every 4 months X 2 years, then every 6 months X 4 years.

Progress: Three patients have been enrolled in this study at MAMC. One patient died in FY 96, two continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/170

Status: Ongoing

Title: SWOG 9313: Phase III Comparison of Adjuvant Chemotherapy With High-Dose Cyclophosphamide + Doxorubicin vs Sequential Doxorubicin Followed by Cyclophosphamide in High-Risk Breast Cancer Patients with 0-3 Positive Nodes

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert B. Ellis, MC; MAJ Timothy P. Rearden, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
09/21/1994

Est. Completion Date:
Sep 98

Periodic Review:
9/28/1999

Study Objective: 1) To compare disease-free survival, overall survival, and toxicity of high-risk primary breast cancer patients with negative axillary lymph nodes or with one to three positive nodes treated with adjuvant high-dose chemotherapy with doxorubicin plus cyclophosphamide, versus high-dose sequential chemotherapy with doxorubicin followed by cyclophosphamide. 2) To obtain tumor tissue for biologic studies.

Technical Approach: Women with primary breast invasive adenocarcinoma, will be randomized to one of two treatments: 1) High dose doxorubicin + cyclophosphamide x 6 cycles, or 2) High dose sequential doxorubicin x 4 cycles, followed by high dose cyclophosphamide x 3. Women who are postmenopausal and have receptor + will receive Tamoxifen for 5 years.

Progress: The protocol was closed to patient entry 1 May 97. One patient has been enrolled in this study at MAMC and continues to be followed.

Detail Summary Sheet

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|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 94/107 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: SWOG 9321: Standard Dose Versus Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma, Phse III

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Patrick L. Gomez, MC; MAJ Timothy P. Rearden, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
05/06/1994

Est. Completion Date:
May 98

Periodic Review:
9/28/1999

Study Objective: 1. To perform a randomized trial, in newly diagnosed patients with symptomatic multiple myeloma (MM), of standard therapy versus myeloablative therapy, in order to examine whether the greater tumor cytoreduction effected by intensive therapy and manifested by higher incidence of complete remission translates into extended overall survival and progression-free survival.

2. To randomize responding patients with $\geq 75\%$ tumor cytoreduction to interferon-alpha 2b (IFN) versus no maintenance in order to evaluate the role of IFN in MM.

Technical Approach: Symptomatic patients of all stages of multiple myeloma with reasonable performance status will be randomized to high dose chemotherapy with autologous bone marrow transplant or standard VBMCP combination chemotherapy after induction VAD therapy. A required peripheral stem cell harvest will be done for those randomized to the ABMT arm for future high dose therapy if failure occurs. This will be an option for those randomized to the standard arm. Those patients that have an HLA compatible sibling donor will be eligible for allogeneic BMT. A second randomization will be done for those with continued greater than 75 percent regression of disease in the ABMT or standard chemotherapy arm while those receiving allo-BMT will be continued on GVHD prophylaxis.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 94/058 **Status:** Ongoing

Title: SWOG 9331 (E2192): Outcome Prediction by Histologic Grading in EST 1180 (SWOG 8294), Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; MAJ Patrick L. Gomez, MC; MAJ Mark E. Robson, MC; LTC Robert B. Ellis, MC; MAJ Richard C. Tenglin, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
02/04/1994

Est. Completion Date:
Nov 03

Periodic Review:
01/26/1999

Study Objective: 1) To evaluate the reproducibility of a combined histopathologic grading system of breast cancer. 2) To evaluate the ability of the grading system to predict time to treatment relapse (TTR) and survival. 3) To use multivariate analyses to evaluate the prognostic importance of the grading data relative to the other clinical and biological factors determined as part of SWOG 8294.

Technical Approach: This is a pathology study utilizing the patient set from SWOG 8294. Patients reviewed as part of that study (where cases with adequate specimens for flow cytometry were evaluated and provisionally graded) will be registered to this study. Slides will be reviewed by three investigators and cases will be grouped into 3 prognostic categories. The power calculation for testing the association of this grading system with survival will be based on the "2 degree of freedom" logrank test. The Cox proportional hazards model will also be used in the analysis to adjust the comparisons for effects of other factors.

Progress: This study closed to patient accrual 5 Oct 95. Seven patients were enrolled in this study in FY 94 and continue to be followed.

Detail Summary Sheet

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|------------------------|-----------------------|--------------------------|
| Date: 30 Sep 99 | Number: 95/147 | Status: Completed |
|------------------------|-----------------------|--------------------------|

Title: SWOG 9333: A Randomized Controlled Trial of Mitoxantrone & Etoposide vs Daunomycin & Cytosine Arabinoside as Induction Therapy in Patients Over Age 55 with Previously Untreated Acute Myeloid Leukemia

Principal Investigator: LTC Kenneth A. Bertram, MC

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| Department: SWOG | Facility: MAMC |
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Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

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|----------------------------------|--|---------------------------------------|
| Start Date: 06/16/1995 | Est. Completion Date: Jun 99 | Periodic Review: 06/19/1998 |
|----------------------------------|--|---------------------------------------|

Study Objective: To compare the complete remission (CR) rate, duration of survival and duration of relapse-free survival (time for CR until relapse or death) for patients aged 56 or older with acute myeloid leukemia (AML) treated with daunomycin (daunorubicin, DNR) and cytosine arabinoside (Ara-C) or with mitoxantrone (Mito) and etoposide. To assess the frequency and severity of toxicities and the durations of neutropenia, thrombocytopenia, and first hospitalization associated with the two induction chemotherapy regimens.

Technical Approach: Acute myelogenous leukemia in the elderly population is usually a fatal disease. Although complete remission rates are about 40-60% with standard chemotherapy induction, relapse rates are high and morbid and sometimes fatal toxicities will occur. This multi-center study aims to improve the remission rate and toxicity profile of induction chemotherapy for AML in the elderly using mitoxantrone and VP-16 and comparing it to standard daunorubicin and Ara-C followed by standard consolidation. Colony stimulating factors with GM-CSF will be given prophylactically as well as prophylactic antibiotics with Fluconazole, Ciprofloxacin, and Acyclovir. We expect 3-4 subjects per year and the entire multi-center recruitment is projected to be 100 per year.

Progress: This protocol closed to patient accrual 1 Dec 98. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 94/121

Status: Ongoing

Title: SWOG 9336: A Phase III Comparison Between Concurrent Chemotherapy Plus Radiotherapy, and Concurrent Chemotherapy Plus Radiotherapy Followed by Surgical Resection for Stage IIIA (N2) Non-Small Cell Lung Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): COL Daniel G. Cavanaugh, MC; COL Walter G. Graves, MC; LTC Maceo Braxton Jr, MC; LTC Blaine R. Heric, MC; MAJ Rahul N. Dewan, MC; LTC Steven S. Wilson, MC; MAJ Nyun C. Han, MC; LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; LTC Robert D. Vallion, MC; MAJ Patrick L. Gomez, MC

Start Date:
06/03/1994

Est. Completion Date:
Jun 98

Periodic Review:
5/25/1999

Study Objective: 1) Assess whether concurrent chemotherapy and radiotherapy followed by surgical resection results in a significant improvement in progression-free, median, and long-term (2 year, 5 year)s survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIa (N2-positive) non-small cell lung cancer.

2) Evaluate the patterns of local and distant failure for patients enrolled in each arm of the study, in order to assess the impact of the therapy on local control and distant metastases.

3) To obtain exploratory descriptive information on the relationship of tobacco use, alcohol use and dietary patterns on toxicity and outcomes in males and females.

Technical Approach: Patients with biopsy-proven Stage IIIa Non-Small Cell carcinoma will be randomized to one of two arms. Arm I and II patients will receive Induction Radiotherapy (45 Gy + concurrent induction chemotherapy (CT) of Cisplatin 50 mg/M2 IVPB days 1, 8, 29, 36 and VP-16 50 mg/M2 IVPB, days 1-5, 29-33. Arm I patients will be re-evaluated 2-4 weeks after completion of induction and Arm II will be re-evaluated 7 days before completion of induction. All patients, after re-evaluation, will proceed to Registration 2. If there is no evidence of local progression or distant metastases patients will be assigned options 3 or 4 (Arm I) or option 5 (Arm II). Option 3 consists of surgery plus 2 additional cycles CT starting 4-6 weeks postoperatively, Option 4 of 2 additional cycles CT at least 3 weeks after cycle 2 and Option 5 of continuing RT with no break and beginning 2 additional cycles of CT 3 weeks after cycle 2, day 8. RT boost field will be planned by CT scan. The major endpoints will be median, 2-year and 5- year progression-free and overall survival. Evaluation of patterns of relapse is a secondary endpoint.

Progress: Two patients were enrolled in this study in FY 95. Both patients are now deceased.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/024

Status: Terminated

Title: SWOG 9349: A Randomized Phase II Trial of CHOP with G-CSF Support or ProMACE-CytaBOM With G-CSF Support for Treatment of Non-Hodgkin's Lymphoma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ James S. D. Hu, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
11/18/1994

Est. Completion Date:
Nov 98

Periodic Review:
10/17/1997

Study Objective: To evaluate the effectiveness of the dose intense CHOP chemotherapy regimen with G-CSF support and the dose intense ProMACE-CytaBOM chemotherapy regimen with G-CSF support in previously untreated patients with intermediate and high grade non-Hodgkin's lymphomas. The effectiveness of the regimens will be based on the estimate of the complete response rate, the time to treatment failure, and ultimately overall survival. To assess the toxicities and side effects associated with the regimens. Also to further utilize the central serum and tissue repositories enabling clinicopathologic correlations with the results of studies on the material collected.

Technical Approach: This study attempts to assess whether dose intense CHOP or Promace-CytaBOM with growth factor support will have any effect on improvement of standard first line therapy in non-Hodgkins lymphoma. Ninety-eight patients will be accrued for each of the two arms. This number of patients will allow for both the complete response rate and probability of treatment failure two years after treatment to be estimated to within at most +/-0.10 for each measure. A successful outcome for either regimen is one that has a true probability of 60% or higher of patients being alive without disease at two years. No formal statistical comparisons between arms will be made.

Progress: This protocol closed to patient accrual 1 Jan 97. Three patients were enrolled in this study in FY 96, and continue to be followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/003

Status: Ongoing

Title: SWOG 9401: A Controlled Phase III Evaluation of 5-FU Combined with Levamisole and Leucovorin as Surgical Adjuvant Treatment Following Total Gross Resection of Metastatic Colorectal Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
10/21/1994

Est. Completion Date:
Oct 98

Periodic Review:
10/17/1997

Study Objective: To determine in patients who have undergone complete gross surgical resection of metastatic colorectal cancer whether postoperative adjuvant chemotherapy with a new regimen of 5-fluorouracil (5-FU) plus leucovorin plus levamisole will result in improved survival compared to postoperative adjuvant chemotherapy with a standard 5-FU plus levamisole regimen.

Technical Approach: Patients will be randomly selected to treatment Arm I or treatment Arm II. Arm I consists of the standard regimen of 5-FU given by rapid intravenous infusion for 5 consecutive days, plus levamisole given by mouth three times daily for three consecutive days every other week for one year. Arm II is a new chemotherapy regimen which adds leucovorin in addition to the 5-FU and levamisole. 5-FU and leucovorin are given by rapid intravenous injection for five consecutive days every four to five weeks for one year. Levamisole is given by mouth three times per day for three days in a row every two weeks during the first two months, then every 2-3 weeks for a total of one year.

Progress: This study closed to patient accrual 10 Sep 96. One patient was enrolled in FY 96 and continues to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/094

Status: Ongoing

Title: SWOG 9415: Phase III Randomized Trial of 5-FU/Leucovorin/Levamisole versus 5-FU Continuous Infusion Levamisole as Adjuvant Therapy for High -Risk Resectable Colon Cancer, Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Howard Davidson, MC; MAJ Timothy P. Rearden, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; CPT Diana S. Willadsen, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
03/17/1995

Est. Completion Date:
Feb 99

Periodic Review:
02/23/1999

Study Objective: To compare the effectiveness of bolus 5-FU, leucovorin, levamisole versus continuous infusion 5-FU, levamisole as adjuvant therapy for patients with Stage B2, C1 or C2 colon cancer. This will be measured in terms of overall survival. Disease-free survival will be a secondary endpoint.

Technical Approach: This trial is an intergroup trial involving the Southwest Oncology Group, Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. Based on previous experience with accrual to INT-0089, and assuming that roughly 1/3 of patients eligible for that study will be entered we anticipate an annual accrual of approximately 600 patients having curative resection of B2, C1, or C2 colon cancer. The primary objective of this study is to compare the survival in patients with high risk resectable colon surgery treated in an adjuvant setting with either 5-FU, leucovorin, levamisole or continuous infusion 5-FU, levamisole. The continuous infusion arm would be judged superior if the true increase in survival is 35%. A secondary endpoint will be disease-free survival. The dose of continuous infusion 5-FU selected for this study of 250 mg/m²/d is currently being piloted at an individual institution, and is lower than the common dose of 300 mg/m²/d, which required dose reductions in a previous pilot. In order to verify the appropriateness of this dose in the intergroup setting, we will evaluate toxicity and compliance in the first 40 patients randomized to the continuous infusion arm. Should the frequency of dose reductions or toxicities warrant concern, the study may be amended or temporarily closed while the continuous infusion therapy is reassessed.

Progress: One patient was enrolled in FY 97 at MAMC and continues to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 95/151

Status: Completed

Title: SWOG 9416: A Phase II Intergroup Trial of Induction Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer Involving the Superior Sulcus (Pancoast Tumors)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC

Start Date:
06/16/1995

Est. Completion Date:
Jun 99

Periodic Review:
06/19/1998

Study Objective: To assess the feasibility and toxicity of treating patients who have pancoast tumors without mediastinal or supraclavicular nodal involvement (T3-4, N0-1) with Cisplatin and VP-16 for two cycle, concurrent with a program of continuous, fractionated chest radiation followed by surgical resection and boost chemotherapy. To assess the objective response rate, resectability rate, and proportion of patients free of microscopic residual disease after such an approach.

Technical Approach: This oncology group protocol is a Phase II chemoradiation induction of superior sulcus (pancoast) tumors, non-small cell lung cancer followed by surgical resection. There are no extraordinary requirements of this study. This study should recruit 4-5 MAMC patients a year, 18 or older, and of either sex with selected Stage IIIa (T3, N0-1) or Stage IIIb (T4, N0-1) tumors involving the superior sulcus. The main goals of this study are to estimate the response, toxicity, and resectability rates following the combined chemoradiotherapy. We plan to accrue a total of 99 patients which will allow for estimation of rates and provide a sufficient number which will undergo resection. The precision of estimation of rates within stage IIIA or IIIB will depend on the breakdown by stage.

Progress: This protocol closed to patient accrual 1 Aug 99. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/134 **Status:** Ongoing

Title: SWOG 9419: Tumor Tissue Biopsy for Thymidylate Synthase Expression in Patients with Colorectal Cancer, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
08/15/1997

Est. Completion Date:
Apr 01

Periodic Review:
07/27/1999

Study Objective: 1) To measure thymidylate synthase (TS) expression by polymerase chain reaction in tumor biopsies prior to initiation of fluorinated pyrimidine based therapy in patients with disseminated colorectal cancer and correlate tumor response with level of TS expression; 2) To correlate TS expression in tumor tissue obtained during a potentially curative resection and disease-free survival in patients with Stage II and III large bowel cancer prior to receiving adjuvant therapy with 5-FU based regimen on targeted Southwest Oncology Group trials.

Technical Approach: Tissue samples from patients already on other SWOG protocols will be used. These protocols are: SWOG 9250, SWOG 9303, SWOG 9304, SWOG 9415, and SWOG 9420. Patient treatment will not be affected by registration on this protocol. TS expression will be measured using polymerase chain reaction. The following comparisons will be made: The relationship of TS expression (which may be the most important determinant of whether 5-FU will be effective) with tumor response in the disseminated setting and the relationship of TS expression with recurrence free survival in the post-operative adjuvant patients.

Progress: Five patients have been enrolled in this study at MAMC and continue to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/006

Status: Completed

Title: SWOG 9420: A Phase III Trial of Continuous Low-Dose Infusion Versus Intermittent High-Dose Infusion of 5-Fluorouracil in Patients with Disseminated Colorectal Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
10/18/1996

Est. Completion Date:
Oct 00

Periodic Review:
9/28/1999

Study Objective: 1) To determine whether dose intensity of 5-FU administered for treatment of disseminated colorectal cancer has an impact upon survival; 2) Compare response to 5-FU therapy by continuous low-dose versus high-dose intermittent infusion in thymidylate synthase gene expression within metastatic colorectal cancer tumor biopsies.

Technical Approach: Metastatic colorectal cancer is incurable. Intervention with chemotherapeutic drugs has shown response rates in the 35 to 50 percent range. Most of these regimens used a biological modulator such as leucovorin in conjunction with 5-FU. Few studies have shown an overall improved survival benefit with chemotherapy compared to observation alone, and in the studies that did show a benefit this prolongation of survival was small. Recently different routes of infusion have been utilized with 5-FU and it is felt that response rates are comparable if not better with continuous infusion as continuous infusion allows perhaps greater total dosage than if given by bolus or it may be related to the greater exposure of drug to tumor in the infusional treatments. This study proposes to compare a treatment incorporating 5-FU by protracted venous infusion compared to high dose weekly infusional 5-FU. The main endpoint is survival. In addition, this study will use data from tumor specimens to correlate Ts gene expression to response rates in the two arms.

Progress: This protocol closed to patient accrual 15 May 99. Three patients were enrolled in this study (FY 97) at MAMC; however all three are deceased.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/039

Status: Ongoing

Title: SWOG 9431: Cytogenetic, Molecular, and Cellular Biology Studies in Metastatic Melanoma Patients, Ancillary

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ Richard F. Williams, MC; MAJ Matthew P. Jones, MC; Rakesh Gaur, M.D.

Start Date:
01/16/1998

Est. Completion Date:
Jul 01

Periodic Review:
1/15/1999

Study Objective: (1) To characterize the frequency of non-random cytogenetic abnormalities in regional and distant melanoma metastases (AJCC Stage III or IV) and explore their association with clinical outcome of melanoma patients enrolled onto Southwest Oncology Group trials; (2) to characterize the frequency of specific genetic alterations at either the DNA, mRNA, or protein level and explore the association of these abnormalities with clinical outcome in patients with regional and distant metastases (AJCC Stage III or IV) who are enrolled on Southwest Oncology Group melanoma trials. The specific genes to be studied in this protocol will initially include: p16 (MTS1), nm23; (3) to characterize the host immunologic response to metastatic melanoma by determining whether the in vitro pattern of cytokine expression is consistent with specific subsets of T helper cells (TH1 or TH2) within melanoma deposits. To explore whether host immunologic response varies based on the site of metastatic disease and/or correlates with clinical outcome in patients enrolled on Southwest Oncology Group trials; (4) To obtain peripheral blood, sera and paraffin embedded tumor blocks from patients with metastatic melanoma to create a tissue, cell and sera bank for future studies.

Technical Approach: Following informed consent, tissue and blood samples taken from biopsies will be sent to a special laboratory for storage and scientific testing.

Progress: No patients were enrolled in this study in FY 99.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 98/113 **Status:** Ongoing

Title: SWOG 9444: Gastrointestinal Tumor Repository Protocol, Ancillary

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC

Start Date:
09/15/1998

Est. Completion Date:
Apr 02

Periodic Review:
8/24/1999

Study Objective: 1) To establish a central gastrointestinal tumor repository to serve as a tissue resource for current and future scientific studies, 2) to utilize the Southwest Oncology Group clinical database to perform clinicopathologic correlation with the results of those studies, and 3) to test new hypotheses as they emerge.

Technical Approach: Tissue samples obtained during biopsies will be forwarded to a special laboratory for storage and scientific testing.

Progress: One patient was enrolled in the study in FY 98. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/102

Status: Terminated

Title: SWOG 9445: Prognostic Factor Panel to Predict Preferred Therapy for Node Positive Postmenopausal Breast Cancer Patients (CAF vs Tamoxifen) (A Companion Protocol to SWOG 8814)

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
05/17/1996

Est. Completion Date:
Apr 96

Periodic Review:
05/22/1998

Study Objective: Overall objective is to correlate a panel of markers with clinical outcome and responsiveness to adjuvant therapy of node positive post menopausal breast cancer patients who participated in SWOG 8814. Specifically: 1) To evaluate if c-erbB-2 can allow the discrimination of node positive breast cancer patients who markedly benefited from adjuvant therapy with CAF (those with over-expressed c-erbB-2) from patients who did not obtain additional benefit from dose intensive CAF (those with low c-erbB-2 expression); 2) to measure a panel of prognostic factors (histologic and nuclear grade, estrogen and progesterone receptors, c-erbB-2, p53, Ki67, flow cytometrically determined DNA index and S-phase), angiogenesis, hsp27 (heat shock protein 27), nuclear and histologic grading, and immunohistochemically measured estrogen and progesterone receptors on node positive postmenopausal breast cancer patients; 3) to test the association of the factors listed above with biological and clinical features, including recurrence, survival and apparent efficacy of CAF chemotherapy in patients entered on SWOG 8814; and 4) to cut and store additional sections to allow the evaluation of markers that are mechanistically interesting but in the early development stage in breast cancer prognostic work which may be identified within the next 2-3 years, to be analyzed for prognostic significance and impact on the apparent benefit obtained by adjuvant CAF.

Technical Approach: This is a prognostic factor study attempting to find a correlation of several molecular, biochemical, and immunohistochemical, markers with outcomes in node positive breast cancer. It also seeks a correlation of C-erB-2 expression with benefits of adjuvant chemotherapy compared to tamoxifen therapy alone. The paraffin blocks will be submitted for all patients that are registered on SWOG 8814 who have adequate tissue to submit. It will be submitted to University of Texas Health Science Center in San Antonio, Texas.

Progress: This study closed to patient accrual 1 Oct 98. Two patients were enrolled in this study at MAMC in previous years. One patient died in FY 96 and the other patient continues to be followed. This protocol has been terminated at MAMC, as it meets the criteria for consolidation to SWOG 9808: Long Term Follow-up Protocol.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/094

Status: Completed

Title: SWOG 9446: Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-Cis Retinoic Acid in Head and Neck Cancer

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Luke M. Stapleton, MC; LTC Robert L. Sheffler, MC; MAJ John R. Caton, MC; LTC Robert B. Ellis, MC; MAJ James S. D. Hu, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; Rakesh Gaur, M.D.

Start Date:
05/17/1996

Est. Completion Date:
Mar 99

Periodic Review:
02/20/1998

Study Objective: 1) To test the efficacy of prolonged low-dose 13-cRA in reducing the risk of second primary tumors (SPTs) in patients who have had head and neck cancer controlled by surgery and/or radiotherapy; and 2) to evaluate the qualitative and quantitative toxicity of low-dose 13-cRA administered daily for three years.

Technical Approach: Head and neck cancer accounts for 5% of all cancers in the US with 45,000 new cases and 15,000 deaths annually. The standard treatment for early Stage I and II disease is either surgical excision or radiotherapy. However, the major cause of failure in early stage patients is the development of second primary tumors (SPT). The prognosis for patients with SPTs, especially of the lung, is very poor, with a median survival of 5 to 10 months, and less than 10% of patients survive more than 2 years. Toxicity data and the necessity for long-term therapy suggest the need for new chemoprevention approaches to controlling head and neck cancer. Based on recent data showing the greater effectiveness of low dose 13-cRA over B-carotene and mild, tolerable toxicity, we will investigate the efficacy and safety of long-term, low dose 13-cRA for preventing second primary tumors in early stage head and neck cancer.

Progress: This protocol closed to patient accrual 30 Jun 99. No patients were enrolled in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 97/059

Status: Completed

Title: SWOG 9503 (NCCTG 93-72-52): Phase III Trial of BCNU and Cisplatin Versus BCNU Alone and Standard Radiation Therapy Versus Accelerated Radiation Therapy in Patients with Grade 4 Glioma

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
02/21/1997

Est. Completion Date:
Feb 00

Periodic Review:
1/26/1999

Study Objective: To conduct a 2 x 2 factorial study to compare treatment outcomes in patients with glioblastoma multiforme treated with AHRT (accelerated hyperfractionated radiation therapy) + BCNU + CDDP and those treated with SRT (standard radiation therapy) + BCNU + CDDP. Primary goals: 1) To compare the survival distributions of patients treated with AHRT vs patients treated with SRT. 2) To compare the survival distributions of patients treated with BCNU + CDDP before, during, and after radiation therapy vs patients treated with BCNU during and after radiation therapy.

Technical Approach: The median survival for patients with high grade gliomas is about 9 to 11 months. The 5 year survival is less than 20% with standard therapy using surgery and radiation therapy. The use of chemotherapy combined with radiation therapy after surgery has shown some small benefit and is considered the standard therapy in most trials. As for radiation therapy, the standard fractionation scheme of 180 cGy has been tested with equivalent results shown in fashion over 15 days (4800 rads total dose). this study will compare 4 treatment Arms using BCNU + standard radiation therapy vs BCNU + accelerated hyperfractionation vs BCNU + Cisplatinum and standard radiation therapy vs BCNU + Cisplatinum and accelerated hyperfractionation for high grade gliomas. The toxicity of the two radiation therapy schedules are equivalent and the addition of Cisplatinum to BCNU may radiosensitive with radiation.

Progress: This protocol closed to patient accrual 18 Jun 99. No patients were enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 97/041 **Status:** Ongoing

Title: SWOG 9510: Evaluation of Topotecan in Hormone Refractory Prostate Cancer, Phase II

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
12/19/1996

Est. Completion Date:
Dec 00

Periodic Review:
11/19/1999

Study Objective: 1) To evaluate the response (CR and PR only) rate to topotecan in patients with metastatic, hormone-refractory prostate cancer. 2) To assess the qualitative and quantitative toxicities of topotecan administered in a phase II study to patients with metastatic, hormone-refractory prostate cancer.

Technical Approach: Prostate cancer that is refractory to standard first line hormonal manipulations including surgical and chemical orchiectomy has a median survival of about 6 months. The standard of care for hormone refractory prostate cancer is not defined. Response to chemotherapy is poor at about 10 to 15%. This study will assess the response rate and toxicities of Topotecan in hormone refractory prostate cancer patients. The schedule with a 21 day infusion had been tested at New York University and showed only some grade 3 and one grade 4 myelotoxicity. Other side effects are fatigue, nausea, vomiting and diarrhea.

Progress: This protocol closed to patient accrual 15 Aug 99. Three patients were enrolled in this study in FY 97 at MAMC and continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/057

Status: Completed

Title: SWOG 9512: A Phase III Study of Adjuvant Ganglioside Vaccination GM2-KLH/QS-21 Therapy vs. High-Dose Interferon Alfa-2b (Intron A) for High-Risk Melanoma (T4>4mm Primary or Regional Lymph Node Metastasis)

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC

Start Date:
03/23/1999

Est. Completion Date:
Mar 03

Periodic Review:
N/A

Study Objective: 1) To compare the effect of immunization with GM2-KLH/QS-21 on the relapse free survival of high-risk melanoma patients in relation to high dose interferon (IFN Alpha-2b). 2) To compare the effect of GM2-KLH/QS-21 immunization on overall survival of high-risk melanoma patients in relation to high-dose IFN Alpha -2b. 3) To characterize the quality of life on both arms of the study, to evaluate the long term effects of these regimens on quality of life, and to evaluate the differences in quality of life between patients receiving high dose IFN alpha-2b therapy and those receiving GM2-KLH/QS-21 therapy. 4) To determine the correlation between pre-existing or vaccine induced IgM antibody response against GM2 and relapse-free, as well as overall survival of high risk melanoma patients on the vaccine arm.

Technical Approach: Pts. must fulfill one of the following criteria: T4 N0 M0, T1-4 N1 M0, T1-4, N1-2 M0, Tx N1-2 M0, T1-4 N1-2 M0; pts. must have undergone an adequate wide excision of the primary lesion; no clinical, radiological/laboratory, or pathological evidence of incompletely resected melanoma or any distant metastatic dz; pts. must not have autoimmune disorders, conditions of immunosuppression or tx with systemic corticosteroids; no history of active ischemic heart disease or cerebro-vascular disease or congestive heart failure (NYHA class < 2); no prior RT, chemo, including infusion or perfusion therapy, or any immunotherapy including tumor vaccines, interferon, interleukins, levamisole or other biologic response modifiers; pts. must have soft tissue involvement by gross extranodal extension of tumor or any gross extracapsular invasion; ECOG PS 0-1; WBC > or = 3,000, platelets > or = 125,000, and hematocrit > or = 33%; AST, LDH, alk phosph and bilirubin < / = 2 x IULN and serum creat < / = 1.8 or BUN < / = 33; pts w/recurrent melanoma at regional lymph nodes must not have been previously entered into this study; pts. must have regional recurrence, in transit; pts w/ history of CNS demyelinating, inflammatory dz or hereditary or acquired peripheral neuropathy are excluded; pts must not have a history of severe allergic reaction to shellfish.

Progress: This protocol closed to patient accrual 15 Oct 99. No patients were enrolled at MAMC in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/095

Status: Ongoing

Title: SWOG 9514: Phase III Double-Blind, Placebo-Controlled, Prospective Randomized Comparison of Adjuvant Therapy with Tamoxifen vs. Tamoxifen & Fenretinide in Postmenopausal Women with Involved Axillary Lymph Nodes and Positive Receptors, Intergroup

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
04/19/1996

Est. Completion Date:
May 99

Periodic Review:
03/23/1999

Study Objective: 1) To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen or progesterone receptors who are treated with standard adjuvant tamoxifen vs. tamoxifen and fenretinide; 2) to gain wider experience and toxicity information on the combination of tamoxifen and fenretinide; and 3) to obtain tumor tissue from these patients for future biologic studies of relevance to this patient population.

Technical Approach: The present standard of therapy for node positive and ER positive post menopausal women is Tamoxifen alone. There are some studies that suggest that the addition of adjuvant chemotherapy combined with hormonal therapy will prolong relapse free and overall survival. However, not all patients, especially in the over 65 year old age group, can tolerate or want the significant side effects of chemotherapy. Thus, a less toxic regimen is needed. This study attempts to use a chemoprophylactic approach along with the standard Tamoxifen treatment for this group of patients. This new retinoid has shown some effectiveness in Phase I and II studies when given in combination with Tamoxifen to untreated metastatic breast cancer patients. This study will test its use in a Phase III randomized, prospective, placebo-controlled trial. The side effects seem to be fairly minimal except for night blindness which will be closely monitored during this trial.

Progress: One patient enrolled in FY 97, three patients enrolled in FY 98 at MAMC. All four patients continue to be followed.

Detail Summary Sheet

Date: 30 Sep 99

Number: 96/118

Status: Ongoing

Title: SWOG 9515: Phase III Intergroup Trial of Surgery Followed by (1) Radiotherapy vs. (2) Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; MAJ James S. D. Hu, MC; LTC Robert B. Ellis, MC; LTC Robert D. Vallion, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.; LTC Steven S. Wilson, MC; MAJ Nyun C. Han, MC; CPT Brent L. Kane, MC

Start Date:
05/17/1996

Est. Completion Date:
Jun 00

Periodic Review:
05/22/1998

Study Objective: 1) To determine the efficacy of concurrent cisplatinium and radiotherapy following surgical resection in patients who have advanced squamous cell carcinoma of the head and neck region; 2) to test whether the use of concurrent chemoradiotherapy following surgery increases locoregional control rates; 3) to determine if the patterns of first failure are changed by the use of concurrent chemotherapy; 4) to determine whether the use of concurrent chemoradiotherapy prolongs disease-free survival and/or overall survival; and 5) to compare the toxicity of concurrent chemoradiotherapy versus radiation alone in the postoperative setting.

Technical Approach: In head and neck squamous cell carcinomas with high risk features, there is a 20 to 50 percent recurrence rate after surgical resection. These high risk features include greater than 2 lymph nodes positive, extracapsular extension of cancer in lymph nodes, and positive resection margins. In the past, patients with these high risk features had received radiation therapy for local control. There is evidence, however, that the addition of cisplatinium with concurrent radiation therapy may help in local control. This data comes from in vitro as well as in vivo data showing cisplatinium may be a radiation sensitizer that may have synergistic local effects on malignancies. The study is a Phase III randomized study that will compare standard radiation therapy against concurrent cisplatinium and radiation therapy for resected squamous cell carcinoma of the head and neck. The added toxicities of neuropathy, nausea and emesis, renal failure, and bone marrow suppression are tolerable and can be prevented with medical measures. It is hoped that local recurrence will be reduced with this approach with minimal added toxicity.

Progress: One patient enrolled in this study in FY 96 at MAMC and continues to be followed. No patients were enrolled in FY 99.

Detail Summary Sheet

| | | |
|--|---------------------------------------|---------------------------------------|
| Date: 30 Sep 99 | Number: 99/019 | Status: Ongoing |
| Title: SWOG 9808: Long-Term Follow-Up Protocol: An Administrative Tool | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| <hr/> | | |
| Department: SWOG | Facility: MAMC | |
| <hr/> | | |
| Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC | | |
| <hr/> | | |
| Start Date: 10/20/1998 | Est. Completion Date: Indef | Periodic Review: 10/26/1999 |

Study Objective: To relieve the burden on Institutional Review Boards at Southwest Oncology Group Institutions for continuing review of protocols that are closed to patient registration, and on which no patients are currently receiving protocol treatment.

Technical Approach: When a study has been closed to patient accrual and patients have finished treatment, it still requires submission of data to the Southwest Oncology Group to report survival and remission status and occurrence of adverse events. On an annual basis, the Southwest Oncology Group Operations Office will notify the institutions as to which protocols are eligible for transfer to the Long Term Follow-Up protocol by periodically revising the list of applicable protocols. The institutional Principal Investigator or IRB will ultimately decide for the local institution whether the protocol should be included in this protocol or continue to be reviewed on its own. A report will be prepared and submitted for annual IRB review at individual institutions. This report will include title and date closed to patient entry.

Progress: This protocol includes consolidation of the following protocols at MAMC. All of the following protocols are closed to patient entry, the treatment phase is completed, and patients are being followed for survival data only: SWOG #s: 7406, 7433, 7436, 7510, 7713/14, 7808, 7827, 8216/38, 8269, 8313, 8410, 8417/19, 8516, 8600, 8736, 8809, 8892, 8957, 9019, 9125 and 9349.

During FY '99, SWOG #s 8854, 9008, 9031 and 9445 were also consolidated.

Detail Summary Sheet

Date: 30 Sep 99

Number: 98/112

Status: Ongoing

Title: SWOG C9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-1A Versus No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC

Start Date:
09/15/1998

Est. Completion Date:
Sep 02

Periodic Review:
8/24/1999

Study Objective: (1) To determine whether adjuvant treatment with MoAb 17-1A will improve the probability of overall and disease-free survival, and increase disease-free intervals in patients who have undergone resection of a Stage II (pT3NO or pT4bNO) colon cancer, (2) to evaluate a panel of prognostic markers, in order to correlate these measures with survival and recurrence after adjuvant therapy in patients who have undergone resection of a Stage II (pT3NO or pT4bNO) colon cancer. The specific aims of the companion study will be: (a) to determine whether alterations in the expression of cell cycle related genes (thymidylate synthase, p53, and the cyclin-dependent kinase inhibitors p21 and p27) predict the risk of survival and recurrence in this patient population, (b) to determine whether alterations in markers of metastatic potential-expression of DCC and measures of tumor angiogenesis (microvascular density and vascular endothelial growth factor expression)-predict the risk of survival and recurrence in this patient population, (c) to determine whether a marker of cellular differentiation-sucrase isomaltase-predicts the risk of survival and recurrence in this patient population, and (d) to determine whether interactions among these tumor markers identify subsets of patients with significantly altered outcome.

Technical Approach: Subjects will be randomized and assigned to one of two treatment groups following standard surgical removal of their tumor. Group 1 will receive standard care which is surgery with no additional therapy after the tumor has been removed. Subjects will continue with routine check-ups, doctor visits and test. Group 2 will receive five antibody treatments using MoAb 17-1A. Subjects will receive the drug by as an intravenous infusion over a 2-hour time period once each 28 days. This 2-hour infusion will be repeated every 4 weeks for a total of 5 treatments. During treatment, various blood tests and x-rays will be used to determine whether the disease has returned.

With subject's approval, tissue, body fluids, and other specimens obtained during the normal course of treatment will be forwarded to a special research laboratory for storage and scientific testing. Subjects will also be asked to complete a background information form to help define groups of patient being treated.

Progress: One patient enrolled in this study in FY 98 at MAMC. No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/014

Status: Ongoing

Title: SWOG C9741: A RANdomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide, or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Kenneth A. Bertram, MC; MAJ Matthew P. Jones, MC

Start Date:
12/15/1998

Est. Completion Date:
Dec 01

Periodic Review:
11/19/1999

Study Objective: (1) To compare sequential chemotherapy with Doxorubicin, Paclitaxel, and Cyclophosphamide to combined Doxorubicin and Cyclophosphamide followed by Paclitaxel for disease-free and overall survival, (2) to determine whether increasing the dose density of adjuvant chemotherapy (decreasing the interval between chemotherapy courses from 21 to 14 days) will improve disease-free and overall survival, and (3) to compare the toxicity for patients treated with sequential Doxorubicin, Paclitaxel, and Cyclophosphamide with toxicity for patients with concurrent Doxorubicin plus Cyclophosphamide followed by Paclitaxel at 14 and 21 day intervals.

Technical Approach: This is a randomized comparison of several aggressive combination chemotherapy regimens in the treatment of high-risk breast cancer due to positive lymph nodes. It compares the current standard of care for node positive breast cancer with several more aggressive variations. All patients will receive the same number of drugs and the same amount of drugs, but the order in which the drugs are given and the time between treatments (2 weeks versus 3 weeks) will be different. Arm 1, patients will receive Doxorubicin once every 3 weeks x 4 total doses followed by Paclitaxel once every 3 weeks x 4 total doses followed by Cyclophosphamide once every 3 weeks x 4 total doses. Arm 2, patient will receive Doxorubicin once every 2 weeks x 4 total doses followed by Paclitaxel once every 2 weeks x 4 total doses followed by Cyclophosphamide once every 2 weeks x 4 total doses. Arm 3, patients will receive Doxorubicin and Cyclophosphamide once every 3 weeks x 4 total doses followed by Paclitaxel once every 3 weeks x 4 total doses. Arm 4, patients will receive patients will receive Doxorubicin and Cyclophosphamide once every 2 weeks x 4 total doses followed by Paclitaxel once every 2 weeks x 4 total doses. G-CSF and Ciprofloxacin will be given concurrent with each arm to help ameliorate side effects of the treatments.

Progress: This study closed to patient accrual 31 Mar 99. Three patients were enrolled at MAMC in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/107

Status: Ongoing

Title: SWOG E1395: A Randomized Phase III Evaluation of Paclitaxel + Cisplatin Versus Cisplatin + 5-FU in Advanced Head and Neck Cancer

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC; MAJ Ines J. Sanchez-Rivera, MC

Start Date:
9/28/1999

Est. Completion Date:
Sep 02

Periodic Review:
N/A

Study Objective: To compare the efficacy and toxicity of Paclitaxel + Cisplatin with Cisplatin + 5-FU.

Technical Approach: Subjects will have a physical exam, blood tests, chest x-ray, and an EKG prior to being enrolled in this study and receiving treatment. These will be done to assess whether it is safe to administer treatment. After completion of initial studies subjects will be randomly assigned to one of two treatment arms: Paclitaxel + Cisplatin or Cisplatin + 5-FU. Treatment will be administered either in the hospital or as an outpatient. Before each cycle. Subjects will take 3 medications at 12 hours, 6 hours and 1 hour prior to receiving Paclitaxel to prevent any allergic reactions. These premedications include Decadron, Benadryl and Tagamet. Paclitaxel will be administered IV over 3 hours on day 1. On day 1 subjects will also receive Cisplatin, IV over 30 to 60 minutes. Prior to receiving the Cisplatin subjects will receive drugs to prevent nausea and vomiting. Intravenous fluids will be administered before, during and after the Cisplatin to help prevent kidney damage. This treatment will be repeated every 3 weeks.

No matter which treatment arm a subject is on, they will see their doctor prior to each cycle for a physical exam and blood tests. This is considered routine for anyone receiving cancer treatment and will be used to monitor side effects. In addition, tumor measurements will be done at least every other cycle to determine their response to treatment. Subjects will continue on their treatment as long as your tumor is not growing. If at any time your tumor starts to grow, they will be taken off the study. The primary endpoint is overall survival at 1 year. Secondary endpoints include comparison of response rates and toxicity.

Progress: This protocol was recently approved and has not yet started enrolling subjects.

Detail Summary Sheet

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|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/071 | Status: Ongoing |
| Title: SWOG E2197: Phase III Study of Adriamycin/Taxotere vs. Adriamycin/Cytosan for the Adjuvant Treatment of Node Positive or High Risk Node Negative Breast Cancer | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): MAJ Matthew P. Jones, MC | | |
| Start Date: 05/25/1999 | Est. Completion Date: Ape 03 | Periodic Review: N/A |

Study Objective: To determine whether Adriamycin/Taxotere will improve disease-free survival and overall survival when compared to Adriamycin/Cytosan in lymph node positive (1-3 positive nodes) and high risk lymph node negative breast cancer. To compare toxicity of Adriamycin/Taxotere to Adriamycin/Cytosan.

Technical Approach: This is multi-site study with randomization to one of two arms: Adriamycin/Taxotere (AT) or Adriamycin/Cytosan (AC). The dosages for the AT group: Adriamycin 60 mg/M2 IV and Taxotere 60 mg/M2 IV over 1 hour infusion every 3 weeks x 4 cycles. Cipro 500 mg PO b.i.d. starting Day 8 and continuing x 10 days. If a patient is allergic to Cipro, an alternative broad spectrum antibiotic may be used. Decadron 8 mg PO b.i.d., beginning one day prior to treatment with Taxotere and continued for two additional days; repeat q 3 weeks x 4 cycles.

The dosages for the AC group: Adriamycin 60 mg/m2 IV and Cytosan 600 mg/ml IV. Every 3 weeks x 4 cycles.

In both groups, post-menopausal patients who are ER and/or PR positive will receive Tamoxifen 20 mg PO daily x 5 years at the completion of chemotherapy. G-CSF: Patients who have an episode of febrile neutropenia should be placed on G-CSF according to ASCO Guidelines. Patients who have febrile neutropenia after a subsequent dose of chemotherapy in spite of G-CSF should have the chemotherapy doses lowered by 25%.

Progress: One patient was enrolled in this study in FY 99 at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/056

Status: Ongoing

Title: SWOG E3695: A Randomized Phase III Trial of Concurrent Biochemotherapy with Cisplatin Vinblastine, Dacarbazine, IL-2, and Interferon A-2b versus Cisplatin, Vinblastine, Dacarbazine (CVD) Alone in Patients with Metastatic Malignant Melanoma

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC

Start Date:
03/23/1999

Est. Completion Date:
Mar 01

Periodic Review:
N/A

Study Objective: 1) To determine whether this inpatient biochemotherapy is superior to CVD alone based on survival in patients with metastatic malignant melanoma. 2) To determine whether this inpatient biochemotherapy is superior to CVD alone based on response rate, response duration, time to treatment failure, percent CR and percent duration CR in patients with metastatic malignant melanoma. 3) To determine the feasibility of administering this in a biochemotherapy regimen to patients with metastatic malignant melanoma in a Cooperative Group setting. 4) To determine the toxicity of this inpatient biochemotherapy regimen relative to CVD alone in patients with metastatic melanoma treated in a Cooperative Group setting.

Technical Approach: Each subject will be randomized to one of two arms: Arm A (CVD): Treatment will consist of Cisplatin 20 mg/m² IV over 30 minutes. daily, days 1-4; Vinblastine 1.2 mg/m² IV daily, days 1-4; Dacarbazine 800 mg/m² IV over 1 hour, day 1 (only). Treatment can be administered in the outpatient setting. Cycles will be repeated every 3 weeks. Arm B (CVD + IL-2/IFN): Cisplatin 20 mg/m² IV over 30 minutes daily, days 1-4; Vinblastine 1.2 mg/m² IV daily, days 1-4; Dacarbazine 800 mg/ml FV over 1 hour, day 1 (only); IL-2 (Chiron) 9 MIU/m²/day by CIV, days 1-4 (96 hours); Interferon alpha 2b (Schering) 5 MU/ml sc days 1-5, 8, 10 and 12; G-CSF 5 ug/kg sc qd days 7-16. All patients will be admitted to the hospital on the morning of day 1. Interferon alpha-2b, the IL-2 infusion and the rehydration for cisplatin should be planned to begin around 3 PM. Patients will be discharged ASAP after day 5 with subsequent doses of interferon to be administered in the outpatient setting or at home. Cycles will be repeated at 3 week intervals.

Tumor measurements will be obtained prestudy and tumor response will be assessed after every 2 cycles. Patients with stable or responding disease will continue on therapy until disease progression, unacceptable toxicity or until they receive the maximum of 4 cycles.

All patients will have renal function tests, blood counts and a thorough physical examination (including neurologic examination) prior to each cycle of chemotherapy. If abnormalities are found, these parameters will be rechecked on a weekly basis and further therapy will be withheld until laboratory values and performance status return to within the eligibility criteria (i.e., ANC > 1500/mm³, Platelets > 100,000/mm³, creatinine < 1.5, bilirubin < 1.5 and Performance Status 0 or 1).

Progress: This protocol has not received final IRB approval; therefore no patients have been enrolled in this study at MAMC.

Detail Summary Sheet

| | | |
|------------------------|-----------------------|------------------------|
| Date: 30 Sep 99 | Number: 97/070 | Status: Ongoing |
|------------------------|-----------------------|------------------------|

Title: SWOG JBR.10 (NCIC CTG BR.10): A Phase III Prospective Randomized Study of Adjuvant Chemotherapy with Vinorelbine and Cisplatin in Completely Resected Non-small Cell Lung Cancer with Companion Tumour .

Principal Investigator: LTC Kenneth A. Bertram, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): LTC Robert L. Sheffler, MC; LTC Robert B. Ellis, MC; MAJ Richard F. Williams, MC; MAJ John R. Caton, MC; Rakesh Gaur, M.D.

Start Date:
03/21/1997

Est. Completion Date:
Mar 00

Periodic Review:
02/23/1999

Study Objective: 1) To compare the duration of overall survival (OS) between completely rejected patients with T2 NO, T1-2N1 non-small cell lung cancer (NSCLC) who have received either adjuvant chemotherapy with vinorelbine and cisplatin or observation alone. 2) To determine disease-free survival. 3) To confirm the prognostic significance of ras mutations when present in the primary tumor. 4) To provide a comprehensive tumor bank linked to a clinical data base for the further study of molecular markers in rejected NSCLC. 5) To measure and compare health related quality of life in both treatment arms throughout the study period. 6) To evaluate toxicity related to chemotherapy.

Technical Approach: The role of adjuvant chemotherapy in Non-small cell lung cancer is controversial. Most clinical trials have shown no benefit to adjuvant chemotherapy. In the early 80's the lung cancer study group showed some benefit with combination chemotherapy in terms of survival, however, the control arm was not a strict observational arm and contained a "biological response modifier" in it. Thus with recent improved survival in Stage IV lung cancer shown compared to observation, it is assumed that using platinum based therapies may enhance survival in patients that have completely rejected non-small cell lung cancer. In patients with rejected Stage I, II, and III Non-small cell lung cancer it is known that the long term survival rates are 50 to 60%, 30 to 50%, and 19 to 49% respectively. It is thus the aim of this study to assess whether adjuvant therapy with Cisplatin and Vinorelbine will improve survival and relapse free survival compared to observation. In addition to the above study, tissue samples will be sent to the University of Washington for evaluation of Ras mutations to assess its prognostic importance.

Progress: No patients were enrolled in FY 99.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/040

Status: Ongoing

Title: SWOG JMA.17: A Phase III Randomized Double-Blinded Study of Letrozole Versus Placebo in Women with Primary Breast Cancer Completing Five or More Years of Adjuvant Tamoxifen (SWOG)

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC

Start Date:
02/23/1999

Est. Completion Date:
Jan 03

Periodic Review:
N/A

Study Objective: Primary: To determine the disease-free survival and overall survival (all cause mortality) for women who have previously received ≥ 5 years of adjuvant tamoxifen, randomized to receive wither Letrozole 2.5 mg daily or placebo daily for 5 years.

Secondary: To evaluate the incidence of contralateral breast cancer. To evaluate the long term clinical and laboratory safety of Letrozole with special attention to: lipid profile as assessed by blood sampling (in a limited number of centers), cardiovascular morbidity and mortality (i.e. significant coronary heart disease, which includes myocardial infarctions and angina requiring percutaneous transluminal coronary angioplasty or coronary artery bypass graft, fatal and nonfatal strokes and all vascular deaths) as assessed by reported toxicity, the incidence of all bone fractures (with particular emphasis on hip and wrist fractures as indicators of osteoporosis) as assessed by reported toxicity, changes in bone density (in a limited number of centers), common toxicities as assessed by reported toxicity.

Third: To evaluate overall quality of life.

Technical Approach: This is a multi-centre, double-blind, placebo-controlled parallel randomized trial of the NCIC Clinical Trials Group, supported by Novartis. Patients will be stratified by: receptor status at diagnosis (positive, unknown), lymph node status at diagnosis (negative, positive, unknown), and a prior adjuvant chemotherapy (yes, no). Patients will be centrally randomized to receive one of the following treatments: Arm 1 (letrozole): 2.5 mg po daily x 5 years or Arm 2 (Placebo): po daily x 5 years.

Progress: Three patients were enrolled in this study in FY 99 at MAMC.

Detail Summary Sheet

Date: 30 Sep 99

Number: 99/072

Status: Ongoing

Title: SWOG S9626: A Phase III Trial of Placebo Versus Megestrol Acetate 20 mg/Day Versus Megestrol Acetate 40 mg/Day as Treatment for Symptoms of Ovarian Failure in Women Treated for Breast Cancer

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG

Facility: MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC

Start Date:
05/25/1999

Est. Completion Date:
Apr 03

Periodic Review:
N/A

Study Objective: 1) To compare the effectiveness and duration of the benefit of placebo and two dose levels of megestrol acetate in the reduction of severe and/or frequent hot flashes in patients with a history of adequate local and regional treatment of invasive breast cancer. 2) To document the effects, if any, of various dose levels of megestrol acetate on atrophic vaginitis and dyspareunia. 3) To evaluate the toxicity of two dose levels of megestrol acetate relative to placebo. 4) To evaluate the feasibility of accrual of patients to a placebo-controlled study evaluating megestrol acetate in patients with a history of invasive breast cancer which has undergone adequate local and regional treatment.

Technical Approach: Stage T1-3, N0-1, M0 infiltrating breast cancer treated with appropriate local and regional therapy; pts w/DCIS are not eligible; pts must have completed all primary therapy for breast cancer; pts taking tamoxifen must have started tamoxifen \geq 4 months prior to randomization; pts must have never participated in any NCI sponsored adjuvant breast protocols; pts must have completed Patient Daily Log of Hot Flashes for 7 days prior to randomization and must have recorded 10 or more hot flashes of any severity or 5 or more severe or very severe hot flashes; pt must not be pregnant; pts must not currently be on steroids or any other hormones except tamoxifen.

Progress: This protocol has not received final IRB approval; therefore no patients have been enrolled in this study at MAMC.

Detail Summary Sheet

| | | |
|---|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/037 | Status: Completed |
| Title: SWOG S9713: A Phase II Trial of Cisplatin/Etoposide and Concurrent Radiotherapy Followed by Paclitaxel/Carboplatin Consolidation for Limited Stage Small Cell Lung Cancer | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): MAJ Matthew P. Jones, MC | | |
| Start Date: 02/23/1999 | Est. Completion Date: Feb 03 | Periodic Review: N/A |

Study Objective: Assess the survival and failure-free survival in patients with limited stage small cell lung cancer treated with concurrent cisplatin and etoposide with chest radiotherapy followed by consolidative paclitaxel and carboplatin and to evaluate the response rates (confirmed plus unconfirmed) and toxicities associated with this regimen in this group of patients with limited small cell lung cancer.

Technical Approach: Cycle 1 of induction chemotherapy with cisplatin and etoposide begins day 1 concurrent with initiation of radiation, prior to the daily radiation, with Day 1 of chemotherapy and radiation beginning on a Monday. Cycle 2 will begin on Day 29. Following 2 cycles of induction chemotherapy and chest radiation, patients who have confirmed or unconfirmed stable disease, partial response or complete response based on restaging disease assessment performed 3-4 weeks after completing chest radiation, will receive 3 cycles of consolidation chemotherapy with paclitaxel and carboplatin. This treatment will be repeated every 21 days for 3 cycles.

Progress: This study met its accrual goals and closed 1 Aug 99. No patients were enrolled at MAMC.

Detail Summary Sheet

Date: 30 Sep 99 **Number:** 99/092 **Status:** Ongoing

Title: SWOG S9714: Phase II Trial of Paclitaxel by 96-Hour Infusion in Stage IIIB and IV Bronchioloalveolar Carcinoma (BAC)

Principal Investigator: MAJ David E. McCune, MC

Department: SWOG **Facility:** MAMC

Associate Investigator(s): MAJ Matthew P. Jones, MC

Start Date:
08/24/1999

Est. Completion Date:
Aug 02

Periodic Review:
N/A

Study Objective: 1) Assess the survival, progression-free survival and response rate in previously untreated patients with bronchioloalveolar carcinoma receiving intravenous paclitaxel by 96-hour continuous intravenous infusion. 2) Evaluate the side effects and overall toxicities of paclitaxel in 96 hour continuous infusion.

Technical Approach: All patients must have a biopsy-proven, incompletely resected or unresectable bronchioloalveolar carcinoma, Stage III B disease or Stage IV disease. Tumors may be multifocal or diffuse. Patients must have measurable or evaluable disease. All tests to assess measurable disease must have been performed within 28 days prior to registration. All tests to assess evaluable disease must have been performed with 42 days prior to registration. Patients must have a SWOG performance status of 0-2. All patients must not have received any prior chemotherapy, radiation therapy or biologics for lung cancer. All patients must have an alkaline phosphatase performed within 28 days prior to registration. No other prior malignancy is allowed except for the following: adequately treated basal cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for five years. Patients with a history of brain metastases are not eligible for this study. Women/men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. The descriptive factors for this study are: Weight loss based on the six months prior to registration (<5% versus >5%), Stage IIIB vs Stage IV, and LDH normal (\leq ULN) versus abnormal ($>$ ULN).

Progress: This protocol was recently approved and has not yet started enrolling subjects.

Detail Summary Sheet

| | | |
|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/058 | Status: Completed |
| Title: SWOG S9718: A Phase II Trial of Gemcitabine Plus Cisplatin in Patients with Extensive Small Cell Lung Cancer | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| Department: SWOG | | Facility: MAMC |
| Associate Investigator(s): MAJ Matthew P. Jones, MC | | |
| Start Date: 03/23/1999 | Est. Completion Date: Mar 03 | Periodic Review: N/A |

Study Objective: 1) Assess the survival of patients with extensive small cell lung cancer (SCLC) treated with a combination of gemcitabine and cisplatin. 2) Assess complete response rates (confirmed plus unconfirmed) of patients with extensive SCLC treated with combination of gemcitabine and cisplatin. 3) Evaluate the side effects and overall toxicities associated with the combination of gemcitabine and cisplatin.

Technical Approach: Patients must have histologically or cytologically confirmed, measurable or evaluable, diagnosis of extensive SCLC documented by CT, MRI, X-ray, physical exam or nuclear exam. All patients must have a pretreatment CT or MRI scan of the brain to evaluate for CNS disease. Patients with brain metastases are only eligible if the brain metastases are controlled. Patients must not have had prior systemic chemotherapy or biologic therapy for SCLC. At least two weeks must have elapsed since surgery (thoracic or other major surgeries) or completion or prior RT and patients must have recovered from all associated toxicities. Patients must have normal hematologic, hepatic, renal and cardiac function and a SWOG performance status of 0-2. Patients with significant clinical hearing loss must be willing to accept the potential for worsening of symptoms. Survival rate, response rate, side effects will be recorded for all subjects.

Progress: This protocol closed to patient accrual 1 Jun 99, prior to final IRB approval. No patients were enrolled at MAMC.

Detail Summary Sheet

| | | |
|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/059 | Status: Ongoing |
| Title: SWOG S9803: The Evaluation of Gemcitabine (Gemzar) in Resistant and Relapsing Multiple Myeloma, Phase II | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): MAJ Matthew P. Jones, MC | | |
| Start Date: 03/23/1999 | Est. Completion Date: Mar 03 | Periodic Review: N/A |

Study Objective: 1) To evaluate the confirmed complete remission, remission and partial remission rate for refractory myeloma treated with gemcitabine. 2) To evaluate the qualitative and quantitative toxicities of gemcitabine administered in a Phase II study.

Technical Approach: Subjects will receive 1000 mg/m² Gemcitabine (IV over 30 minutes, days 1, 8, and 15 every 28 days) until the study ends (approximately March 2003). Subjects will have Gemcitabine discontinued if any of the following occur: progress of disease, unacceptable toxicity, subject requests withdrawal, delay of more than 3 weeks in protocol treatment due to toxicity. All patients will be followed until death.

Progress: This protocol has not received final IRB approval; therefore, no patients have been enrolled in this study at MAMC.

Detail Summary Sheet

| | | |
|--|--|--------------------------------|
| Date: 30 Sep 99 | Number: 99/038 | Status: Ongoing |
| Title: SWOG S9832: Enhancing Well-Being During Breast Cancer Recurrence | | |
| Principal Investigator: MAJ David E. McCune, MC | | |
| Department: SWOG | Facility: MAMC | |
| Associate Investigator(s): MAJ Matthew P. Jones, MC | | |
| Start Date: 02/23/1999 | Est. Completion Date: Feb 03 | Periodic Review: N/A |

Study Objective: To assess the effectiveness of a telephone intervention delivered by breast cancer survivors on well-being of patients experiencing a first recurrence of breast cancer, to examine the impact of sociodemographic, clinical, and psychosocial predictors of well-being in patients experiencing a first recurrence of breast cancer and to examine changes in well-being over time since recurrence.

Technical Approach: This is a randomized study with two arms: 1) standard institutional support or 2) intervention support by Y-ME. Intervention will be delivered by women who are particularly well-qualified to provide support and information: breast cancer survivors who have themselves experienced recurrence. Subjects will be asked to fill out several questionnaires. The questions asked are about how they are feeling and problems they've experienced related to their cancer. A peer counselor (a women who has also had a recurrence of breast cancer) will be administering 4-8 questionnaires by phone over the course of 4 weeks for those in the intervention group. The subjects will also be asked to fill out a questionnaire 2 and 5 months after their least session. This data will analyzed to determine if the intervention was helpful.

Progress: This protocol has not received final IRB approval; therefore, no patients have been enrolled in this study at MAMC.

Index

(See Investigators for investigator names and
Protocol Number for protocols listed by number)

- 5-fluorouracil • 377, 381, 385, 386, 437, 440,
443, 444, 457, 460, 461, 462, 464, 468, 469,
473, 475, 480, 488, 490, 491, 498, 501, 503,
504, 518, 524
- 62nd Medical Group • 9, 242
- 6-mercaptopurine • 57, 394, 409, 412, 423, 446
- 6-thioguanine • 446
- abdominal aorta • 291
- academic ability • 109
- access to care • 121, 187, 190
- acetic acid • 124
- ACML • 392, 404
- ACOP • 390
- actinomycin D • 391, 418, 421, 430
- active duty • 9, 22, 27, 36, 120, 122, 128, 179,
180, 223, 246, 252, 301, 303, 305
- acute mountain sickness (AMS) • 115
- adenocarcinoma • 344, 346, 348, 357, 374,
377, 380, 381, 386, 437, 455, 457, 460, 481,
492, 524, 528, 530
- adrenomedullin • 43, 207
- Adriamycin • 374, 390, 391, 400, 403, 408,
441, 453, 478, 519
- adult primary care clinic • 36, 122, 361
- akathisia • 114
- albumin • 168, 218, 219
- albuterol • 166
- alpha-interferon • 392, 454
- alternative medicine • 284
- anesthesia • 103, 110, 202, 225, 279, 291,
305, 322, 325, 328, 329
- aneurysm
 - abdominal aortic (AAA) • 361
- angiostatin • 366
- animal study • 42, 308
- ankle • 50
- antibiotic • 54, 102, 160, 308, 450, 471, 495,
519
- APFT • 117, 179
- APO • 390, 402
- apoptosis • 195, 367, 369
- Ara-C • 402, 403, 404, 409, 412, 414, 423, 446,
448, 450, 471, 495
- arteriogram • 260
- aspiration • 26, 262, 264, 283, 407, 408, 410,
413, 414, 432, 466, 489
- asthma • 35, 111, 230, 247, 253
- asymptomatic • 27, 49, 232, 425
- AT • 519
- ATLS • 273
- attitudes • 36, 58, 122, 128, 159, 198, 211, 243,
260
- autoimmune • 47, 512
- autonomy • 180
- azimilide dihydrochloride • 137
- bacteremia • 26
- BCG • 338, 341, 437, 438, 441, 447, 477
- BCG immunotherapy • 338, 441, 447
- BCNU • 446, 510
- Behavior Assessment System for Children • 17,
35, 62
- BEP • 376, 382, 465
- biochemotherapy • 520
- biological parameters • 471
- bladder • 333, 338, 339, 341, 349, 355, 447,
509
 - overactive • 333
- bleomycin • 376, 382, 415, 416, 434, 439, 445,
448, 453, 465
- blood culture • 54, 160
- blood flow • 272, 313
- blood loss • 40, 196
- blunt trauma • 298
- bone marrow transplantation • 404, 414,
476
- bowel motility • 290
- bowel preparation • 291
- bracing • 317
- brain metastases • 173, 526, 527
- BRCA1 • 271, 370
- BRCA2 • 271
- bronchogenic • 173
- bronchoscopy • 60, 170, 171, 172, 328, 329
- CAF • 455, 457, 461, 476, 507
- calcium carbonate • 474
- calcium leucovorin • 448
- cancellous trough • 316
- cancer • 48, 59, 118, 145, 148, 149, 150, 151,
152, 153, 171, 188, 195, 245, 253, 271, 276,
283, 284, 340, 341, 344, 345, 346, 347, 349,
351, 352, 353, 355, 357, 366, 367, 369, 370,
373, 377, 378, 379, 380, 410, 418, 440, 444,

451, 452, 455, 457, 458, 459, 461, 462, 464,
 468, 469, 473, 474, 476, 480, 481, 483, 488,
 490, 491, 492, 494, 498, 500, 501, 503, 504,
 507, 508, 509, 511, 513, 514, 516, 517, 518,
 519, 521, 522, 523, 524, 525, 526, 527, 528,
 531
 bladder • 339, 341, 349, 355
 bowel • 503
 breast • 59, 148, 153, 188, 195, 245, 271, 366,
 367, 369, 370, 440, 444, 455, 457, 458,
 461, 476, 492, 494, 500, 507, 513, 517,
 519, 522, 523, 531
 cervical • 118, 377, 378, 381, 383, 526
 colon • 276, 370, 462, 474, 488, 490, 501,
 516
 colorectal • 145, 498, 503, 504
 endometrial • 370
 head & neck • 459, 464, 475, 508, 514
 lung • 60, 149, 171, 470, 485, 496, 502, 521,
 525, 526, 527, 530
 metastatic • 171
 non-small cell lung • 470, 485, 496, 502,
 521, 530
 ovarian • 59, 370, 373, 376, 379
 pancreatic • 524
 prostate • 340, 344, 345, 346, 351, 352, 353,
 355, 357, 452, 481, 483, 511
 rectal • 473, 491
 rhabdomyosarcoma • 397, 421, 429, 430
 testicular • 347
 thyroid • 283
 uterine cervical • 381
 captopril • 131
 carbon monoxide diffusing capacity • 361
 carboplatin • 509, 525, 530
 carcinoma
 clear cell • 380
 cardiac catheterization • 133
 carotid endarterectomy • 360
 casting • 310
 CCNU • 428, 437
 cell culture • 285, 287, 288
 cell cycle • 367, 516
 cervical intraepithelial neoplasia • 124
 cervical smears • 118
 chemoendocrine therapy • 455
 chemoprevention • 508
 chemoradiation • 468, 502
 chemoradiotherapy • 502, 514
 chemotherapy • 54, 149, 375, 376, 379, 381,
 382, 383, 385, 386, 388, 389, 391, 395, 398,
 400, 401, 404, 406, 409, 410, 412, 414, 415,
 416, 417, 419, 420, 421, 422, 423, 424, 425,
 427, 428, 429, 430, 434, 435, 436, 437, 438,
 439, 440, 441, 442, 443, 444, 445, 447, 448,
 449, 450, 451, 453, 454, 455, 457, 459, 461,
 462, 464, 465, 468, 469, 470, 473, 475, 476,
 478, 479, 480, 482, 488, 491, 492, 493, 495,
 496, 497, 498, 499, 500, 502, 504, 507, 510,
 511, 513, 514, 517, 519, 520, 521, 522, 525,
 526, 527, 528, 532
 perioperative • 488
 Chest tube insertion • 108
 CHF • 130
 Child Behavior Checklist • 17, 35, 62
 children • 35, 164, 188, 230, 231, 232, 243, 253,
 306, 308, 328, 329, 389, 390, 394, 395, 397,
 398, 400, 401, 404, 407, 409, 414, 417, 418,
 420, 421, 422, 423, 424, 428, 429
 cholesterol levels • 136, 361
 CHOP • 438, 448, 451, 497, 532
 chronic myelogenous • 392, 404
 Ciprofloxacin • 495, 517
 cirrhosis • 524
 cisapride • 290
 cisplatin • 375, 376, 377, 379, 381, 382, 383,
 395, 401, 406, 424, 428, 460, 464, 465, 470,
 475, 480, 496, 502, 510, 518, 520, 521, 525,
 527, 528, 530
 cisplatinum • 374, 442, 449, 469, 509, 514
 clavicle fractures • 20, 314
 clinical practice guidelines • 122
 clonidine • 115
 colposcopic visual impression • 123
 compression • 311, 313
 congenital • 47, 215, 306, 308, 418
 congenital defects • 418
 congestive heart failure • 132, 168, 185,
 418, 439, 512
 consolidation regimens • 446, 450
 contraception • 120
 contraceptive behavior • 125
 controlled compression cryotherapy • 237
 COPD • 111, 166, 169, 361
 Coreg • 130
 corneal shape • 51, 296, 303, 304
 coronary artery bypass • 169, 522
 cortical bone • 316, 319
 cost analysis • 157, 158

cost effectiveness • 266
 CoTA test strip • 145
 Cricothyroidotomy • 108
 cruciate ligament reconstruction • 40, 317
 CSF • 171, 407
 CT • 48, 54, 173, 255, 256, 257, 261, 262, 264, 496, 499, 524, 527
 CVAD • 478
 cyclophosphamide • 374, 379, 390, 391, 401, 403, 415, 417, 419, 420, 421, 424, 428, 429, 430, 440, 443, 444, 445, 446, 448, 457, 461, 476, 478, 492, 500
 cyclosporine • 414
 cytometry • 369, 393, 396, 397, 458, 459, 460, 461, 494
 cytoreduction • 493
 cytosine arabinoside • 399, 438, 450, 471, 495
 cytoxan • 418, 442, 445, 478, 519
 Dacarbazine • 520
 dactinomycin • 429, 446
 database • 22, 119, 123, 192, 202, 208, 327, 352, 398, 463, 506, 521
 daunomycin • 446, 495
 daunorubicin • 450, 471, 495
 DEPMEDS • 228
 depo-provera • 345
 depression • 39, 195, 247
 dexamethasone • 46, 445, 448, 478
 diabetes • 169, 253
 diphenhydramine • 114
DNA • 285, 292, 299, 347, 368, 369, 370, 371, 393, 396, 397, 408, 417, 428, 456, 458, 459, 461, 487, 499, 505, 507
 dopamine • 272
 doxorubicin • 391, 402, 406, 409, 415, 416, 418, 422, 445, 448, 457, 478, 492, 500
 drug therapy • 134, 185
 DT-60 • 228
 DVT • 345
 ECG • 107, 137, 362
 echocardiography • 27, 161
 education • 21, 23, 37, 58, 118, 120, 174, 180, 181, 184, 198, 242, 260, 271, 279
 elastase • 361
 electrical stimulation • 251
 emergency department • 36, 106, 122, 205
 emergency medicine • 106, 109, 260
 Emergency Medicine • 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115
 emergency room • 247
 emesis • 514
 endarterectomy • 360
 endoscopy • 42, 146, 225, 328, 329
 endotracheal intubation • 110, 268, 278
 endotracheal tube (ETT) • 364
 energy restriction • 140
 episiotomy • 222, 226
 epithelial • 326, 355, 444
 erectile dysfunction • 331, 336, 337, 350
 esotropia • 306
 etoposide • 382, 415, 416, 417, 418, 424, 465, 495, 525
 Eulexin • 348
 exercise • 108, 117, 132, 140, 179, 221, 223, 238, 240, 244, 268, 273, 278
 exercise induced • 117, 190, 221
 expression • 195, 207, 270, 284, 285, 355, 366, 367, 369, 370, 371, 406, 414, 503, 504, 505, 507, 516
 external fixation • 20, 314
 external fixator • 20, 314
 eye • 51, 295, 296, 298, 300, 304, 305, 322
 family practice • 33, 36, 118, 119, 122, 123, 260, 361
 female soldiers • 58, 120, 179, 190, 221, 223, 243
 femoral vein • 47, 312, 313
 fenretinide • 513
 fentanyl citrate • 151
 ferret (*Mustela putorius furo*) • 46, 110, 323
 fertility rates • 418
 fever • 54, 193, 410, 484
 fibrin glue • 280
 fibroblast • 42
 Finasteride • 483
 flutamide • 348
 FNA • 283, 432
 Fort Lewis • 12, 18, 19, 36, 120, 121, 122, 223, 244, 252, 267, 268
 fracture • 20, 265, 266, 286, 309, 310, 314, 522
 gallbladder • 144
 gallstones • 144
 gastric • 193, 272, 279, 468
 gastrin releasing peptide • 270
 G-CSF • 401, 412, 415, 419, 420, 422, 427, 497, 500, 517, 519, 520
 gene disorders • 418
 genetics • 46, 59, 245
 Gentamicin • 218, 219

GERD • 256
 germ cell • 60, 342, 376, 465
 goat (*Capra hircus*) • 108, 268, 273, 278, 308, 319
 Hawkins III wires • 263
 headache • 106, 223, 249, 251, 410
 health care resource use • 111
 Hemashield • 360
 hematuria • 117
 heparin • 218, 219, 315, 355
 Hepatitis • 142, 143, 157, 158, 261
 Hepatitis C • 142, 143
 hip arthroplasty • 315
 histologic grading • 507
 HIV • 232, 398, 407
 home exercise • 240
 hormonal manipulation • 511
 hormonal therapy • 381, 457, 513
 hormone refractory • 511
 hot flash • 345, 523
 HRCT • 256
 hydrocortisone • 399, 409, 423
 hydroxyurea • 377, 404, 489
 hyperbaric environment • 303
 Hypertension • 272, 297
 hypoxia • 51, 296, 304
 hysterectomy • 373, 378, 380, 381, 382, 383
 ifosfamide • 403, 406, 419, 422, 465
 IGF • 346
 immunity • 157
 immunotherapy • 338, 381, 437, 438, 439, 441, 447, 472, 512
 infantile spasms • 164
 infection • 42, 48, 54, 56, 102, 105, 112, 157, 192, 193, 232, 242, 244, 326, 398, 412, 471
 infection rates • 105
 influenza • 111
 inhaler • 174
 injuries • 19, 238, 239, 274, 295
 inodilator milrinone • 138
 interferon • 142, 341, 342, 407, 472, 520
 Interleukin-4 • 484
 interleukin-6 • 194, 218, 219
 interpersonal skills • 109
 intraocular pressure • 296, 298, 303
 Intron A • 142, 143, 512
 Investigator
 Abrams DA • 66
 Acosta N • 66
 Adams MC • 238
 Ahuja SK • 331, 332, 333, 334, 336, 337, 338, 339, 340, 341, 358
 Ainbinder DJ • 66, 71, 72, 295
 Alderman BW • 144
 Aldous WK • 63, 67, 68, 171, 172, 276, 282, 283, 284, 289, 347, 349, 368
 Allen RC • 334, 336, 337, 338, 339, 340, 341, 344, 358
 Allison S • 240
 Andersen CA • 274, 291, 360, 361, 362
 Anderson AJ • 65
 Anderson FD • 187
 Apodaca CC • 63, 65, 69, 70, 207, 208, 209, 211, 212, 213, 214, 215, 217, 218, 219, 225
 Archer W • 71
 Arendt MA • 68, 134, 137, 161
 Armstrong PJ • 361
 Arnold BF • 63
 Asato AJ • 69, 213
 Auber AE • 67
 Azarow KS • 67, 270, 273, 274, 275, 276, 277, 279, 281, 282, 283, 285, 287, 289, 290, 292, 321
 Babu SS • 432
 Baechler VR • 70
 Baer GR • 108
 Bagg MD • 346, 452
 Baker TM • 441, 442, 443, 444, 445, 446, 447, 448, 449, 450
 Baker TP • 370
 Bal GK • 311, 318
 Bandrowsky T • 102
 Barfield W • 64
 Barfield WA • 217, 233
 Barker AJ • 126
 Barrett JP • 126
 Bates G • 72
 Baum SE • 64
 Bauman JM • 71, 260, 266
 Beachy JC • 232
 Beaudoin DR • 235, 300
 Beck R • 65
 Beekley AC • 66, 270, 274, 275
 Beitler AL • 279
 Bell BK • 283
 Bell RH Jr. • 66
 Belville WD • 441, 447
 Bender GN • 66

Benson AJ • 71, 255
 Benson PJ • 111
 Benson WL • 373, 374, 375, 376, 377, 378,
 379, 380
 Bentsen CM • 114
 Berkenbaugh JT • 70
 Bertram KA • 148, 149, 150, 151, 152, 385,
 386, 419, 434, 435, 436, 437, 438, 439,
 440, 441, 442, 443, 444, 445, 446, 447,
 448, 449, 450, 451, 452, 453, 454, 455,
 456, 457, 458, 459, 460, 461, 462, 463,
 464, 465, 466, 467, 468, 469, 470, 471,
 472, 473, 474, 475, 476, 478, 479, 480,
 481, 482, 484, 485, 486, 487, 488, 489,
 490, 491, 492, 493, 494, 495, 496, 497,
 498, 499, 500, 501, 502, 503, 504, 505,
 506, 507, 508, 509, 510, 511, 513, 514,
 515, 516, 517, 521
 Bianchi AM • 190
 Bickley B • 72
 Billingsley J • 265
 Birch E • 65
 Blackburn ST • 186
 Blake TL • 109
 Blakeslee DB • 449
 Blanchard JR • 167
 Blaser J • 67
 Blaser JL • 319, 349
 Blough D • 230
 Bolger B • 327
 Bolt JL • 72, 164
 Borris TJ • 63, 102
 Borson S • 63
 Bouvier DP • 447, 451, 453, 454, 455, 457,
 460, 461, 462, 465
 Boyko EJ • 144
 Brady SM • 72, 304
 Braxton M • 263, 496
 Brencick M • 251
 Brisette MD • 70, 369
 Brosch LR • 179, 180, 181, 182
 Brown B • 171
 Brown FB • 65, 222
 Brown TA • 66, 71, 172, 276, 289, 290
 Bryant M • 123
 Bryson DR • 442, 445, 446, 448, 449, 450
 Buck CP • 105
 Buettner M • 113
 Buller JL • 65, 69, 70, 214, 221, 222, 332
 Bullock JM • 285, 366
 Burgess AW • 105
 Burke A • 358
 Burney RO • 202, 212
 Bushley DM • 296, 305
 Bybee LB • 242, 243
 Cadiz JL • 456, 459, 463, 464, 466, 467,
 468, 469, 470, 471, 473, 476, 478, 479,
 481, 485, 486, 487
 Calhoun BC • 64, 65, 69, 70, 144, 205, 207,
 208, 209, 210, 211, 212, 213, 214, 215,
 216, 217, 218, 219, 225
 Calkins MD • 364
 Cambier PA • 134
 Campbell CS • 65
 Campbell W • 70
 Cannon CP • 308, 309
 Caras WE • 68, 166, 171, 172
 Carpenter CT • 72, 308
 Carrougher JG • 145
 Carter ER • 65, 230
 Carter PL • 271, 279, 432
 Carter PS • 65
 Carter S • 70, 216
 Carter SL • 370
 Case B • 66
 Case S • 63, 68
 Casha LM • 71, 263
 Caton JR • 149, 150, 419, 472, 475, 480,
 484, 488, 492, 495, 497, 498, 499, 500,
 501, 502, 503, 504, 507, 508, 509, 510,
 511, 513, 514, 521
 Cavalcanti R • 198
 Cavanaugh DG • 469, 496
 Chambers SE • 186
 Champeaux AL • 325
 Chamusco RF • 134
 Chan AH • 441, 443
 Chilton JC • 194
 Chismire KJ • 297, 300
 Christensen ED • 65
 Chun BB • 66, 71, 298, 299, 300, 306
 Chun GG • 303
 Chun YH • 117
 Chung MH • 272
 Clark GW • 118, 125
 Clark JB • 120
 Clark K • 246
 Clark SJ • 189, 193

Cobb GA • 183
 Cobos E • 454, 455, 456, 457, 459, 460, 461,
 462, 463, 464, 465, 469, 473
 Collier HE • 134
 Collins DM • 63, 168
 Collins GJ • 360
 Colman LK • 446, 447, 448, 450
 Congdon JE • 443
 Connolly B • 66, 72
 Cook BA • 391, 393, 395, 396, 397, 398,
 399, 400, 401, 403, 406, 407, 408, 410,
 412, 414
 Cook JE • 244
 Coomes TR • 106
 Coonan K • 68
 Cooper R • 64
 Cooper RH • 160
 Coppit GL • 72, 321
 Costabile RA • 338, 339, 340, 341, 342,
 343, 344, 355, 358, 483
 Cote MG • 532
 Coughlin WF • 66, 71
 Cragun WH • 168, 361
 Crawford JV • 322
 Creedon JF • 239
 Crocker JD • 266
 Crothers BA • 432
 Cunningham PJ • 262
 Cupero TM • 72, 323, 324
 Cushner HM • 214
 Dabe IB • 440, 441, 442, 443, 444, 445, 446,
 447, 448, 449, 450, 451, 453, 462
 Dahlhauser KF • 296, 297, 300
 Dainty LA • 69, 203
 Dalrymple-Kaufman L • 128
 D'Amico M • 198
 Dance VD • 215, 223, 226
 Daniels D • 65
 Daniels JL • 271
 Davidson H • 386, 434, 435, 436, 437, 438,
 439, 440, 441, 442, 443, 444, 445, 446,
 447, 448, 449, 450, 451, 453, 454, 455,
 456, 457, 458, 459, 460, 461, 462, 463,
 464, 465, 466, 467, 468, 469, 470, 471,
 472, 473, 474, 476, 478, 479, 482, 484,
 485, 486, 487, 488, 489, 491, 492, 493,
 494, 496, 497, 498, 499, 500, 501
 Davis BE • 70, 231
 Davis BJ • 70
 Davis F • 71
 Davis G • 64
 Davis GD • 64, 65, 221, 222, 223, 225, 226,
 332
 Dawson KL • 65
 Decker C • 113
 Decker LA • 221, 222, 225
 DeHart MJ • 63, 71, 281, 284, 289, 292,
 355
 Della-Giustina DA • 105
 Depaul D • 179
 Dequattro N • 69
 Dettori JR • 64, 71, 237, 239
 Devine J • 66
 Devine JG • 318
 Dewan RN • 451, 468, 473, 496
 Deyle G • 240
 Dillard TA • 63, 64, 68, 161, 166, 167, 169,
 170, 171, 172, 174, 361
 Do NV • 63, 68, 140
 Dougherty RW • 237, 316
 Downey GO • 374, 377
 Downey TJ • 72, 325
 Drivdahl RH • 72
 Drotts DL • 68
 Dugel PU • 66
 Duncan MB • 72, 157, 158
 Dunning DM • 447, 448, 450
 Edmond CV • 327
 Edson T • 303
 Effenhauser RK • 66
 Eggebrotten WE • 273, 279
 Eisenhauer MD • 134
 Elliott DC • 66, 277, 278, 279, 286
 Ellis J • 64, 69
 Ellis RB • 149, 150, 369, 386, 419, 456, 459,
 463, 464, 466, 467, 468, 469, 470, 471,
 472, 473, 474, 475, 476, 478, 479, 480,
 481, 482, 484, 485, 486, 487, 488, 489,
 490, 491, 492, 493, 494, 495, 497, 498,
 499, 500, 501, 502, 503, 504, 508, 509,
 510, 511, 513, 514, 521
 Ellsworth JB • 331, 332, 333, 334, 336,
 337, 345, 350, 358
 Erickson RL • 246
 Eusterman VD • 322
 Evans KC • 332, 333, 334, 336, 337, 338,
 339, 340, 341, 358
 Evans MI • 69

Evans W • 69
 Everett A • 278
 Fagan J • 230
 Fairchok MP • 65, 232
 Fannin LA • 71
 Farrow DC • 146
 Faucette KJ • 388, 389, 390, 391, 392, 393,
 394, 395, 396, 397, 398, 399, 400, 402,
 403, 404, 406, 407, 408, 409, 410, 412,
 414, 415, 416, 417, 418, 419, 420, 421,
 422, 423, 424, 425, 426, 427, 428, 429, 430
 Fawcett D • 327
 Feber KM • 67
 Fife L • 106
 Fincher RK • 64
 Finger DR • 162, 176, 177
 Fink WA • 114
 Finney N • 63, 68
 Finney NS • 140
 Fitzgerald SE • 160
 Flores MS • 71
 Floyd DT • 66
 Flynn DM • 68, 120, 125
 Foglia LM • 209, 210
 Foley BJ • 180
 Foley JP • 349
 Forsythe MA • 128, 179
 Francis LE • 63
 Frank L • 106
 Frayer C • 70, 202
 Frayer CA • 65
 Frietch SR • 63
 Fuller FP • 107
 Fuller GM • 195
 Gagliano RA • 71, 275, 286
 Gagnon-Bailey S • 68, 170
 Gallucci BJ • 195
 Gant A • 286
 Garber M • 240
 Gates GA • 322
 Gaur R • 148, 149, 150, 151, 152, 171, 475,
 480, 503, 504, 505, 507, 508, 509, 510,
 511, 513, 514, 521
 George RK • 297, 300
 Gerlinger T • 66
 Gerlinger TL • 310, 319
 Gernon WJ • 449
 Giacoppe GN • 63, 167
 Gibbons RB • 64, 68, 71, 159, 160, 161, 260
 Gibbons RV • 64
 Gibson CR • 66
 Gilman MD • 256
 Gohdes D • 240
 Gomez PL • 386, 452, 454, 455, 456, 457,
 459, 460, 461, 463, 464, 465, 466, 467,
 468, 469, 470, 471, 473, 474, 476, 478,
 479, 481, 482, 485, 486, 487, 489, 490,
 491, 493, 494
 Gomez RR • 346
 Gonik B • 65
 Goolsby C • 344
 Grathwohl KW • 63
 Grathwohl KWA • 167, 170, 193
 Graves WG • 496
 Grazko MB • 71, 299
 Gries D • 64
 Groo SC • 353
 Gunzenhauser JD • 120, 125, 242, 243,
 245, 246, 247
 Haik BG • 66
 Han NC • 369, 480, 496, 514
 Hanaford B • 327
 Hancock E • 210, 225
 Hanisch RK • 63
 Hansberry KL • 348, 452
 Hansen BR • 280, 291
 Hansen EA • 71, 72, 297
 Haque MI • 274
 Hare JC • 198
 Harkins GJ • 64, 70
 Harrington BC • 121, 122, 124
 Harris MD • 63
 Harvey S • 180
 Heflin • 122
 Heiner SL • 189, 191
 Heitkemper MM • 189
 Henderson NE • 238, 239, 240
 Heric BR • 496
 Hermsmeyer JT • 237
 Hetz S • 282
 Hibbert M • 64
 Hibbert ML • 64, 65, 69, 203, 221, 222, 223
 Hicks KA • 137
 Hicks RD • 231, 249
 Hildreth PJ • 183, 184, 191
 Hinson RM • 70, 219, 233
 Hirota WK • 142, 143, 146, 157, 158
 Hite S • 198

Ho VB • 65, 432
 Hoeldtke NJ • 65, 70
 Holland RHG • 124, 208
 Hollifield RD • 66
 Holman JR • 63, 122, 123
 Holt CP • 271, 432
 Holt KR • 113
 Homann JF • 469
 Horne TA • 137, 185
 Howell JE • 169
 Hoyt RA • 64, 71
 Hu JSD • 149, 150, 386, 419, 456, 463, 466,
 467, 468, 470, 471, 472, 474, 475, 476,
 478, 479, 480, 481, 482, 484, 485, 486,
 487, 488, 489, 490, 491, 492, 493, 494,
 495, 497, 498, 499, 500, 501, 502, 503,
 504, 507, 508, 509, 510, 511, 513, 514
 Hume RF • 64, 65, 69, 70, 120, 125, 144,
 202, 205, 207, 211, 214, 216, 218, 219,
 225, 238, 367
 Hume RF • 70
 Hutton J • 240
 Hyers J • 182
 Inglis A • 328, 329
 Irvin TL • 176, 177
 Irwin RG • 402, 408, 416
 Jackson JL • 64, 159
 Jarvik G • 144
 Jenkins CS • 169
 Jennings BM • 180, 181, 184, 187, 214
 Johnson B • 63
 Johnson CA • 67, 361, 362
 Johnson RE • 67
 Johnstone FL • 72, 310, 318
 Jones DEC • 311
 Jones MP • 71, 148, 149, 150, 152, 153,
 235, 260, 385, 505, 506, 512, 515, 516,
 517, 518, 519, 520, 522, 523, 524, 525,
 526, 527, 528, 529, 530, 531, 532
 Jones P • 198
 Jordan RA • 159
 Jordan SA • 200
 Jorgensen JE • 168
 Joseph JC • 230
 Joyner BD • 333, 334, 336, 337, 338, 339,
 340, 341, 350, 358
 Judge K • 205, 208
 Kambiss SM • 70
 Kanar EA • 360
 Kane BL • 152, 480, 514
 Kane C • 349
 Kanne TJ • 66
 Katakkar SB • 439, 440
 Kavolius J • 282, 283
 Keadle DM • 256, 257
 Kee CC • 180
 Kelley RI • 65
 Kelly DA • 223
 Kiesling VJ • 447
 Kim DG • 66
 Kim NW • 349
 Kim SY • 324
 Kim-Ahn GJ • 71, 258, 260
 King JJ • 130, 131, 133, 135, 136, 137, 138
 Kinney JB • 65
 Kirk ME • 72, 317
 Koch DD • 66
 Kostner L • 198
 Kovac C • 64, 70
 Kowalski KL • 72, 312, 313
 Kozakowski MH • 454, 455, 457, 460, 461,
 462, 465
 Krause SW • 169
 Krauss MR • 246
 Kriebel G • 71
 Krober MS • 232
 Krolicki TJ • 71, 297, 299
 Krueger MV • 124
 Kull DH • 378
 Lacsina EQ • 65
 Ladwig ML • 225
 Lancaster AK • 120
 Lance RS • 67, 72, 283, 331, 333, 334, 336,
 337, 338, 339, 340, 341, 346, 347, 348,
 349, 350, 351, 352, 353, 354, 355, 357,
 358, 483
 Landry FJ • 167
 Landry RJ • 63
 Larkin HR • 70
 Larsen FW • 64, 65, 69, 70
 Larsen LH • 63
 Lauder TD • 65
 LeBrun CR • 162
 LeClerc KM • 68, 131, 132, 137
 Lee AG • 66
 Lee RB • 373, 374, 375, 376, 377, 378, 379,
 380
 Lee SP • 144

Leefers VJ • 169
 LeMar HJ • 140
 Lester KS • 252, 253
 Levy WC • 132
 Liening DA • 67
 Linskens P • 268
 Loan LA • 179, 181, 182, 184, 185, 186,
 187, 188, 189, 190, 191, 192
 Lombardi W • 64
 Low LL • 167
 Lynch S • 349
 Lyons MF • 66
 MacDonald DC • 63
 Mader TH • 66, 71, 72, 296, 297, 298, 300,
 301, 302, 303, 304, 305
 Madoff RD • 66
 Mahnke CB • 71
 Mais DD • 280
 Makuch R • 66
 Makuch RS • 266
 Malone KE • 247
 Maniscalco-Theberg M • 282
 Manuel K • 66
 Manzo AR • 259
 Marcantoni HW • 102, 103
 Marchant BG • 312, 313
 Marean A • 284, 355
 Marean AJ • 63
 Marinkovich G • 217
 Martin LS • 69, 70, 211, 216
 Martin MJ • 275
 Martin R • 282
 Martin RK • 368
 Marx JL • 66
 Mascette AM • 63, 107, 131, 134, 137
 Maslow AS • 65
 Matej LA • 63, 284
 Matekel RL • 240
 May EF • 66, 72, 297
 Mazzoli RA • 66, 71, 72, 297
 McCarthy MS • 192, 193, 194
 McClain R • 65, 70
 McClure G • 64, 222
 McCune DE • 149, 150, 151, 152, 153, 235,
 340, 385, 452, 506, 512, 515, 516, 517,
 518, 519, 520, 522, 523, 524, 525, 526,
 527, 528, 529, 530, 531, 532
 McDonald JM • 66, 71, 276, 277, 370
 McGranahan M • 71
 McHenry JA • 134
 McIlmail D • 110
 McKinley BT • 169
 McKinney LA • 72
 McLaughlin NE • 251
 McMann LP • 112
 McMann MA • 302, 305
 McManus JG • 68, 115
 McTiernan A • 247
 Merriam GR • 63
 Mesaros GJ • 327
 Messner E • 155
 Meyer CA • 256
 Meyers K • 332
 Michaud MJ • 72
 Migala A • 68
 Migala AF • 114, 115
 Miklos-Essenber ME • 310
 Miles KA • 253
 Miller MD • 66
 Miller SE • 131, 133, 137
 Miller TH • 195
 Millmann-Thorndike A • 251
 Minick P • 180
 Mino L • 63, 68
 Miser FW • 63
 Misko CA • 210
 Mitchell PH • 184
 Mizelle KM • 65
 Moe KE • 63
 Moffitt DR • 230
 Moonka R • 66
 Moore KH • 63, 65, 70, 144, 207, 218, 219,
 270, 277, 281, 284, 285, 287, 357, 366,
 367, 368, 369, 370
 Morales MS • 194
 Morgan RE • 71, 255
 Morris JT • 64, 155
 Morris MR • 460
 Moul JW • 349
 Moureau PM • 195
 Mulhall BP • 68, 160
 Mullon JJ • 174
 Munaretto JA • 67, 72
 Murphy GP • 357
 Murphy MS • 278
 Murray SP • 68, 71, 172, 255, 257, 260,
 261, 262, 263, 274
 Murray TR • 170

Musgrave S • 66
 Myers JB • 70, 171, 172, 191, 276
 Myers M • 64
 Myers MA • 432
 Mygrant BI • 183
 Napolitano PG • 217
 Nelson JM • 226
 Nelson ML • 71, 72, 296, 298, 299, 300,
 303, 304
 Nessel MJM • 367
 Newcomb S • 112
 Newman RJ • 65
 Newmark J • 64
 Nichols CA • 128
 Nielsen PE • 65, 70, 202, 203, 205, 208,
 209, 211, 212, 213, 214, 215, 216, 217, 218
 Nielsen RE • 67, 72, 274, 308, 319, 321
 Nieman D • 268
 Nindl BC • 71
 Noel JM • 290
 Noonburg GE • 314
 Norbeck JC • 332, 333, 348, 350, 452
 North J • 282, 283
 Norvell DC • 239
 Novia MV • 71, 72
 O'Bryant LK • 67, 321, 325
 O'Connor A • 270, 281, 285
 Offner PJ • 272, 280
 Olsen SB • 67, 257, 274, 291, 360, 361, 362
 Olson JP • 130, 131, 134, 137, 138
 O'Neill JT • 70
 Ono CM • 278
 O'Reilly KJ • 332, 333, 334, 336, 337, 338,
 339, 340, 341, 345, 347, 350, 357, 358
 O'Rourke TJ • 441, 443, 444, 445, 449
 Overly TW • 212, 213
 Pace SA • 107, 108, 109, 110, 111, 112
 Padilla JM • 191
 Palacio PE • 64
 Palinkas LA • 63, 68
 Palmer SR • 388, 389, 390, 391, 392, 393,
 394, 395, 396, 397, 398, 399, 400, 401,
 402, 403, 404, 406, 407, 408, 409, 410,
 412, 414, 415, 416, 417, 418, 419, 420,
 421, 422, 423, 424, 425, 426, 427, 428,
 429, 430
 Parmley VC • 71, 72, 297, 298, 300, 301,
 302, 303, 305
 Patience TH • 63, 71, 72, 203, 209, 245,
 257, 262, 296, 301, 347
 Patterson SJ • 109
 Payne C • 117
 Pekow C • 292
 Peniston JB • 64
 Perez R • 64
 Perez RP • 64, 65, 205, 208, 221, 222, 223,
 226
 Perious M • 198
 Perkins JA • 66, 67, 72, 321, 328
 Perkins TA • 232
 Peterson AC • 72, 334, 336, 337, 338, 339,
 340, 341, 358
 Peterson RP • 130, 138
 Phillips JO • 322
 Phillips WA • 464, 469
 Piecek R • 208
 Pierce B • 65
 Pierce BT • 70, 208, 209, 211, 212, 213,
 214, 215, 216, 217, 218, 219
 Pierce HI • 434, 435, 436, 437, 438, 439
 Pierce LM • 347, 355
 Pike JD • 167
 Pitcher JD • 66, 72, 259, 264, 312, 313,
 315, 318
 Place RJ • 226
 Plumlee CL • 191
 Plymate SR • 72, 346
 Porter C • 66
 Porter CA • 279, 283
 Potter H • 316
 Potter JH • 125
 Potter ME • 124, 225, 373, 374, 375, 376,
 377, 378, 379, 380, 381, 382, 383
 Price C • 364
 Prinz PN • 63
 Pulos E • 65, 71, 184
 Puttler EG • 72
 Qabar AN • 284, 366, 368, 371
 Quinn KL • 173
 Quinn MW • 63, 68, 161, 174
 Quintanilla A • 68, 196
 Ramakrishna RR • 68, 170, 171, 172
 Randall DC • 68
 Rawlings JS • 232
 Raymond WR • 71, 72, 295, 297, 306
 Rearden TP • 386, 466, 470, 472, 474, 476,
 479, 482, 484, 485, 486, 487, 488, 489,

490, 491, 492, 493, 494, 497, 498, 499,
 500, 501
 Reddoch SE • 391, 393, 395, 396, 397, 398,
 399, 400, 401, 402, 403, 404, 406, 407,
 408, 409, 410, 412, 414, 415, 416, 417,
 419, 421, 422, 423, 428, 429
 Reece WB • 152
 Reed HL • 63, 68, 140
 Reedy K • 63, 68
 Reedy KR • 63
 Regan NA • 174
 Regnery HL • 65
 Reinschmidt JP • 71, 263
 Rice MM • 205
 Rice MS • 63
 Rich L • 298
 Richards TL • 64
 Robson L • 66
 Robson Me • 476
 Robson ME • 386, 466, 470, 474, 479, 481,
 482, 485, 486, 487, 489, 490, 491, 493, 494
 Roe TM • 134
 Ronningen LD • 332, 333, 345, 350
 Root SS • 142, 143, 146, 157, 158
 Roth B • 66
 Roth BJ • 71, 168, 169, 170, 173, 174, 193,
 260
 Rovira MJ • 71, 173
 Rowbotham LL • 198
 Royer MC • 172, 262, 282
 Rudman NT • 108, 109, 110
 Ruegemer JL • 67
 Ruiz HE • 67, 331, 332, 333, 340, 348, 350,
 358
 Runkle GP • 126
 Russell AA • 228
 Ruttkay D • 344
 Ryder M • 240
 Sahn DJ • 65
 Salafia C • 70
 Salafia CM • 216
 Salerno SM • 168
 Salminen ER • 65
 Sanborn CK • 280, 281
 Sanchez-Rivera IJ • 153, 235, 518, 532
 Sanford EG • 71, 72, 295, 302
 Santee V • 124
 Sawin RS • 270, 281, 285, 287, 289, 292
 Scanlan JM • 63
 Schachter DT • 131, 133, 135, 137, 138
 Schaefer L • 66
 Schallenberg G • 144
 Scheer SP • 266
 Schlicher ML • 64
 Schmidt BD • 196
 Schulte SJ • 144
 Schwartz BF • 452
 Schweitzer D • 65
 Sebesta JA • 270, 282, 283, 284, 285, 286,
 287, 292
 Seip R • 63, 68
 Seymour SD • 223, 225
 Shaffer N • 264
 Sharpe GC • 217
 Shaves ME • 152, 480
 Sheffler RL • 148, 149, 150, 151, 152, 454,
 455, 456, 457, 459, 460, 461, 463, 464,
 465, 467, 468, 469, 471, 473, 475, 478,
 480, 481, 503, 504, 505, 507, 508, 509,
 510, 511, 513, 514, 521
 Shepherd PJ • 265
 Sherman R • 64
 Sherman RA • 65, 66, 190, 221, 222, 223,
 249, 309
 Shry EA • 361
 Sierra RD • 447, 450
 Silva AB • 72, 275, 324, 325, 328, 329
 Silvasy AM • 68, 196
 Simon R • 205
 Simurdak JH • 70
 Sipperley JO • 66
 Sluis D • 327
 Smith DV • 432
 Smith PN • 208
 Soderdahl DW • 331, 348, 350
 Song KM • 308
 Sonkin PL • 66
 Souter V • 211
 Sowray PC • 446, 450, 454, 455, 456, 457,
 459, 460, 461, 463, 464, 465, 467, 471,
 473, 478
 Spahn J • 198
 Spence CR • 257
 Spigner C • 121
 St.Pierre P • 66
 Stager D • 65
 Staggers N • 184
 Stajduhar KC • 63, 134

Stang J • 240
 Stapleton LM • 150, 386, 419, 452, 456,
 463, 464, 466, 467, 468, 469, 470, 471,
 472, 474, 476, 478, 479, 481, 482, 484,
 485, 486, 487, 488, 489, 490, 491, 492,
 493, 494, 495, 496, 497, 498, 499, 500,
 501, 502, 508
 Steedman JT • 315
 Steele SR • 274
 Steigerwald L • 164
 Stephan MJ • 65, 72
 Stephenson SR • 396, 400, 401
 Stone MD • 441, 442, 444, 445, 446, 449
 StPierre P • 68, 196, 237, 314, 316, 317,
 319
 Stracener JC • 283, 432
 Stredney D • 327
 Strong JS • 64, 159
 Stuessi KA • 63
 Stutz FH • 435, 436, 437, 438, 439, 440,
 441, 443, 444, 445, 449
 Stutz, FH • 434
 Sudduth RH • 142, 143, 145, 146
 Sullivan NR • 162
 Sullivan SD • 230
 Sweeney JK • 233
 Taquino LT • 186
 Taylor C • 268
 Taylor TO • 452
 Tencer AF • 308
 Tenglin RC • 386, 456, 463, 466, 467, 468,
 470, 471, 474, 476, 478, 479, 481, 482,
 485, 486, 487, 489, 490, 491, 493, 494
 Terrio HP • 245
 Terrio J • 112
 Thach AB • 66
 Thegerge MM • 283
 Thomas KA • 186
 Thomas RW • 67, 72
 Thrasher JB • 67, 331, 332, 333, 345, 346,
 347, 348, 349, 350, 351, 352, 357, 452, 483
 Timmons JH • 66, 148, 257, 263
 Toivola B • 63
 Tollefson DFJ • 67, 257, 274, 291, 312,
 313, 360, 361, 362
 Tomasini C • 72
 Torres MF • 72, 300
 Torres MF • 72
 Tracy DP • 68, 172, 263, 274
 Trementozzi DP • 65
 Tribble D • 244
 Trione MA • 114
 Trombetta LJ • 275, 285, 287, 289, 290,
 291, 292
 Truxal AR • 71, 297, 299
 Tsuchida A • 66
 Tsuchida AM • 142, 143, 144, 145, 146,
 157, 158, 261, 282
 Turner CE • 72
 Turner CG • 314
 Twomey PA • 346
 Ulnick KM • 72, 321
 Vaccaro JA • 465
 Vallion RD • 150, 386, 419, 466, 470, 472,
 474, 476, 479, 481, 482, 484, 485, 486,
 488, 489, 490, 491, 492, 493, 494, 495,
 496, 497, 498, 499, 500, 501, 502, 507,
 508, 513, 514
 Valrey MK • 106, 113
 Vandenberg JT • 68, 108, 110, 113, 114
 Varma MK • 256, 264
 Vinson DR • 68, 114
 Vitaliano PP • 63
 Vorono AA • 102
 Vos JA • 70, 292
 Wagner RK • 65, 69, 70, 207, 208, 209,
 212, 213, 214, 215, 217, 218, 219, 225
 Wagner RK • 70
 Walker WO • 65, 231
 Walsh DW • 261
 Wang R • 111
 Ward TP • 66
 Ware JL • 72
 Watanabe FU • 193
 Watts DM • 279
 Weber CR • 63, 102, 103
 Wedmore IS • 68, 115
 Weghorst S • 327
 Weichmann D • 290
 Weiss A • 306
 Weiss KB • 230
 Welch R • 308
 Wempe JM • 246
 Westphal KW • 347
 Wettlaufer JN • 348, 452
 White L • 72, 298, 302, 304
 Whitney JD • 189, 191
 Wickizer TM • 121

Wicks AB • 63, 137
 Wiet GJ • 327
 Willadsen DS • 386, 472, 474, 481, 482,
 484, 487, 488, 489, 490, 491, 492, 493,
 494, 497, 498, 499, 500, 501
 Williams MV • 65
 Williams RF • 148, 149, 150, 151, 152, 367,
 369, 370, 419, 472, 475, 480, 484, 488,
 490, 492, 495, 497, 498, 499, 500, 501,
 502, 503, 504, 505, 507, 508, 509, 510,
 511, 513, 514, 521
 Williams SC • 71, 255, 260, 263
 Williamson RV • 318, 319
 Williard WC • 66, 71, 274, 276, 279, 282,
 283, 432
 Wilson MJ • 131
 Wilson S • 64
 Wilson SK • 181, 187
 Wilson SS • 173, 451, 473, 480, 496, 514
 Wink JS • 136
 Winn B • 327
 Winter D • 230
 Winter MG • 166, 174
 Wittich AC • 65
 Woerman A • 249
 Wong M • 64
 Wong MF • 64
 Wood S • 202, 212
 Woodman PJ • 222, 223, 225, 226
 Woods NF • 188
 Woolman BA • 126
 Wright JR • 63, 68, 71, 72, 218, 366, 370
 Wright K • 65
 Wroblewski KJ • 66, 72, 300
 Yagel R • 327
 Yamamoto K • 144, 145, 256
 Yancey MK • 217
 Yancy MK • 65
 Yandel ML • 130, 137, 138
 Yeager CL • 214
 Yetter JF • 118, 121, 123
 Yoder LH • 183
 Yoest SM • 257
 Young AL • 285
 Young SYN • 71, 247
 Youngberg RA • 66, 258, 259, 264, 265,
 266
 Zhou Q • 182
 Zimba FA • 173
 Zimbelman E • 64
 ipratropium bromide • 166
 irradiation • 149, 377, 381, 416, 419, 424,
 479, 482, 530
 ischemia • 53, 277, 299
 keratectomy
 phototherapeutic • 298
 knee • 50, 189, 240, 264, 312, 317
 Korea • 252
 LASIK • 51, 61, 304
 L-asparaginase • 399, 412, 423, 446
 Latanoprost • 297
 length of stay • 26, 180, 183, 233, 290
 lesions • 57, 282, 432, 530
 letrozole • 148, 522
 leucovorin • 386, 445, 448, 462, 473, 498, 501,
 504
 leukemia • 54, 371, 388, 389, 392, 399, 403,
 404, 408, 410, 412, 413, 423, 438, 446, 450,
 471, 495
 lymphoblastic • 399, 403, 409, 423, 446
 levamisole • 438, 439, 462, 473, 488, 490, 491,
 498, 501, 512
 LH • 344, 457
 life-saving procedures • 108
 liver • 47, 157, 247, 277, 279, 286, 451, 469
 lymph nodes • 172, 276, 373, 377, 380, 381,
 386, 461, 472, 476, 492, 512, 514, 517
 lymphadenectomy • 373, 381, 452
 lymphadenopathy • 261
 lymphoblastic • 388, 399, 403, 408, 409, 423,
 446, 451
 lymphoma • 388, 390, 398, 400, 402, 409, 435,
 438, 445, 448, 451, 454, 456, 463, 478, 484,
 487, 497, 532
 Madigan Army Medical Center • 7, 12, 18,
 26, 46, 128, 134, 174, 181, 183, 203, 222, 279
 Madigan Consolidated Education Division • 127
 magnesium • 106, 126, 135, 219
 magnesium oxide • 126
 magnesium sulfate • 135, 219
 mammography • 121, 245
 mastectomy • 280
 m-BACOD • 445, 448
 MDX-RA • 300
 mechanical devices • 221
 medical facility • 484
 melphalan • 375
 memory • 39, 140

Mental Disorders • 159
 Mesna • 401, 465
 metered dose • 166, 174
 methicillin resistant • 155
 methotrexate • 389, 394, 399, 402, 403, 406,
 409, 410, 412, 413, 423, 440, 442, 443, 444,
 445, 446, 448, 461
 Migraine • 249
 military • 18, 20, 22, 24, 27, 37, 55, 58, 121,
 128, 140, 153, 158, 180, 182, 184, 187, 205,
 210, 217, 244, 246, 247, 301, 303, 305, 352,
 353, 394, 402
 military occupational specialty • 22
 military women • 58
 mitomycin-C • 42
 mitoxantrone • 495
 MMPI-2 • 252
 molecular biology • 368
 molecular studies • 393, 422, 456, 487
 monoclonal antibody • 287, 355, 371, 397,
 478, 532
 mood • 39, 140
 MOPP • 434, 439, 453
 morbidity • 130, 164, 169, 209, 217, 256, 295,
 378, 416, 417, 425, 469, 522
 morphine • 151, 152
 morphine sulfate • 151, 152
 mortality • 26, 130, 131, 134, 135, 137, 138,
 164, 169, 180, 209, 217, 418, 469, 522
 MRI • 47, 173, 264, 265, 266, 316, 524, 527
 MTP-PE • 406
 multicenter study • 151, 152, 176, 177, 232,
 297, 331, 340, 348, 360, 495
 multidrug resistance • 414, 478
 muscle
 leg • 126
 myelogenous • 54, 392, 404, 495
 myeloid • 408, 471, 495
 myeloid leukemia • 471, 495
 myocardial infarction • 53, 107, 131, 135, 137,
 345, 522
 myopia • 301, 305
 natural history • 130, 443
 Natural Killer Cell Activation • 195
 nausea • 511, 514, 518
 neonatal • 34, 186, 208, 209, 215, 217, 233
 neuroblastoma • 270, 281, 285, 287, 289, 292,
 396, 425
 neuroblastoma cells • 270, 396
 niacin • 136
 NICU • 208, 233
 node positive • 444, 507, 509, 513, 517, 519
 norepinephrine • 132, 189
 Nosocomial pneumonia • 26
 nursing • 34, 106, 180, 184, 185, 186, 231, 242,
 290, 291, 524
 oncogenes • 369, 499
 Orb scan • 302
 orbital • 295, 298, 430
 Osmolite • 194
 osteoarthritis • 240
 osteotomies • 102, 308
 Osteotomy • 258
 Oxepa • 194
 oxygen kinetics • 132
 oxygen therapy • 191
 oxygen uptake • 132
 P32 • 379
 p53 • 17, 41, 61, 276, 369, 408, 409, 507, 516
 mutation • 41, 276
 paclitaxel • 235, 509, 525, 526, 530
 pain • 20, 53, 54, 106, 107, 150, 151, 152, 170,
 235, 237, 253, 264, 309, 314, 316, 324, 410
 breakthrough • 150, 151, 152
 chest • 53, 107, 170
 patency • 274
 patient attitudes • 133, 180, 184, 190, 203,
 204, 331
 patient outcomes • 180, 184, 192, 194
 patient productivity • 111
 PCR • 43, 60, 143, 172, 285, 289, 292, 355, 366,
 368, 371, 408
 pediatric • 46, 55, 110, 253, 290, 328, 388, 393,
 397, 398, 402
 pediatrics • 36, 122
 PEMF • 249, 309
 Penile Prosthesis • 331
 Pericardiocentesis • 108
 peritoneal lavage • 108, 273, 278
 phacoemulsification • 300
 physical therapy • 233, 240
 pilomatrixoma • 49
 placebo • 39, 40, 42, 106, 112, 115, 126, 132,
 135, 136, 137, 138, 140, 142, 151, 176, 196,
 203, 249, 251, 297, 300, 309, 334, 336, 337,
 339, 340, 350, 354, 362, 471, 474, 485, 522,
 523
 placenta • 43, 207, 216, 218

| | |
|--|--------------|
| plantar puncture wounds • 105 | 84/059 • 444 |
| Platinol • 374 | 84/074 • 376 |
| platinum • 521 | 85/009 • 445 |
| pleconaril • 112 | 85/073 • 449 |
| pleural effusion • 168 | 85/076 • 442 |
| pleural fluid • 60, 168, 171 | 86/007 • 446 |
| pneumonia • 26, 60, 193 | 86/080 • 448 |
| Polar T3 Syndrome • 17, 39, 62, 140 | 86/089 • 377 |
| porcine (<i>Sus scrofa</i>) • 42, 225, 272, 274, 275, 279, 286, 321, 328, 329 | 87/028 • 379 |
| porcine model • 272, 274 | 87/045 • 450 |
| positive nodes • 385, 492, 519 | 87/091 • 380 |
| postmenopausal • 148, 440, 455, 492, 507, 513 | 87/104 • 378 |
| postpartum • 55, 144, 208, 214, 226, 238 | 87/107 • 447 |
| predictors • 531 | 88/065 • 451 |
| Prednisone • 400, 410, 435, 436, 448, 451, 453 | 88/066 • 453 |
| pregnancy • 21, 58, 120, 125, 137, 144, 203, 207, 211, 214, 226, 256, 418 | 89/021 • 462 |
| premenopausal • 440, 457 | 89/080 • 455 |
| preterm infants • 233 | 90/027 • 457 |
| procarbazine • 434, 439 | 90/029 • 461 |
| prochlorperazine • 114 | 90/047 • 458 |
| progesterone • 455, 476, 507, 513 | 90/055 • 460 |
| prognostic factors • 352, 389, 400, 408, 466, 507 | 90/056 • 465 |
| prostate disease • 357 | 90/064 • 454 |
| prostate specific antigen (PSA) • 121, 340, 344, 348, 354, 357, 483 | 90/092 • 232 |
| Prostate Specific Membrane Antigen (PSMA) • 357 | 90/099 • 168 |
| prostatectomy • 346, 452, 467 | 91/007 • 464 |
| prostatic hyperplasia • 346 | 91/033 • 469 |
| prostatic intraepithelial neoplasia • 346 | 91/067 • 459 |
| Proteinuria • 214 | 91/069 • 473 |
| Protocol Number | 91/074 • 382 |
| 77/018 • 437 | 91/086 • 381 |
| 77/024 • 436 | 91/087 • 456 |
| 77/053 • 435 | 91/089 • 463 |
| 77/054 • 434 | 91/094 • 467 |
| 78/002 • 438 | 92/017 • 478 |
| 78/047 • 439 | 92/024 • 173 |
| 79/096 • 440 | 92/051 • 468 |
| 81/035 • 373 | 92/052 • 471 |
| 81/105 • 374 | 93/032 • 476 |
| 83/056 • 443 | 93/056 • 466 |
| 84/018 • 441 | 93/063 • 383 |
| 84/033 • 375 | 93/092 • 487 |
| | 93/097 • 481 |
| | 93/108 • 486 |
| | 93/136 • 485 |
| | 93/141 • 391 |
| | 93/143 • 470 |
| | 93/147 • 386 |

93/148 • 401
93/164 • 396
93/166 • 490
94/010 • 483
94/029 • 167
94/033 • 400
94/051 • 346
94/058 • 494
94/072 • 403
94/073 • 489
94/092 • 406
94/097 • 479
94/104 • 474
94/107 • 493
94/111 • 491
94/115 • 482
94/119 • 452
94/121 • 496
94/161 • 488
94/163 • 500
94/170 • 492
94/177 • 327
95/003 • 498
95/008 • 397
95/018 • 395
95/022 • 280
95/023 • 484
95/024 • 497
95/025 • 368
95/052 • 393
95/056 • 399
95/058 • 408
95/059 • 410
95/060 • 412
95/062 • 472
95/076 • 193
95/084 • 398
95/087 • 407
95/089 • 414
95/093 • 499
95/094 • 501
95/097 • 361
95/104 • 347
95/130 • 252
95/134 • 348
95/136 • 432
95/138 • 369
95/147 • 495

95/151 • 502
95/166 • 266
95/168 • 404
95/190 • 186
96/035 • 421
96/039 • 419
96/044 • 328
96/045 • 272
96/046 • 102
96/049 • 150
96/069 • 134
96/081 • 256
96/086 • 316
96/090 • 126
96/092 • 317
96/094 • 508
96/095 • 513
96/096 • 402
96/097 • 417
96/102 • 507
96/118 • 514
96/120 • 423
96/125 • 187
96/127 • 117
96/132 • 183
96/137 • 188
96/138 • 170
96/142 • 264
96/144 • 409
96/158 • 331
96/163 • 360
96/164 • 144
97/006 • 504
97/009 • 509
97/012 • 145
97/013 • 371
97/016 • 159
97/020 • 107
97/026 • 149
97/033 • 370
97/041 • 511
97/042 • 480
97/047 • 271
97/050 • 120
97/051 • 311
97/054 • 416
97/056 • 233
97/059 • 510

97/060 • 298
97/064 • 276
97/068 • 189
97/070 • 521
97/071 • 415
97/077 • 184
97/083 • 164
97/086 • 297
97/088 • 428
97/089 • 422
97/090 • 429
97/095 • 318
97/096 • 475
97/097 • 349
97/098 • 308
97/099 • 319
97/106 • 195
97/107 • 221
97/108 • 222
97/110 • 148
97/111 • 151
97/112 • 152
97/117 • 268
97/119 • 301
97/120 • 350
97/121 • 303
97/124 • 140
97/125 • 314
97/127 • 115
97/128 • 367
97/129 • 357
97/132 • 174
97/134 • 503
97/140 • 137
97/141 • 282
97/143 • 283
97/144 • 225
97/145 • 430
97/147 • 351
98/002 • 108
98/003 • 321
98/004 • 146
98/005 • 142
98/006 • 143
98/015 • 160
98/021 • 109
98/023 • 332
98/028 • 110

98/029 • 249
98/030 • 240
98/031 • 333
98/032 • 302
98/034 • 263
98/039 • 505
98/044 • 179
98/047 • 260
98/048 • 420
98/050 • 300
98/053 • 190
98/054 • 166
98/055 • 171
98/056 • 306
98/058 • 155
98/060 • 214
98/063 • 194
98/064 • 426
98/065 • 425
98/066 • 427
98/068 • 207
98/069 • 284
98/070 • 228
98/072 • 388
98/073 • 389
98/074 • 392
98/075 • 394
98/076 • 390
98/077 • 345
98/078 • 275
98/079 • 132
98/080 • 161
98/081 • 310
98/082 • 315
98/083 • 274
98/084 • 364
98/085 • 309
98/086 • 172
98/087 • 312
98/088 • 313
98/090 • 418
98/091 • 251
98/092 • 352
98/093 • 259
98/094 • 237
98/096 • 285
98/097 • 289
98/098 • 270

98/099 • 290
98/100 • 291
98/101 • 304
98/102 • 169
98/103 • 295
98/104 • 366
98/105 • 219
98/106 • 261
98/107 • 180
98/108 • 133
98/109 • 111
98/110 • 114
98/111 • 230
98/112 • 516
98/113 • 506
98/114 • 353
99/001 • 385
99/002 • 323
99/003 • 354
99/004 • 278
99/005 • 273
99/006 • 281
99/007 • 255
99/008 • 324
99/009 • 196
99/010 • 103
99/011 • 113
99/012 • 286
99/013 • 135
99/014 • 517
99/015 • 122
99/016 • 253
99/017 • 299
99/018 • 215
99/019 • 515
99/020 • 125
99/021 • 277
99/022 • 185
99/023 • 212
99/024 • 213
99/025 • 191
99/026 • 216
99/027 • 238
99/028 • 181
99/029 • 192
99/030 • 247
99/031 • 202
99/032 • 157

99/033 • 245
99/034 • 123
99/035 • 208
99/036 • 138
99/037 • 525
99/038 • 531
99/039 • 528
99/040 • 522
99/041 • 296
99/042 • 130
99/043 • 358
99/044 • 334
99/045 • 424
99/046 • 217
99/047 • 121
99/048 • 336
99/049 • 231
99/050 • 329
99/051 • 209
99/052 • 305
99/053 • 131
99/054 • 337
99/055 • 136
99/056 • 520
99/057 • 512
99/058 • 527
99/059 • 529
99/060 • 530
99/061 • 242
99/062 • 243
99/063 • 246
99/064 • 218
99/065 • 325
99/066 • 162
99/067 • 124
99/068 • 322
99/069 • 262
99/070 • 105
99/071 • 519
99/072 • 523
99/073 • 524
99/074 • 158
99/075 • 210
99/076 • 244
99/077 • 203
99/078 • 176
99/079 • 177
99/080 • 338

99/081 • 362
 99/082 • 198
 99/083 • 128
 99/084 • 205
 99/085 • 258
 99/086 • 292
 99/087 • 279
 99/088 • 257
 99/089 • 339
 99/090 • 340
 99/091 • 341
 99/092 • 526
 99/093 • 153
 99/094 • 239
 99/095 • 342
 99/096 • 343
 99/097 • 287
 99/098 • 118
 99/099 • 265
 99/100 • 211
 99/101 • 344
 99/102 • 223
 99/103 • 226
 99/104 • 106
 99/105 • 112
 99/106 • 235
 99/107 • 518
 99/108 • 532
 99/109 • 355
 99/110 • 182
 99/111 • 200
 pull-out strength • 311
 pulmonary • 26, 48, 111, 169, 170, 255, 256,
 260, 272, 291, 361, 415, 416, 439, 469
 pulmonary embolism • 260
 quality of life • 58, 130, 134, 185, 188, 223,
 230, 331, 332, 341, 348, 350, 351, 385, 395,
 444, 467, 482, 499, 512, 521, 522
 quinine • 478
 radial keratotomy • 298, 302, 303
 radiation • 173, 188, 257, 369, 377, 378, 380,
 381, 383, 386, 388, 390, 391, 401, 409, 415,
 416, 417, 418, 424, 428, 430, 435, 436, 440,
 442, 449, 451, 452, 454, 457, 460, 461, 464,
 465, 468, 469, 470, 473, 475, 476, 480, 490,
 499, 502, 510, 514, 525, 526
 radiotherapy • 173, 354, 374, 375, 377, 378,
 380, 381, 383, 386, 388, 391, 395, 401, 409,
 415, 416, 417, 418, 422, 424, 426, 428, 430,
 435, 436, 439, 440, 442, 448, 449, 451, 452,
 453, 454, 457, 459, 460, 461, 464, 465, 467,
 468, 469, 470, 473, 475, 476, 479, 490, 491,
 496, 499, 500, 508, 510, 514, 525, 526
 ras • 521
 reagent • 228, 292
 receptors • 207, 444, 455, 507, 513
 recurrent • 56, 338, 339, 349, 376, 382, 420,
 426, 427, 428, 453, 473, 487, 512, 528, 530
 refraction • 51, 209, 296, 297, 303, 305, 407,
 420, 427, 484, 486, 509, 511, 529
 refractive changes • 51
 refrigeration • 228
 rehabilitation • 317
 resection • 173, 286, 323, 326, 338, 347, 385,
 386, 406, 422, 441, 447, 462, 465, 468, 469,
 470, 472, 473, 485, 488, 496, 498, 501, 502,
 503, 509, 514, 516, 524, 530
 residency • 109, 123
 training • 109
 Ribavirin • 142, 143
 right ventricular systolic pressure • 161
 risk factors • 25, 26, 144, 157, 239, 245, 398
 RNA • 43, 285, 289, 355, 356, 456, 487
 ROTC cadets • 158
 safety • 126, 142, 143, 149, 150, 152, 153, 155,
 176, 177, 184, 225, 262, 279, 300, 315, 329,
 331, 333, 334, 336, 337, 344, 350, 358, 362,
 416, 508, 522
 saphenous vein • 47, 313
 scintigraphy • 265, 266
 screening test utilization • 121
 second malignancy • 418
 sedation • 103, 114
 sepsis • 217
 seroma • 280
 serum repository • 463, 478
 sex hormone binding globulin (SHBG) •
 357, 367
 Sigmoidoscopy • 17, 33
 single women • 188
 Skin temperature • 34
 sling procedure • 332
 sludge • 144
 small cell • 60, 149, 171, 172, 287, 442, 525,
 527
 SNAC • 315
 soft tissue sarcoma • 422
 spontaneous resolution • 306

spouse • 252
 stability • 228, 317
 standard radiation • 475, 510, 514
 sternum • 259
 stethoscope, amplified precordial • 103
 stress • 189, 194, 218, 223, 233, 265, 309, 332
 surgery
 gynecologic • 225
 orthognathic • 102
 vascular • 257
 surgical resection • 347, 406, 422, 468, 469,
 470, 485, 496, 498, 502, 514, 530
 surgical staging • 373, 375, 377, 382
 suture anchors • 319
 swelling • 302
 swine • 329
 tamoxifen • 148, 367, 369, 440, 455, 457, 461,
 476, 492, 500, 507, 513, 519, 522, 523
 Taxol • 500, 509
 Taxotere • 519
 T-cell • 388
 telomerase • 41, 60, 171, 172, 281, 282, 283,
 284, 287, 288, 289, 292, 347, 349, 355, 356
 Temodal • 426
 Temozolomide • 426
 tensile strength • 274
 tension • 251, 296, 304
 teratoma • 376, 465
 thermocouple sensor placement • 34
 Thioplex • 149
 Thoracotomy • 108
 thrombolytics • 107
 thrombospondin • 371
 thymidylate synthase • 503, 504, 516
 thyroxine • 39, 140
 tidal volume breathing method • 170
 Timolol • 297
 tissue repository • 353, 456
 tolerability • 130, 148, 164
 tolterodine • 333
 topotecan • 419, 420, 421, 429, 486, 511
 tracheobronchial • 328, 329
 training • 7, 9, 19, 37, 46, 108, 109, 110, 117,
 205, 225, 273, 278, 279, 295, 327, 328, 329
 endoscopic • 329
 transfemoral • 133
 transmucosal fentanyl citrate • 151
 transradial • 133
 trauma • 48, 108, 208, 210, 259, 273, 295, 298
 triage • 105, 117, 295
 TRICARE • 187, 245, 247
 tricuspid regurgitation • 161
 triiodothyronine • 140
 TSH • 39, 136, 140
 TSP1 • 366, 371
 tumor
 ovarian • 375
 sinus • 376
 tumor repository • 506
 tumors
 CNS • 426
 ultrasonography • 209, 222, 315
 ultrasound • 144, 203, 209, 211, 215, 222,
 226, 257, 312, 313, 360, 405, 432
 urinalysis • 117
 urinary tract • 190, 223, 225, 358
 urine • 117, 162, 193, 214, 223, 315, 338, 349,
 362, 417, 489
 urine protein/creatinine ratio • 214
 VAC • 421, 429, 430
 vaccine • 244, 472, 512
 valsartan • 131
 vancomycin • 54, 155
 vascular templates • 274
 Venous cutdown • 108
 ventilation • 192, 364
 verapamil • 478
 veterinarian • 108, 110, 329
 VIAGRA • 350
 vigabatrin • 164
 vinblastine • 376, 453, 479, 520
 Vincristine • 400, 401, 422, 430, 436, 451, 453
 Vinorelbine • 521, 530
 viral respiratory infection • 112
 visual acuity • 51, 296, 297, 300, 301, 303, 304,
 305
 VM-26 • 412
 vomiting • 410, 511, 518
 VP-16 • 149, 376, 382, 395, 401, 403, 442, 448,
 470, 495, 496, 502
 washings • 171, 349, 373, 376, 379, 380, 382
 weaning • 167
 work ethic • 109
 wound healing • 42, 189, 191, 371
 Wrist • 266
 Zanamivir • 111
 Zinocard • 409, 415, 416